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Longitudinal changes in regional cerebral blood flow in late middle-aged and older adults with treated and untreated obstructive sleep apnea

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Abstract

Obstructive sleep apnea (OSA) is associated with abnormal cerebral perfusion at wakefulness, but whether these anomalies evolve over time is unknown. Here, we examined longitudinal changes in regional cerebral blood flow (rCBF) distribution in late middle-aged and older adults with treated or untreated OSA. Twelve controls (64.8 ± 8.0 years) and 23 participants with newly diagnosed OSA (67.8 ± 6.2 years) were evaluated with polysomnography and cerebral ^{99m}Tc-HMPAO single-photon emission computed tomography during wakeful rest. OSA participants were referred to a sleep apnea clinic and 13 of them decided to start continuous positive airway pressure (CPAP). Participants were tested again after 18 months. Voxel-based analysis and extracted relative rCBF values were used to assess longitudinal changes. Untreated OSA participants showed decreased relative rCBF in the left hippocampus and the right parahippocampal gyrus over time, while treated participants showed trends for increased relative rCBF in the left hippocampus and the right parahippocampal gyrus. No changes were found over time in controls. Untreated OSA is associated with worsening relative rCBF in specific brain areas over time, while treated OSA shows the opposite. Considering that OSA possibly accelerates cognitive decline in older adults, CPAP treatment could help reduce risk for cognitive impairment.

KEYWORDS
aging, continuous positive airway pressure, neuroimaging, obstructive sleep apnea, regional cerebral blood flow

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repeated obstructions of the upper airway during sleep causing episodes of decrease (hypopnea) or complete cessation (apnea) of the respiratory flow. OSA is common, especially in the elderly population where the prevalence can reach 50% according to some studies (Senaratna et al., 2017), with the majority of cases being undiagnosed (Braley et al., 2018). The disturbed respiratory flow leads to intermittent hypoxemia and micro-arousals (Malhotra & White, 2002) and together, they may cause

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excessive daytime sleepiness, cognitive dysfunction and decreased efficiency in daily activities (Ferini-Strambi, Marelli, Galbiati, & Castronovo, 2013; Gagnon et al., 2014). More recently, OSA has been identified as a possible risk factor for incident mild cognitive impairment and dementia (Gosselin, Baril, Osorio, Kaminska, & Carrier, 2019).

During nocturnal respiratory events, an initial increase in cerebral blood flow (CBF) is seen, followed by a decrease in CBF below resting values (Franklin, 2002). Disturbed nocturnal CBF combined with the intermittent decrease in blood oxygen saturation cause regional cerebral hypoxia, potentially damaging neural and vascular tissues (Angelo et al., 2014; de Lima et al., 2010; Feng, Zhang, & Chen, 2012; Pizza, Biallas, Wolf, Werth, & Bassetti, 2010), which may impact cerebral functioning during wakefulness. Indeed, in the case of neuronal and vascular damage, we could expect a decrease in regional CBF (rCBF) during wakefulness, as rCBF is strongly coupled with brain activity and metabolism (Lecrux & Hamel, 2011).

In agreement with this hypothesis, neuroimaging studies using arterial spin labeling to assess rCBF during wakefulness found hypoperfusion in the right frontal lobe, the temporal lobes, the parahippocampal gyri, the right hippocampus, the basal ganglia, the cerebellum and the brainstem in moderate to severe OSA relative to controls (Chen et al., 2017; Innes, Kelly, Hlavac, Melzer, & Jones, 2015; Nie et al., 2017; Yadav et al., 2013). Similar brain regions were found to be affected in OSA using single photon emission computed tomography (SPECT) to assess rCBF pattern and positron emission tomography (PET) to quantify metabolism distribution (Joo, Tae, Han, Cho, & Hong, 2007; Kim et al., 2017; Shiota et al., 2014; Yaouhi et al., 2009). While most studies have included middle-aged subjects (mostly between 30 and 60), our group recently studied rCBF in late middle-aged to elderly participants (mean age: 64.5) (Baril et al., 2015). In severely affected patients, as defined by an apnea-hypopnea index (AHI) >30, we found decreased relative rCBF in the left parietal lobe, the left precentral gyrus, the bilateral postcentral gyri and the right precuneus. Since this pattern of hypoperfusion is seen in early Alzheimer's disease and given the potential causal role played by OSA in neurodegenerative processes (Gosselin et al., 2019), it is of the utmost importance to clarify whether OSA treatment with continuous positive airway pressure (CPAP) can slow down or reverse rCBF anomalies.

In the present study, our first objective was to explore relative rCBF changes during wakefulness over 1.5 years in late middle-aged to elderly individuals with treated or untreated OSA compared to a control group. We hypothesized that participants with untreated OSA would present decreased relative rCBF over time in regions previously found to be sensitive to OSA and that CPAP treatment would increase relative rCBF in these regions.

2 | METHODS

2.1 | Participants

Participants aged between 56 and 82 years were recruited for this project from the *Hôpital du Sacré-Coeur de Montréal* Sleep Apnea Clinic's waiting list and from local newspaper ads. Inclusion and exclusion criteria were described in details in our previous studies (Baril et al., 2015; Baril et al., 2017; Baril, Gagnon, Brayet, et al., 2018). Exclusion criteria were (a) neurological (including neurodegenerative), psychiatric or pulmonary diseases; (b) sleep disorders other than OSA; (c) uncontrolled hypertension or diabetes; (d) body mass index >40 kg/m^2 (Braley et al., 2018); (e) medication affecting the central nervous system or substance abuse. Claustrophobic subjects, preventing prolonged SPECT acquisition, were also excluded. Written and informed consent was obtained for all participants. The research protocol was approved by the *Centre intégré universitaire de santé et des services sociaux du Nord-de-l'Île-de-Montréal* Ethic's Committee (#2012-697). This study was part of a larger research program on OSA and mild cognitive impairment, which aims to understand the contribution of OSA on cognitive decline as well as cerebral structure and function in middle-aged and elderly people.

2.2 | Protocol overview

Following a phone interview, participants meeting the inclusion criteria were invited to the sleep laboratory. All participants filled out the following questionnaires: Epworth Sleepiness Scale (Johns, 1991), Beck Depression Inventory-II (Beck, Steer, Ball, & Ranieri, 1996) and Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988). A vascular burden score was also calculated for each participant to assess cardiovascular risk factors (hypertension, dyslipidemia, diabetes, carotid stenosis, coronary diseases, angina pectoris, myocardial infarction, coronary artery bypass, arrythmia and transitory ischemic attacks) (Villeneuve, Belleville, Massoud, Bocti, & Gauthier, 2009). The Montreal Cognitive Assessment was administered (Nasreddine et al., 2005) and mild cognitive impairment diagnoses at Time 1 were made using a comprehensive neuropsychological assessment described in our previous study (Gagnon et al., 2019). All participants were recorded for a full night of in-laboratory polysomnography and underwent a brain SPECT scanning during wakeful rest (Time 1) in the morning. SPECT statistical analyses were not conducted blind to group, but all participants were offered the possibility to undergo SPECT imaging. Participants presenting OSA were then referred to the sleep apnea clinic and were offered a CPAP treatment, which they were free to accept or refuse. Approximately 18 months after their first assessment, participants were called for a follow-up (Time 2), during which a follow-up brain SPECT recording was performed, again during wakeful rest. For subjects who started CPAP treatment, compliance was followed using either information from the CPAP unit (n = 7) or self-reported by the participants during telephone interviews (n = 6). Compliance to CPAP treatment was considered adequate when participants used the CPAP device on average >4 hr/night and used it at least 70% of nights/month (Weaver & Grunstein, 2008). Four participants started CPAP treatment but did not meet the compliance criteria and were therefore considered untreated. Of those four subjects, three barely used CPAP and one used it on average 3 hr/night for the first 5 months only. Subjects

were separated in three groups: Controls (AHI <5), untreated OSA (AHI >15) and treated OSA. Participants with an AHI between 5 and 15 (n = 19) were not included in the untreated group as our previous study, in line with the literature in middle-aged patients, showed that a higher severity of OSA is needed to observe changes in rCBF (Baril et al., 2015; Innes et al., 2015; Kim et al., 2017; Nie et al., 2017). The exclusion of participants with an AHI between 5 and 15 from the untreated group was also chosen to better match the treated OSA groups: as it is the case in the present study, OSA individuals that are proposed and accept treatment generally present with a higher severity. However, as a sensitivity analysis, we explored whether our findings extended to this group of OSA participants with an AHI between 5 and 15.

