



Medial temporal lobe and obstructive sleep apnea: Effect of sex, age, cognitive status and free-water

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ABSTRACT

Medial temporal structures, namely the hippocampus, the entorhinal cortex and the parahippocampal gyrus, are particularly vulnerable to Alzheimer's disease and hypoxemia. Here, we tested the associations between obstructive sleep apnea (OSA) severity and medial temporal lobe volumes in 114 participants aged 55–86 years (35 % women). We also investigated the impact of sex, age, cognitive status, and free-water fraction correction on these associations. Increased OSA severity was associated with larger hippocampal and entorhinal cortex volumes in women, but not in men. Greater OSA severity also correlated with increased hippocampal volumes in participants with amnesic mild cognitive impairment, but not in cognitively unimpaired participants, regardless of sex. Using free-water corrected volumes eliminated all significant associations with OSA severity. Therefore, the increase in medial temporal subregion volumes may possibly be due to edema. Whether these structural manifestations further progress to neuronal death in non-treated OSA patients should be investigated.

1. Introduction

Obstructive sleep apnea (OSA) is possibly the most harmful sleep

disorder for brain health, as it fragments sleep chronically and provokes intermittent episodes of hypoxemia that lead to oxidative stress, neuroinflammation and neuronal death (Lim and Pack, 2014). OSA is

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associated with increased amyloid and tau burden, two hallmarks of Alzheimer's disease (AD) (Bubu et al., 2019). In addition, most epidemiological studies have shown an increased risk of cognitive decline and dementia in apneic adults (Leng et al., 2017).

Neuroimaging studies have investigated whether neurodegenerative changes occur in middle-aged and older adults with OSA. The entorhinal cortex, the hippocampi and the parahippocampal gyri are particularly important to investigate, as they are early affected in AD (Braak and Braak, 1991) and vulnerable to hypoxemia (Bartsch et al., 2015). Previous studies found a loss of grey matter volume in these regions (Marchi et al., 2020; Owen et al., 2019; Shi et al., 2017), others did not report changes (André et al., 2020; Baril et al., 2017), and a few observed increased volumes (Cross et al., 2018; Macey et al., 2018; Rosenzweig et al., 2013). The latter phenomenon is intriguing and might be due to intra- or extracellular fluid accumulation (cerebral edema) affecting grey matter volume estimates (André et al., 2020; Baril et al., 2017; Baril et al., 2020; Rosenzweig and Morrell, 2017). In accordance with this hypothesis, experimental models showed reactive gliosis and higher brain water content in mice exposed to intermittent hypoxia compared to non-exposed mice (Baronio et al., 2013; Wang et al., 2018). In humans, an abnormally low whole brain free-water (FW) fraction (Baril et al., 2020) has been observed in adults with OSA compared to non-apneic participants, suggesting intracellular edema. FW fraction is a neuroimaging algorithm applied to diffusion magnetic resonance imaging (MRI) that measures water diffusing freely in the extracellular space, providing an estimate of edema and neuroinflammation. Abnormally low FW fraction suggests intracellular edema or reactive gliosis (Anderova et al., 2011; Montal et al., 2018), while a high FW fraction suggests extracellular edema, and is observed concomitantly with age-related atrophy (Edde et al., 2020), mild cognitive impairment (MCI) and AD (Dumont et al., 2019; Montal et al., 2018).

Individual characteristics may also impact how OSA severity increases risks of neurodegeneration. These characteristics include being a woman, younger age (middle-aged in comparison with the elderly) and ongoing neurodegenerative processes (Bubu et al., 2020; Legault et al., 2021). Most OSA and neuroimaging studies have controlled for these variables but have not tested whether they interact with OSA severity to predict changes in brain structure. These factors have the potential to explain part of the heterogeneity observed in previous studies and could orient clinical strategies regarding OSA screening and treatment.

The present study aimed at 1) characterizing the links between OSA severity and grey matter volume in the hippocampi, the entorhinal cortex and the parahippocampal gyri, 2) testing how sex, age, and cognitive status affect these associations and 3) verify whether associations between OSA and medial temporal grey matter volumes could be partly explained by changes in water content by applying a FW fraction correction to volumes. We hypothesized that OSA severity, particularly hypoxemia, would be associated with medial temporal lobe hypertrophy and that these associations would be stronger in women, younger participants and those with amnesic MCI (aMCI). We also expected that part of the hypertrophy would be explained by cerebral edema.