2.3 | Polysomnographic recording

In-laboratory polysomnography included an electroencephalogram using an 18-channel montage according to the international system (Fz, F3, F4, F7, F8, Cz, C3, C4, T7, T8, Pz, P3, P4, P7, P8, Oz, O1 and O2) with a contralateral mastoid reference (American Electroencephalographic Society, 1991). Polysomnography also included an electrooculogram, electromyogram and electrocardiogram, as described in our previous studies (Baril et al., 2015; Baril et al., 2017). Respiratory events were recorded with thoraco-abdominal gauges, a nasal cannula with a thermal sensor and a transcutaneous finger oximeter. Sleep and respiratory events were identified by an electrophysiology technologist in accordance with recent rules (Berry, Budhiraja, Gottlieb, et al., 2012; Iber, Ancoli-Israel, Chesson & Quan, 2007). Apnea was defined as a reduction in airflow ≥90% from the baseline which lasted ≥10 s. A hypopnea was defined by a reduction of the airflow ≥30% compared to the reference and which lasted ≥10 s and was accompanied by either a desaturation ≥3% or by a micro-arousal on the electroencephalogram. The AHI was computed as the total apneas and hypopneas divided by total sleep time.

2.4 | SPECT image acquisition

The morning after the PSG recording, participants received an intravenous dose of 750 MBq of ^{99m}Tc-HMPAO, followed by a saline flush of 30 cc during which participants laid on a stretcher with their eyes closed. ^{99m}Tc-HMPAO uptake in the brain takes about a minute, and thus, this fast uptake reduces the likelihood of drowsiness or even sleep during the uptake phase. Next, using a high-resolution brain-dedicated scanner (NeuroFOCUS, NeuroPhysics, Shirley, MA), we performed a static 30 min scan during wakeful rest. The scanner provided a 2.5 mm full-width half-maximum spatial resolution. Using a filtered back projection, 32 slices were reconstructed on a 128 × 128 matrix, followed by attenuation correction using Chang's method with a coefficient of 0.01/cm. The cerebellum was not accurately evaluated in all participants with this SPECT system, and we therefore excluded the cerebellum in all subsequent analyses. Images were visually reviewed for artifacts. The same procedure was used for Time 1 and Time 2.

2.5 | SPECT image analysis

Images were processed using SPM8 (Statistical Parametric Mapping 8, Wellcome Department of Imaging Neurosciences, Institute of Neurology, University of London, United Kingdom) in MATLAB 8.5 (The MathWorks, Natick, MA), as previously described (Baril et al., 2015; Baril et al., 2018). Briefly, images were co-registered and normalized to the SPECT template in SPM8. For voxel-based analyses, images were then smoothed using a 12-mm FWHM Gaussian filter. We used a proportional scaling normalization of individual images, so that the final regional results were relative to the mean global signal of CBF fixed at 50 ml/100 g/min. For extraction analyses, we used the toolbox Marsbar (Brett, Anton, Valabregue & Proline, 2002) to extract rCBF values from normalized images in 90 different brain regions, as defined by the Automated Anatomical Labelling Atlas (Tzourio-Mazoyer et al., 2002). We also used a proportional scaling normalization during extraction to adjust for mean global signal of CBF fixed at 50 ml/100 g/min. At the end of the extraction processing, we finished with a rCBF value, relative to the global CBF, for each region of the brain, excluding the cerebellum since it was partially outside the field of view of our SPECT scanner. To reduce the number of statistical analyses, we excluded occipital regions since they do not appear to be altered in OSA (Baril et al., 2015; Chen, Lin, Lu, et al., 2017; Innes et al., 2015; Joo et al., 2007; Kim et al., 2017; Nie et al., 2017; Shi et al., 2017).

The technique we used to assess rCBF only allows commenting on the relative distribution of CBF. It does not yield, as used, a true quantification of rCBF values (although a different type of acquisition using this technique can; [Matsuda et al., 1993]). However, other authors (Chen, Lin, Lu, et al., 2017; Innes et al., 2015; Nie et al., 2017; Yadav et al., 2013) have studied OSA with arterial spin labeling, which measures rCBF in values of ml/100 g/min tissue, and those authors have shown that OSA is linked to absolute decreases of rCBF values. It would then appear reasonable to consider that the regions we report here as showing hypoperfusion relative to the global CBF are actually hypoperfused in absolute terms. We will therefore characterize those areas as such.

2.6 | Statistical analysis

All statistical analyses, except for voxel-based ones, were performed using SPSS 24 (IBM SPSS Statistics, New York). Chi-square tests and one-way analyses of variance (ANOVAs) with Tukey's post-hoc tests were used to determine if there were significant differences between the three groups for demographic, clinical and polysomnographic variables. We used two-way repeated measures ANOVAs (three groups and one repeated measure) to test for group and time effects for the Beck Depression Inventory-II, the Beck Anxiety Inventory, the Epworth sleepiness scale and the Montreal Cognitive Assessment. The results were considered significant at $p < .05$.

Regarding rCBF, we used two statistical analyses approaches, one based on voxel analysis and one based on extracted regions of

interest. For the voxel-based analyses, we used SPM 8 and paired *t* tests in each group to examine changes in rCBF over time. Results were considered significant when at least 200 contiguous voxels reached a height threshold of $p < .001$ uncorrected. For the regions of interest analyses, we used ANOVAs with three groups and one repeated measure for each of the extracted regions of interest of the associative, sensorimotor, limbic and subcortical structures. Results were considered significant at $p < .01$ for the Group x Time interaction, a more stringent level of significance in order to reduce multiple comparisons effect, and $p < .05$ for post-hoc analyses when significant interactions were observed.

3 | RESULTS

3.1 | Demographic and clinical variables.

Seventy-seven participants underwent SPECT imaging at Time 1 and 38 participants came back for Time 2. All subjects with OSA were newly diagnosed at Time 1 and untreated at the beginning of the study. Three participants were excluded from the analyses due to poor SPECT quality. The final sample consisted of 35 participants (mean age: 66.8 ± 6.9 years, 6 women). Among the 35 participants, 12 were controls (mean AHI at baseline: 2.0 ± 1.5 events/hr, range: 0.2–4.5), 10 had untreated OSA (mean AHI at baseline: 28.8 ± 6.2 events/hr, range: 20.6–39.2) and 13 decided to use CPAP to treat their OSA after the baseline assessment (mean AHI at baseline: 37.0 ± 25.1 events/hr, range: 7.7–96.6). Demographic, clinical and polysomnographic variables at baseline are presented in Table 1. BMI was significantly lower in the control group (mean: 26.0, range: 20.7–32.3) than in the treated group (mean: 30.1, range: 25.5–36.4) while the untreated group (mean: 27.6, range: 25.6–32.4) did not statistically differ from the other groups. At Time 1, 2 controls, 3 non-treated OSA and 5 treated OSA participants had a mild cognitive impairment based on their neuropsychological assessment. They were evaluated with SPECT at Time 2 on average 18.3 ± 1.7 months (range: 14–22 months) after the Time 1 evaluation, with no difference between groups. The symptomatology, including sleepiness, mood and global cognition are presented in Table 2. No Group X Time interaction as well as no Group or Time effects were observed on any of the questionnaires nor on the Montreal Cognitive Assessment.

TABLE 1 Demographic, clinical and polysomnographic variables at baseline for control, untreated OSA and treated OSA groups

Variables	Controls (A)	Untreated OSA (B)	Treated OSA (C)	*F* or X^2 values	Post-hoc tests
Number of subjects	12	10	13		
Sex	9 M; 3F	10M	10 M; 3F	2.9	
Education (years)	16.3 (2.5)	16.1 (3.4)	14.3 (3.4)	1.4	
Age (years)	64.8 (8.0)	67.4 (4.1)	68.2 (7.6)	0.8	
BMI (kg/m^2)	26.0 (3.0)	27.6 (2.0)	30.1 (3.4)	6.1*	A < C
Time between SPECT scans (months)	18.8 (1.9)	18.2 (1.5)	18.1 (1.7)	0.5	
Index of vascular burden score (Time 1)	1.0 (1.0)	0.8 (0.8)	1.8 (1.2)	2.5	
PSG variables—Time 1					
Total sleep time (min)	363.3 (76.6)	365.0 (57.9)	377.7 (67.0)	0.2	
Wake duration after sleep onset (min)	104.4 (56.2)	99.6 (63.3)	99.4 (43.1)	0.03	
Sleep efficiency (%)	77.3 (13.3)	79.0 (12.8)	78.9 (9.5)	0.07	
Micro-arousal index (events/hr)	11.3 (3.8)	18.1 (8.5)	21.9 (9.6)	5.9*	A < C
Sleep latency (min)	13.0 (7.7)	5.8 (4.8)	12.8 (14.0)	1.8	
Stage N1 (%)	16.8 (8.2)	27.6 (10.6)	30.8 (15.1)	4.7*	A < C
Stage N2 (%)	58.5 (6.9)	53.0 (7.6)	52.5 (12.1)	1.5	
Stage N3 (%)	9.7 (10.6)	5.2 (6.1)	4.3 (4.1)	1.9	
REM sleep (%)	15.0 (5.0)	14.3 (5.1)	12.4 (4.0)	1.0	
Apnea-hypopnea index (events/hr)	2.0 (1.5)	28.8 (6.2)	37.0 (25.1)	16.4**	A < B,C
Total sleep time with apnea (%)	1.4 (1.2)	20.1 (10.5)	22.7 (15.8)	9.8**	A < B,C
Mean SpO_2 (%)	95.0 (1.0)	94.2 (1.0)	93.8 (1.2)	3.5*	A > C
Minimal SpO_2 (%)	89.7 (2.9)	82.5 (6.4)	81.2 (6.0)	9.0**	A > B,C
Time spent with SpO_2 < 90% (min)	0.1 (0.3)	11.8 (15.2)	16.3 (25.0)	2.9	

Note: Results are presented as means (standard deviations).
Abbreviations: BMI, body mass index; F, females; M, males; NREM, non-REM sleep; ns, non-significant; OSA, obstructive sleep apnea; REM, rapid eye movement sleep; SpO_2, oxygen saturation.
*$p < .05$.
**$p < .001$.

TABLE 2 Symptomatology of OSA groups using two-way repeated measures ANOVA

Variables	Controls	Untreated OSA	Treated OSA	Interaction (time X groups)	
				F	*p* value
Epworth sleepiness scale					
Time 1	8.4 (6.0)	11.7 (5.2)	8.2 (4.8)	0.042	.959
Time 2	7.4 (5.9)	10.1 (6.2)	6.9 (3.5)		
Beck anxiety inventory					
Time 1	3.9 (4.9)	4.7 (4.9)	4.3 (4.8)	0.074	.929
Time 2	3.1 (2.6)	3.9 (7.5)	2.9 (2.8)		
Beck depression inventory-II					
Time 1	4.1 (3.8)	9.4 (5.9)	7.5 (6.0)	0.035	.966
Time 2	4.2 (3.3)	8.8 (8.7)	7.4 (7.2)		
Montreal cognitive assessment					
Time 1	27.7 (2.3)	28.1 (2.0)	28.5 (1.6)	0.825	.447
Time 2	26.7 (2.8)	27.4 (1.3)	26.5 (2.1)		

Note: Results are presented as means (*SD*).
Abbreviation: OSA, obstructive sleep apnea.

3.2 | Relative rCBF changes over 18 months

Using the voxel-based approach, no significant difference in rCBF distribution was found between Time 1 and Time 2 when measured in the three groups separately. However, when using the relative rCBF of extracted regions of interest, we observed a significant Group X Time interaction for the left hippocampus ($F(2,32) = 6.161$, $p = .005$, $\eta_p^2 = 0.278$). Post-hoc ANOVAs with one-repeated measure (Time) in each group separately revealed no changes with time in the control group ($F(1,11) = 2.977$, $p = .112$), while the untreated OSA group showed significant decrease in relative perfusion ($F(1,9) = 7.915$, $p = .020$) and the treated OSA group showed a trend for increased relative perfusion as compared to the baseline ($F(1,12) = 3.486$, $p = .086$) (see Figure 1). Also, we found a significant interaction for the right parahippocampal gyrus ($F(2,32) = 5.391$, $p < .010$, $\eta_p^2 = 0.252$), where no changes were found in the control group over time. Again, untreated subjects showed decreased relative perfusion ($F(1,9) = 14.806$, $p = .004$) and treated subjects showed a trend for increased relative perfusion over time ($F(1,12) = 3.808$, $p = .075$).

As a sensitivity analysis, we explored whether rCBF changes over time that we observed in the left hippocampus and right parahippocampal gyrus were present in OSA individuals with an AHI between 5 and 15, corresponding to a mild severity ($n = 19$, mean age: 64.1 ± 7.0 years; 3 women; AHI: 9.9 ± 2.8 events/hour). No rCBF changes over time were observed in this group, suggesting that longitudinal changes over 18 months did not display a dose–response pattern and were limited to the OSA population with a higher severity.

4 | DISCUSSION

In this study, we investigated longitudinal changes in rCBF during wakefulness in late middle-aged and elderly adults with untreated or treated OSA and compared them to controls. We found that OSA participants with CPAP showed a trend for increased relative rCBF over time in hippocampal and parahippocampal areas, while untreated participants showed decreased relative rCBF in those same areas over time. No changes were found in control subjects. The hippocampal and parahippocampal regions seemed particularly sensitive to the presence of OSA and its treatment. Interestingly, despite regional perfusion changes over time, general cognitive functioning and symptoms of depression, anxiety and sleepiness remained stable. Our findings suggest that OSA might affect medial temporal functioning before significant clinical symptoms occur, and these focal perfusion alterations might be prevented by an efficient CPAP treatment.

4.1 | Decreased relative rCBF in untreated OSA over time

Participants with untreated OSA showed a significant decrease of relative rCBF in the left hippocampus and the right parahippocampal gyrus over the 18-month duration of the study. These regions were previously reported as being either absolutely (Innes et al., 2015; Nie et al., 2017) or relatively hypoperfused (Joo et al., 2007; Kim et al., 2017) in a younger sample (mean age ranging from 38 to 57 years) of OSA patients compared to controls.

In the present study, these changes were observed even if many of our untreated OSA participants had relatively asymptomatic OSA (5 out of 10 patients had an Epworth Sleepiness Score ≤10). Reduced rCBF could be explained by endothelial dysfunction (e.g., inability of the vessels to properly dilate in response to metabolic activity). In fact, intermittent hypoxemia has the potential to increase oxidative stress, inflammation and cell apoptosis while reducing nitric oxide availability, and impairing repair processes (Büchner et al., 2011; Feng

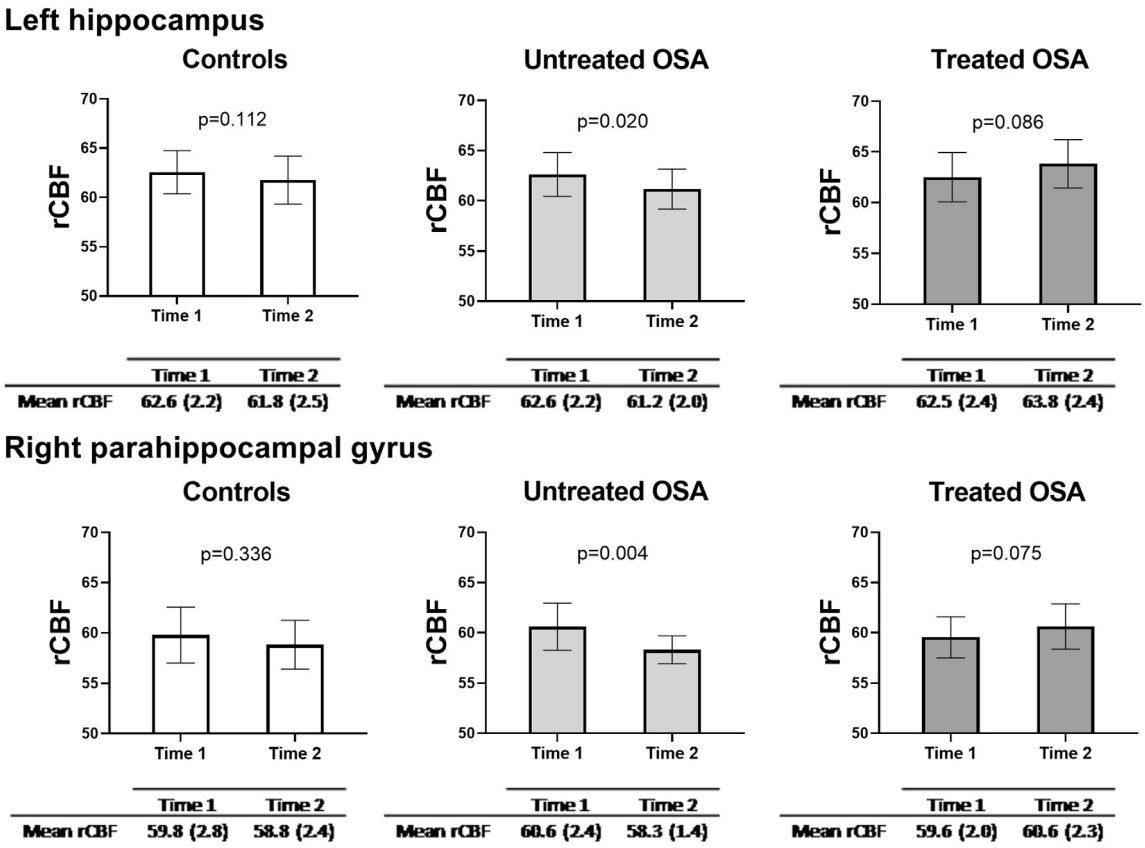

FIGURE 1 Changes in relative regional cerebral blood flow (rCBF) between Time 1 and Time 2 in the control, untreated obstructive sleep apnea (OSA) and treated OSA groups. Significant decreases in relative rCBF over time are seen in the left hippocampus and the right parahippocampal gyrus in the untreated OSA group. Trends for increases in relative rCBF are seen in the left hippocampus and right parahippocampal gyrus of the treated OSA group. Relative rCBF values correspond to adjusted signal of the given area to the mean global signal set at 50 ml/100 g/min. Error bars represent the *SD*s. Results in tables are presented as means (*SD*)

et al., 2012; Gaspar, Álvaro, Moita, & Cavadas, 2017; May & Mehra, 2014); all of those can impact vascular function. Moreover, one study has reported increased oxidative stress and inflammation specifically in the hippocampus and the enthorinal cortex, a part of the parahippocampal gyrus, suggesting high vulnerability of these regions to OSA (Snyder, Shell, Cunningham, & Cunningham, 2017). Several studies also found decreased vasoreactivity in OSA, which could explain reduced rCBF (Coloma Navarro, Jiménez Caballero, Vega, Ayo-Martín, & Segura Martín, 2016; Gregori-Pla et al., 2018; Prilipko, Huynh, Thomason, Kushida, & Guilleminault, 2014; Urbano, Roux, Schindler, & Mohsenin, 2008).

Reduced rCBF in OSA could also be explained by neuronal, synaptic and glial impairment, since perfusion is tightly coupled with brain activity. In animal models, intermittent hypoxemia leads to neuronal cell death (Douglas et al., 2010; Xu et al., 2004). Moreover, a meta-analysis found reduced gray matter volume in the bilateral parahippocampal gyri and in the left middle temporal gyrus, suggesting tissue loss (Weng et al., 2014). Thus, our results raise the possibility that neglecting to treat OSA might maintain intermittent hypoxemia capable of inflicting ongoing damage to neuronal cells, leading to decreased relative rCBF over time in these sensitive areas.

4.2 | Increased relative rCBF in treated OSA

The main treatment for OSA is CPAP, which keeps the upper airway open during sleep. CPAP considerably reduces the number of respiratory events, thus improving sleep efficiency, oxygen saturation, sleepiness and overall quality of life (Giles, Lasserson, Smith, et al., 2006). CPAP also improves diurnal systolic and diastolic blood pressure, highlighting the effects of OSA on blood flow regulation as well as the impact of an efficient treatment of vascular health (Jonas et al., 2017). Few neuroimaging studies have evaluated the impact of CPAP on brain function during wakefulness. One PET study in middle-aged OSA patients found hypometabolism before treatment in several brain regions, notably the bilateral precentral gyri and the left cingulate cortex, which increased after 3 months of CPAP treatment without reaching control levels (Ju et al., 2012). Two studies have evaluated changes in relative rCBF following CPAP treatment using a similar imaging technique as ours. In the first one, hypoperfusions were observed during wakefulness in the superior and middle frontal gyri in severe OSA before treatment in middle-aged subjects, which re-normalized after a 3-month CPAP treatment (Shiota et al., 2014). By comparing the rCBF of OSA patients before and after CPAP treatment, they found an increase from baseline in rCBF in the

parahippocampal gyri, the right lingual gyrus, the cuneus, and the frontal area. Finally, one study showed hypoperfusion during wakefulness in multiple brain regions including the left parahippocampal gyrus, the bilateral medial frontal gyri, the right anterior cingulum and the right cingulate gyrus in middle-aged subjects, which all increased compared to baseline after a 7.9-month CPAP treatment (Kim et al., 2017).

In our study, participants with treated OSA over 18 months showed a trend toward increasing relative rCBF in the left hippocampus and the right parahippocampal gyrus, a pattern also seen in previous studies (Kim et al., 2017; Shiota et al., 2014). CPAP may increase rCBF by attenuating the pathological stress caused by intermittent hypoxemia and sleep fragmentation. Indeed, CPAP is known to reduce blood markers of oxidative stress after a 2-month treatment (Alonso-Fernandez et al., 2009; Christou et al., 2009; de Lima et al., 2010; Zhou, Chen, Peng, & Ouyang, 2016). However, it remains unclear if CPAP reduces inflammation as studies have reported conflicting results using different blood markers. These inconsistencies might be explained by differences in studied populations and biomarkers, and that patient-specific factors such as adipose tissue distribution (android vs. gynecoid) could modulate the inflammatory response to CPAP (Cheng, 2003; McNicholas, 2009; Unnikrishnan, Jun, & Polotsky, 2015). A meta-analysis found that a 1 to 6-month CPAP treatment leads to significant and clinically relevant improvement in endothelial function (Schwarz, Puhan, Schlatzer, Stradling, & Kohler, 2015). Another study concluded that a minimum of 6 months of CPAP treatment is needed to decrease carotid intima-media thickness, an indicator of atherosclerosis (Chen et al., 2017). Consequently, long treatment duration seems necessary to reverse severe impairment in vascular function. Thus, by reducing intermittent hypoxemia, CPAP could allow vascularization recovery in areas sensitive to OSA, resulting in an increase in rCBF. Additionally, treatment studies found increased gray matter volume (Canessa et al., 2011; Kim et al., 2016), as well as the reversal of white matter abnormalities after treating OSA (Castronovo et al., 2014). The authors hypothesized that hypertrophy and proliferation of the neuropil could explain the increase in gray matter volume, which could explain increasing rCBF with treatment as well.

Surprisingly, in the present study, CPAP treatment did not significantly reduce daytime sleepiness as measured by the Epworth Sleepiness Scale. However, our treated CPAP group did not display particularly elevated levels of excessive daytime sleepiness to begin with. Although sleepiness is commonly associated with OSA, only 15% of older individuals with OSA report excessive daytime sleepiness (Sforza, Pichot, Martin, Barthélémy, & Roche, 2015). An animal model suggested that sleepiness might not only be a consequence of sleep fragmentation induced by OSA, but might also be caused by hypoxic damage to wake-promoting neuronal networks (Zhu et al., 2007). Treated elderly participants with OSA and excessive daytime sleepiness might thus have a different rCBF pattern over time than our treated group with minimal sleepiness. Our findings might therefore not be generalizable to other older OSA patients experiencing excessive daytime sleepiness.

4.3 | OSA, aging and risk of neurodegeneration

At Time 2, 9 of our 23 OSA participants showed a performance <26/30 on the MoCA, which suggests the presence of mild cognitive impairment (Gagnon et al., 2018). It is therefore possible that a proportion of our participants had ongoing neurodegenerative processes. Interestingly, the parahippocampal region and the hippocampus were the most susceptible to show either reduced perfusion in untreated participants or improved perfusion in treated participants. These regions are also among the earliest regions to show changes (i.e., atrophy or reduced metabolism and perfusion) in mild cognitive impairment and Alzheimer's disease and these changes appear even before behavioral or clinical manifestations of neurodegeneration (Mak et al., 2017; Wierenga, Hays, & Zlatar, 2014). Moreover, hypoperfusion in the parahippocampal gyrus and hippocampus has been linked to conversion from mild cognitive impairment to Alzheimer's disease, suggesting the importance of these areas in neurodegenerative progression (Caroli et al., 2007; Chao et al., 2010; Eskildsen, Coupe, Fonov, et al., 2015; Park et al., 2012). Whether reduced perfusion of those structures found in our untreated OSA participants could represent vulnerability for neurodegeneration is unknown and needs to be investigated in larger longitudinal studies. The increase in the relative rCBF as compared to baseline observed in the treated OSA group might provide protection against neurodegeneration. Concordant with this hypothesis, one study showed that CPAP delays the appearance of mild cognitive impairment (Osorio, Gumb, Pirraglia, et al., 2015) and reduces cognitive decline in Alzheimer's disease (Troussière et al., 2014).

4.4 | Limitations

We used an observational approach to explore longitudinal changes in rCBF in treated OSA, untreated OSA and control subjects. Our results reinforce the idea that larger randomized and controlled studies of the effects of CPAP are needed to understand the impact of OSA and its treatment on brain function in middle-aged and older adults. However, there are some limitations to our study. First, we were not able to analyze the cerebellum due to limitations of our SPECT scanner. The cerebellum seems to be sensitive to OSA, as it has been reported to be atrophied (Shi et al., 2017) and hypoperfused in middle-aged participants (Chen, Lin, Lu, et al., 2017; Kim et al., 2017; Nie et al., 2017). Second, we found relative rCBF changes in untreated and treated OSA groups using the extraction analyses, while we found no difference using the voxel-based approach. This can likely be explained by the fact that changes in perfusion are possibly diffuse within a specific region and were not localized enough to reach significance on a voxel-by-voxel analysis. Extracting a global value from a region of interest might be more suitable to capture changes in rCBF in OSA. Another explanation might be a lack of power due to our small sample size. However, with 35 participants (12 controls, 23 OSA) and considering the longer study period, our study presents an average sample size comparable to other longitudinal CBF studies

(Kim et al., 2017; Prilipko et al., 2014; Shiota et al., 2014). Moreover, we did not adjust for BMI and AHI in our models because these variables did not differ significantly between the untreated and treated participants with OSA. However, future studies with larger sample sizes could include these as variables to verify whether they influence the brain response to treatment. Also, the regions observed as susceptible to OSA reached significance only in a unilateral pattern, raising the question of whether OSA affects certain regions in a hemisphere preferentially. This pattern could be explained because there is a true lateralization of affected regions in OSA or, more probably, because our study lacked statistical power to observe bilateral changes. Even though individual neuroimaging studies in OSA commonly report lateralization in affected regions, when we pool results from different studies, we can notice an absence of a clear lateralization pattern (Shi et al., 2017). Therefore, we hypothesize that the lateralization observed in our study is the consequence of a lack of statistical power. Another limitation of the study is the absence of data form the CPAP unit for 6 participants. Though we confirmed CPAP adherence with telephone interviews, we were not able to confirm the normalization of AHI in these participants. However, the general ability of CPAP treatment to reduce the AHI below 5 (Jonas et al., 2017) and the efficacy seen in other participants in the study leads us to believe it is a minor limitation. Lastly, this study did not use a randomized and controlled protocol, because using a placebo CPAP for a long period of time (i.e., 18 months) in symptomatic subjects would bring considerable ethical issues. However, symptomatology and sleepiness (Brin, Reuveni, Greenberg, Tal, & Tarasiuk, 2005; Chai-Coetzer et al., 2013; Mehrtash, Bakker, & Ayas, 2019), cognitive impairment (Sierra-Marcos, 2017; Wierenga et al., 2014; Zhang, Gordon, & Goldberg, 2017) and socioeconomic factors (Brin et al., 2005; Cadar et al., 2018; Hackman, Kuan, Manuck, & Gianaros, 2018; Hasselgren et al., 2018; Shahrabani, Tzischinsky, Givati, & Dagan, 2014; Simon-Tuval et al., 2009; Tzischinsky, Shahrabani, & Peled, 2011; Yaffe, Falvey, Harris, et al., 2013) could influence both the participant's choice of whether or not to start CPAP treatment and the rCBF pattern observed.

A strength of our study is that by using an 18-month delay between visits, we were able to explore the long-term changes in rCBF associated with CPAP, as compared to previous studies with a treatment duration of 3–8 months (Kim et al., 2017; Shiota et al., 2014). Moreover, by including participants that refused CPAP treatment, we were also able to compare the time course of untreated OSA to an efficient treatment. While shorter randomized and controlled protocols are necessary to assess the effects of CPAP on brain function, longitudinal observational studies over long periods of time offer the possibility to explore changes associated with long-term CPAP use.

5 | CONCLUSION

Our study suggests that using CPAP in OSA cases could have beneficial effects on brain function. Considering that more than 40% of people refuse treatment at diagnosis, and between 29 and 83% of people using CPAP are considered non-adherent (Lee, Leow, Song, Li, & Ong, 2017), our study brings important information regarding the longitudinal changes that could be expected in brain function when CPAP is not used. Given recent evidence that OSA is associated with increased risk of dementia, our findings of rCBF changes in key areas for the development of Alzheimer's disease suggest that CPAP treatment might be an important consideration in OSA individuals at high risk for dementia. This study also highlights the needs to investigate the long-term impact of treated and untreated OSA on risk of neurodegeneration in large cohorts of late middle-aged and older adults.

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CONFLICT OF INTEREST

The authors report no corporate financial or non-financial relationships relevant to the present study that would result in a conflict of interest.

AUTHOR CONTRIBUTIONS

Francis L'Heureux: Contributed to the conception and design of the work, the acquisition, the analysis and the interpretation of the data. **Francis L'Heureux:** Also drafted the work and revised it following the author's comments. **Andrée-Ann Baril:** Contributed to the design of the study, the acquisition, the interpretation and analysis of the data and revised the work critically. **Katia Gagnon:** Contributed to the study design, the acquisition and the interpretation of the data and revised the work critically. **Jean-Paul Soucy**, **Chantal Lafond** and **Jacques Montplaisir:** Contributed to the conception and design of the work, the interpretation of the data, and revised the work critically. **Nadia Gosselin:** Contributed to the conception and design of the work, and to the analysis and interpretation of the data. **Nadia Gosselin:** Helped draft the work and revised it critically. All authors approved the submitted version and revised versions of this article. Authors are also accountable for this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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REFERENCES

Alonso-Fernandez, A., Garcia-Rio, F., Arias, M. A., Hernanz, A., de la Pena, M., Pierola, J., … Agusti, A. (2009). Effects of CPAP on oxidative stress and nitrate efficiency in sleep apnoea: A randomised trial. *Thorax*, *64*, 581–586. https://doi.org/10.1136/thx.2008.100537

American Electroencephalographic Society. (1991). American Electroencephalographic Society guidelines for standard electrode position nomenclature. *Journal of Clinical Neurophysiology*, *8*, 200–202.

Angelo, M. F., Aguirre, A., Avilés Reyes, R. X., Villarreal, A., Lukin, J., Melendez, M., … Ramos, A. J. (2014). The proinflammatory RAGE/NF-kappaB pathway is involved in neuronal damage and reactive gliosis in a model of sleep apnea by intermittent hypoxia. *PLoS One*, *9*, e107901. https://doi.org/10.1371/journal.pone.0107901

Baril, A. A., Gagnon, K., Arbour, C., Soucy, J. P., Montplaisir, J., Gagnon, J. F., & Gosselin, N. (2015). Regional cerebral blood flow during wakeful rest in older subjects with mild to severe obstructive sleep apnea. *Sleep*, *38*, 1439–1449. https://doi.org/10.5665/sleep.4986

Baril, A. A., Gagnon, K., Brayet, P., Montplaisir, J., de Beaumont, L., Carrier, J., … Gosselin, N. (2017). Gray matter hypertrophy and thickening with obstructive sleep apnea in middle-aged and older adults. *American Journal of Respiratory and Critical Care Medicine*, *195*, 1509–1518. https://doi.org/10.1164/rccm.201606-1271OC

Baril, A. A., Gagnon, K., Brayet, P., Montplaisir, J., Carrier, J., Soucy, J. P., … Gosselin, N. (2020). Obstructive sleep apnea during REM sleep and daytime cerebral functioning: A regional cerebral blood flow study using high-resolution SPECT. *Journal of Cerebral Blood Flow and Metabolism*, *40*, 1230–1241. https://doi.org/10.1177/0271678X18814106

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*, 893–897.

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. F. (1996). Comparison of Beck depression inventories -IA and -II in psychiatric outpatients. *Journal of Personality Assessment*, *67*, 588–597. https://doi.org/10.1207/s15327752jpa6703_13

Berry, R. B., Budhiraja, R., Gottlieb, D. J., Gozal, D., Iber, C., Kapur, V. K., … American Academy of Sleep Medicine. (2012). Rules for scoring respiratory events in sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *Journal of Clinical Sleep Medicine*, *8*, 597–619. https://doi.org/10.5664/jcsm.2172

Braley, T. J., Dunietz, G. L., Chervin, R. D., Lisabeth, L. D., Skolarus, L. E., & Burke, J. F. (2018). Recognition and diagnosis of obstructive sleep apnea in older Americans. *Journal of the American Geriatrics Society*, *66*, 1296–1302. https://doi.org/10.1111/jgs.15372

Brett, M., Anton, J.-L., Valabregue, R., & Proline, J.-B. (2002). Region of interest analysis using an SPM toolbox. Paper presented at the 8th International Conference on Functional Mapping of the Human Brain. Sendai, Japan. Available on CD-ROM in NeuroImage.

Brin, Y. S., Reuveni, H., Greenberg, S., Tal, A., & Tarasiuk, A. (2005). Determinants affecting initiation of continuous positive airway pressure treatment. *The Israel Medical Association Journal*, *7*, 13–18.

Büchner, N. J., Quack, I., Woznowski, M., Stähle, C., Wenzel, U., & Rump, L. C. (2011). Microvascular endothelial dysfunction in obstructive sleep apnea is caused by oxidative stress and improved by continuous positive airway pressure therapy. *Respiration*, *82*, 409–417. https://doi.org/10.1159/000323266

Cadar, D., Lassale, C., Davies, H., Llewellyn, D. J., Batty, G. D., & Steptoe, A. (2018). Individual and area-based socioeconomic factors associated with dementia incidence in England: Evidence from a 12-year follow-up in the English Longitudinal Study of Ageing. *JAMA Psychiatry*, *75*, 723–732. https://doi.org/10.1001/jamapsychiatry.2018.1012

Canessa, N., Castronovo, V., Cappa, S. F., Aloia, M. S., Marelli, S., Falini, A., … Ferini-Strambi, L. (2011). Obstructive sleep apnea: Brain structural changes and neurocognitive function before and after treatment. *American Journal of Respiratory and Critical Care Medicine*, *183*, 1419–1426. https://doi.org/10.1164/rccm.201005-0693OC

Caroli, A., Testa, C., Geroldi, C., Nobili, F., Barnden, L. R., Guerra, U. P., … Frisoni, G. B. (2007). Cerebral perfusion correlates of conversion to Alzheimer's disease in amnestic mild cognitive impairment. *Journal of Neurology*, *254*, 1698–1707. https://doi.org/10.1007/s00415-007-0631-7

Castronovo, V., Scifo, P., Castellano, A., Aloia, M. S., Iadanza, A., Marelli, S., … Falini, A. (2014). White matter integrity in obstructive sleep apnea before and after treatment. *Sleep*, *37*, 1465–1475. https://doi.org/10.5665/sleep.3994

Chai-Coetzer, C. L., Luo, Y. M., Antic, N. A., Zhang, X. L., Chen, B. Y., He, Q. Y., … McEvoy, R. D. (2013). Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. *Sleep*, *36*, 1929–1937. https://doi.org/10.5665/sleep.3232

Chao, L. L., Buckley, S. T., Kornak, J., Schuff, N., Madison, C., Yaffe, K., … Weiner, M. W. (2010). ASL perfusion MRI predicts cognitive decline and conversion from MCI to dementia. *Alzheimer Disease and Associated Disorders*, *24*, 19–27. https://doi.org/10.1097/WAD.0b013e3181b4f736

Chen, H. L., Lin, H. C., Lu, C. H., Chen, P. C., Huang, C. C., Chou, K. H., … Lin, W. C. (2017). Systemic inflammation and alterations to cerebral blood flow in obstructive sleep apnea. *Journal of Sleep Research*, *26*, 789–798. https://doi.org/10.1111/jsr.12553

Chen, L. D., Lin, L., Lin, X. J., Ou, Y. W., Wu, Z., Ye, Y. M., … Cai, Z. M. (2017). Effect of continuous positive airway pressure on carotid intima-media thickness in patients with obstructive sleep apnea: A meta-analysis. *PLoS One*, *12*, e0184293. https://doi.org/10.1371/journal.pone.0184293

Cheng, T. O. (2003). Could elevated C-reactive protein in patients with obstructive sleep apnea be due to obesity per se? *Circulation*, *107*, e9; author reply e9. https://doi.org/10.1161/01.cir.0000046771.12875.6c

Christou, K., Kostikas, K., Pastaka, C., Tanou, K., Antoniadou, I., & Gourgoulianis, K. I. (2009). Nasal continuous positive airway pressure treatment reduces systemic oxidative stress in patients with severe obstructive sleep apnea syndrome. *Sleep Medicine*, *10*, 87–94. https://doi.org/10.1016/j.sleep.2007.10.011

Coloma Navarro, R., Jiménez Caballero, P. E., Vega, G., Ayo-Martín, O., & Segura Martín, T. (2016). Cerebral hemodynamics is altered in patients with sleep apnea/hypopnea syndrome. *Springerplus*, *5*, 51. https://doi.org/10.1186/s40064-016-1691-x

de Lima, A. M., Franco, C. M., de Castro, C. M., Bezerra, A. A., Ataíde, Jr, L., & Halpern, A. (2010). Effects of nasal continuous positive airway pressure treatment on oxidative stress and adiponectin levels in obese patients with obstructive sleep apnea. *Respiration*, *79*, 370–376. https://doi.org/10.1159/000227800

Douglas, R. M., Ryu, J., Kanaan, A., del Carmen Rivero, M., Dugan, L. L., Haddad, G. G., & Ali, S. S. (2010). Neuronal death during combined intermittent hypoxia/hypercapnia is due to mitochondrial dysfunction. *American Journal of Physiology. Cell Physiology*, *298*, C1594–C1602. https://doi.org/10.1152/ajpcell.00298.2009

Eskildsen, S. F., Coupé, P., Fonov, V. S., Pruessner, J. C., Collins, D. L., & Alzheimer's Disease Neuroimaging Initiative. (2015). Structural imaging

biomarkers of Alzheimer's disease: Predicting disease progression. *Neurobiology of Aging*, *36*(Suppl. 1), S23–S31. https://doi.org/10.1016/j.neurobiolaging.2014.04.034

Feng, J., Zhang, D., & Chen, B. (2012). Endothelial mechanisms of endothelial dysfunction in patients with obstructive sleep apnea. *Sleep & Breathing*, *16*, 283–294. https://doi.org/10.1007/s11325-011-0519-8

Ferini-Strambi, L., Marelli, S., Galbiati, A., & Castronovo, C. (2013). Effects of continuous positive airway pressure on cognitition and neuroimaging data in sleep apnea. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *89*, 203–212. https://doi.org/10.1016/j.ijpsycho.2013.03.022

Franklin, K. A. (2002). Cerebral haemodynamics in obstructive sleep apnoea and Cheyne-Stokes respiration. *Sleep Medicine Reviews*, *6*, 429–441.

Gagnon, K., Baril, A. A., Gagnon, J. F., Fortin, M., Décary, A., Lafond, C., … Gosselin, N. (2014). Cognitive impairment in obstructive sleep apnea. *Pathologie-Biologie*, *62*, 233–240. https://doi.org/10.1016/j.patbio.2014.05.015

Gagnon, K., Baril, A. A., Montplaisir, J., Carrier, J., Chami, S., Gauthier, S., … Gosselin, N. (2018). Detection of mild cognitive impairment in middle-aged and older adults with obstructive sleep apnoea. *The European Respiratory Journal*, *52*, 1801137. https://doi.org/10.1183/13993003.01137-2018

Gagnon, K., Baril, A. A., Montplaisir, J., Carrier, J., de Beaumont, L., D'Aragon, C., … Gosselin, N. (2019). Disconnection between self-reported and objective cognitive impairment in obstructive sleep apnea. *Journal of Clinical Sleep Medicine*, *15*, 409–415. https://doi.org/10.5664/jcsm.7664

Gaspar, L. S., Álvaro, A. R., Moita, J., & Cavadas, C. (2017). Obstructive sleep apnea and hallmarks of aging. *Trends in Molecular Medicine*, *23*, 675–692. https://doi.org/10.1016/j.molmed.2017.06.006

Giles, T. L., Lasserson, T. J., Smith, B. J., White, J., Wright, J., & Cates, C. J. (2006). Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database of Systematic Reviews*, *1*, CD001106. https://doi.org/10.1002/14651858.CD001106.pub2

Gosselin, N., Baril, A. A., Osorio, R. S., Kaminska, M., & Carrier, J. (2019). Obstructive sleep apnea and the risk of cognitive decline in older adults. *American Journal of Respiratory and Critical Care Medicine*, *199*, 142–148. https://doi.org/10.1164/rccm.201801-0204PP

Gregori-Pla, C., Cotta, G., Blanco, I., Zirak, P., Giovannella, M., Mola, A., … Mayos, M. (2018). Cerebral vasoreactivity in response to a head-of-bed position change is altered in patients with moderate and severe obstructive sleep apnea. *PLoS One*, *13*, e0194204. https://doi.org/10.1371/journal.pone.0194204

Hackman, D. A., Kuan, D. C., Manuck, S. B., & Gianaros, P. J. (2018). Socioeconomic position and age-related disparities in regional cerebral blood flow within the prefrontal cortex. *Psychosomatic Medicine*, *80*, 336–344. https://doi.org/10.1097/PSY.0000000000000566

Hasselgren, C., Dellve, L., Ekbrand, H., Zettergren, A., Zetterberg, H., Blennow, K., … Halleröd, B. (2018). Socioeconomic status, gender and dementia: The influence of work environment exposures and their interactions with APOE varepsilon4. *SSM - Population Health*, *5*, 171–179. https://doi.org/10.1016/j.ssmph.2018.06.009

Iber, C., Ancoli-Israel, S., Chesson, A., & Quan, S. F. (2007). *The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications*. Westchester, IL: American Academy of Sleep Medicine.

Innes, C. R., Kelly, P. T., Hlavac, M., Melzer, T. R., & Jones, R. D. (2015). Decreased regional cerebral perfusion in moderate-severe obstructive sleep apnoea during wakefulness. *Sleep*, *38*, 699–706. https://doi.org/10.5665/sleep.4658

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep*, *14*, 540–545.

Jonas, D. E., Amick, H. R., Feltner, C., Weber, R. P., Arvanitis, M., Stine, A., … Harris, R. P. (2017). Screening for obstructive sleep apnea in adults: Evidence report and systematic review for the US preventive services task force. *JAMA*, *317*, 415–433. https://doi.org/10.1001/jama.2016.19635

Joo, E. Y., Tae, W. S., Han, S. J., Cho, J. W., & Hong, S. B. (2007). Reduced cerebral blood flow during wakefulness in obstructive sleep apnea-hypopnea syndrome. *Sleep*, *30*, 1515–1520.

Ju, G., Yoon, I. Y., Lee, S. D., Kim, Y. K., Yoon, E., & Kim, J. W. (2012). Modest changes in cerebral glucose metabolism in patients with sleep apnea syndrome after continuous positive airway pressure treatment. *Respiration*, *84*, 212–218. https://doi.org/10.1159/000338117

Kim, H., Joo, E., Suh, S., Kim, J. H., Kim, S. T., & Hong, S. B. (2016). Effects of long-term treatment on brain volume in patients with obstructive sleep apnea syndrome. *Human Brain Mapping*, *37*, 395–409. https://doi.org/10.1002/hbm.23038

Kim, J. S., Seo, J. H., Kang, M. R., Seong, M. J., Lee, W. G., Joo, E. Y., & Hong, S. B. (2017). Effect of continuous positive airway pressure on regional cerebral blood flow in patients with severe obstructive sleep apnea syndrome. *Sleep Medicine*, *32*, 122–128. https://doi.org/10.1016/j.sleep.2016.03.010

Lecrux, C., & Hamel, E. (2011). The neurovascular unit in brain function and disease. *Acta Physiologica (Oxford, England)*, *203*, 47–59. https://doi.org/10.1111/j.1748-1716.2011.02256.x

Lee, C. H. K., Leow, L. C., Song, P. R., Li, H. H., & Ong, T. H. (2017). Acceptance and adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea (OSA) in a southeast Asian privately funded healthcare system. *Sleep Science*, *10*, 57–63. https://doi.org/10.5935/1984-0063.20170010

Mak, E., Gabel, S., Mirette, H., Su, L., Williams, G. B., Waldman, A., … O'Brien, J. (2017). Structural neuroimaging in preclinical dementia: From microstructural deficits and grey matter atrophy to macroscale connectomic changes. *Ageing Research Reviews*, *35*, 250–264. https://doi.org/10.1016/j.arr.2016.10.001

Malhotra, A., & White, D. P. (2002). Obstructive sleep apnoea. *Lancet*, *360*, 237–245. https://doi.org/10.1016/S0140-6736(02)09464-3

Matsuda, H., Tsuji, S., Shuke, N., Sumiya, H., Tonami, N., & Hisada, K. (1993). Noninvasive measurements of regional cerebral blood flow using technetium-99m hexamethylpropylene amine oxime. *European Journal of Nuclear Medicine*, *20*, 391–401. https://doi.org/10.1007/bf00208997

May, A. M., & Mehra, R. (2014). Obstructive sleep apnea: Role of intermittent hypoxia and inflammation. *Seminars in Respiratory and Critical Care Medicine*, *35*, 531–544. https://doi.org/10.1055/s-0034-1390023

McNicholas, W. T. (2009). Obstructive sleep apnea and inflammation. *Progress in Cardiovascular Diseases*, *51*, 392–399. https://doi.org/10.1016/j.pcad.2008.10.005

Mehrtash, M., Bakker, J. P., & Ayas, N. (2019). Predictors of continuous positive airway pressure adherence in patients with obstructive sleep apnea. *Lung*, *197*, 115–121. https://doi.org/10.1007/s00408-018-00193-1

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., … Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*, 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nie, S., Peng, D. C., Gong, H. H., Li, H. J., Chen, L. T., & Ye, C. L. (2017). Resting cerebral blood flow alteration in severe obstructive sleep apnoea: An arterial spin labelling perfusion fMRI study. *Sleep & Breathing*, *21*, 487–495. https://doi.org/10.1007/s11325-017-1474-9

Osorio, R. S., Gumb, T., Pirraglia, E., Varga, A. W., Lu, S. E., Lim, J., … Beckett, L. (2015). Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology*, *84*, 1964–1971. https://doi.org/10.1212/WNL.0000000000001566

Park, K. W., Yoon, H. J., Kang, D. Y., Kim, B. C., Kim, S. Y., & Kim, J. W. (2012). Regional cerebral blood flow differences in patients with mild cognitive impairment between those who did and did not develop

Alzheimer's disease. *Psychiatry Research*, *203*, 201–206. https://doi.org/10.1016/j.pscychresns.2011.12.007

Pizza, F., Biallas, M., Wolf, M., Werth, E., & Bassetti, C. L. (2010). Nocturnal cerebral hemodynamics in snorers and in patients with obstructive sleep apnea: A near-infrared spectroscopy study. *Sleep*, *33*, 205–210.

Prilipko, O., Huynh, N., Thomason, M. E., Kushida, C. A., & Guilleminault, C. (2014). An fMRI study of cerebrovascular reactivity and perfusion in obstructive sleep apnea patients before and after CPAP treatment. *Sleep Medicine*, *15*, 892–898. https://doi.org/10.1016/j.sleep.2014.04.004

Schwarz, E. I., Puhan, M. A., Schlatzer, C., Stradling, J. R., & Kohler, M. (2015). Effect of CPAP therapy on endothelial function in obstructive sleep apnoea: A systematic review and meta-analysis. *Respirology*, *20*, 889–895. https://doi.org/10.1111/resp.12573

Senaratna, C. V., Perret, J. L., Lodge, C. J., Lowe, A. J., Campbell, B. E., Matheson, M. C., … Dharmage, S. C. (2017). Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Medicine Reviews*, *34*, 70–81. https://doi.org/10.1016/j.smrv.2016.07.002

Sforza, E., Pichot, V., Martin, M. S., Barthélémy, J. C., & Roche, F. (2015). Prevalence and determinants of subjective sleepiness in healthy elderly with unrecognized obstructive sleep apnea. *Sleep Medicine*, *16*, 981–986. https://doi.org/10.1016/j.sleep.2015.03.010

Shahrabani, S., Tzischinsky, O., Givati, G., & Dagan, Y. (2014). Factors affecting the intention and decision to be treated for obstructive sleep apnea disorder. *Sleep & Breathing*, *18*, 857–868. https://doi.org/10.1007/s11325-014-0957-1

Shi, Y., Chen, L., Chen, T., Li, L., Dai, J., Lui, S., … Gong, Q. (2017). A meta-analysis of voxel-based brain morphometry studies in obstructive sleep apnea. *Scientific Reports*, *7*, 10095. https://doi.org/10.1038/s41598-017-09319-6

Shiota, S., Inoue, Y., Takekawa, H., Kotajima, M., Nakajyo, M., Usui, C., … Takahashi, K. (2014). Effect of continuous positive airway pressure on regional cerebral blood flow during wakefulness in obstructive sleep apnea. *Sleep & Breathing*, *18*, 289–295. https://doi.org/10.1007/s11325-013-0881-9

Sierra-Marcos, A. (2017). Regional cerebral blood flow in mild cognitive impairment and Alzheimer's disease measured with arterial spin labeling magnetic resonance imaging. *International Journal of Alzheimer's Disease*, *2017*, 5479597. https://doi.org/10.1155/2017/5479597

Simon-Tuval, T., Reuveni, H., Greenberg-Dotan, S., Oksenberg, A., Tal, A., & Tarasiuk, A. (2009). Low socioeconomic status is a risk factor for CPAP acceptance among adult OSAS patients requiring treatment. *Sleep*, *32*, 545–552. https://doi.org/10.1093/sleep/32.4.545

Snyder, B., Shell, B., Cunningham, J. T., & Cunningham, R. L. (2017). Chronic intermittent hypoxia induces oxidative stress and inflammation in brain regions associated with early-stage neurodegeneration. *Physiological Reports*, *5*, e13258. https://doi.org/10.14814/phy2.13258

Troussière, A. C., Monaca Charley, C., Salleron, J., Richard, F., Delbeuck, X., Derambure, P., … Bombois, S. (2014). Treatment of sleep apnoea syndrome decreases cognitive decline in patients with Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*, 1405–1408. https://doi.org/10.1136/jnnp-2013-307544

Tzischinsky, O., Shahrabani, S., & Peled, R. (2011). Factors affecting the decision to be treated with continuous positive airway pressure for obstructive sleep apnea syndrome. *The Israel Medical Association Journal*, *13*, 413–419.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., … Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, *15*, 273–289. https://doi.org/10.1006/nimg.2001.0978

Unnikrishnan, D., Jun, J., & Polotsky, V. (2015). Inflammation in sleep apnea: An update. *Reviews in Endocrine & Metabolic Disorders*, *16*, 25–34. https://doi.org/10.1007/s11154-014-9304-x

Urbano, F., Roux, F., Schindler, J., & Mohsenin, V. (2008). Impaired cerebral autoregulation in obstructive sleep apnea. *Journal of Applied Physiology*, *105*, 1852–1857. https://doi.org/10.1152/japplphysiol.90900.2008

Villeneuve, S., Belleville, S., Massoud, F., Bocti, C., & Gauthier, S. (2009). Impact of vascular risk factors and diseases on cognition in persons with mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, *27*, 375–381. https://doi.org/10.1159/000209965

Weaver, T. E., & Grunstein, R. R. (2008). Adherence to continuous positive airway pressure therapy: The challenge to effective treatment. *Proceedings of the American Thoracic Society*, *5*, 173–178. https://doi.org/10.1513/pats.200708-119MG

Weng, H. H., Tsai, Y. H., Chen, C. F., Lin, Y. C., Yang, C. T., Tsai, Y. H., & Yang, C. Y. (2014). Mapping gray matter reductions in obstructive sleep apnea: An activation likelihood estimation meta-analysis. *Sleep*, *37*, 167–175. https://doi.org/10.5665/sleep.3330

Wierenga, C. E., Hays, C. C., & Zlatar, Z. Z. (2014). Cerebral blood flow measured by arterial spin labeling MRI as a preclinical marker of Alzheimer's disease. *Journal of Alzheimer's Disease*, *42*(Suppl. 4), S411–S419. https://doi.org/10.3233/JAD-141467

Xu, W., Chi, L., Row, B. W., Xu, R., Ke, Y., Xu, B., … Liu, R. (2004). Increased oxidative stress is associated with chronic intermittent hypoxia-mediated brain cortical neuronal cell apoptosis in a mouse model of sleep apnea. *Neuroscience*, *126*, 313–323. https://doi.org/10.1016/j.neuroscience.2004.03.055

Yadav, S. K., Kumar, R., Macey, P. M., Richardson, H. L., Wang, D. J. J., Woo, M. A., & Harper, R. M. (2013). Regional cerebral blood flow alterations in obstructive sleep apnea. *Neuroscience Letters*, *555*, 159–164. https://doi.org/10.1016/j.neulet.2013.09.033

Yaffe, K., Falvey, C., Harris, T. B., Newman, A., Satterfield, S., Koster, A., … Health ABC Study. (2013). Effect of socioeconomic disparities on incidence of dementia among biracial older adults: Prospective study. *BMJ*, *347*, f7051. https://doi.org/10.1136/bmj.f7051

Yaouhi, K., Bertran, F., Clochon, P., Mézenge, F., Denise, P., Foret, J., … Desgranges, B. (2009). A combined neuropsychological and brain imaging study of obstructive sleep apnea. *Journal of Sleep Research*, *18*, 36–48. https://doi.org/10.1111/j.1365-2869.2008.00705.x

Zhang, N., Gordon, M. L., & Goldberg, T. E. (2017). Cerebral blood flow measured by arterial spin labeling MRI at resting state in normal aging and Alzheimer's disease. *Neuroscience and Biobehavioral Reviews*, *72*, 168–175. https://doi.org/10.1016/j.neubiorev.2016.11.023

Zhou, L., Chen, P., Peng, Y., & Ouyang, R. (2016). Role of oxidative stress in the neurocognitive dysfunction of obstructive sleep apnea syndrome. *Oxidative Medicine and Cellular Longevity*, *2016*, 1–15. https://doi.org/10.1155/2016/9626831.

Zhu, Y., Fenik, P., Zhan, G., Mazza, E., Kelz, M., Aston-Jones, G., & Veasey, S. C. (2007). Selective loss of catecholaminergic wake active neurons in a murine sleep apnea model. *The Journal of Neuroscience*, *27*, 10060–10071. https://doi.org/10.1523/JNEUROSCI.0857-07.2007

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