2. Methods

We included participants aged 55 to 86 years old, recruited between August 2012 and March 2020. Most participants included in this study were from a project on OSA and MCI ($n = 91$) and were also included in past studies from our group (Baril et al., 2015; Baril et al., 2018; Baril et al., 2017; Baril et al., 2020; Gosselin et al., 2016; L'Heureux et al., 2021). The remaining participants included in the sample were part of a recent multicenter study on sleep and MCI ($n = 45$). These participants were recruited in Montreal ($n = 25$), or Sherbrooke ($n = 20$). Exclusion criteria were inability to communicate in French or English, diagnosed neurological or psychiatric diseases, sleep disorders other than OSA, treated OSA, cerebrovascular or pulmonary diseases, body mass index $> 40 \text{ kg/m}^2$, < 7 years of education, uncontrolled diabetes or

hypertension, drugs or alcohol addiction or abuse, contraindications for MRI, dementia suspicion and use of psychoactive medication. We also excluded non-amnesic MCI participants from our sample, as medial temporal lobe changes are more central to the pathophysiology of participants with aMCI. Data from four protocols were used, all approved by institutional ethics committees (#2012-697, #12-13-008, #2010-468 and #MP-32-2018-1537), and participants gave their written consent.

All potential participants were scheduled for an initial visit, which allowed obtaining information regarding their eligibility for the study. Eligible participants proceeded to a second visit, which included an overnight polysomnography, a neuropsychological assessment, and questionnaires. Participants were then asked to return for a 3T MRI session (range: 3 days to 13 months; mean delay: $111 \text{ days} \pm 72 \text{ days}$).

2.1. Polysomnography

The polysomnography included a 12 to 19-channel electroencephalography montage based on the international 10-20 system and used mastoid references. Participants were recorded using a Grass system and digitized using Harmonie software ($n = 91$ participants; bandpass 0.3-100 Hz; sampling rate 256 Hz), or with Natus system (Brain Monitor, Trex or Embla NDx) ($n = 45$ participants; bandpass 0.3-300 Hz; sampling rate 512 Hz). The montage included an electrooculogram, an electrocardiogram, as well as chin and anterior tibialis electromyogram. An oronasal canula, an oronasal thermistor and a thoraco-abdominal strain gauge were used in addition to transcutaneous finger pulse oximeter. Apneas were defined as a reduction of airflow $\geq 90\%$ for at least 10 s, and hypopneas as a diminution of airflow $\geq 30\%$ for at least 10 s, ending with an oxygen desaturation $\geq 3\%$ or with an arousal (Berry et al., 2012). Sleep stage scoring was done according to the American Academy of Sleep Medicine criteria by an experienced sleep technologist (Berry et al., 2012).

2.2. Principal components analysis of OSA severity

Based on the methodology of past OSA neuroimaging studies (Cross et al., 2018; Baril et al., 2017), we used a principal components analysis (PCA) to extract independent variables of OSA severity. This allowed to include multiple markers of OSA severity into our analyses, while limiting multicollinearity and the number of statistical tests done. Briefly, we used a criterion of eigenvalues higher than 1 and a varimax rotation, and obtained two components (sleep fragmentation and hypoxemia; see Table 1).

2.3. MRI acquisition

All neuroimaging data were acquired between December 2012 and December 2019. The sample included 136 participants which underwent neuroimaging acquisition at the Neuroimaging Functional Unit of

Table 1
Results from the principal component analysis of respiratory and sleep variables.

	Component	
	Sleep fragmentation	Hypoxemia
Number of arousals associated with a respiratory event	0.92	0.16
Number of stage transitions from NREM1 and wakefulness	0.81	-0.05
Apnea-hypopnea index, events/h	0.73	0.41
Micro-arousal index, events/h	0.64	0.52
Inverted minimum oxygen saturation, %	0.22	0.81
Inverted mean oxygen saturation, %	-0.02	0.82
3 % oxygen desaturation index, events/h	0.57	0.66
Accounted variance, %	40.5	31.9

NREM1: stage 1 of non rapid-eye movement sleep.

the Montreal Geriatric University Institute, with either the Siemen Magneton Trio Tim ($n = 91$) or the upgraded Siemen Prisma Fit scanner ($n = 25$), or at University Institute of Geriatrics of Sherbrooke with a 3T Ingenia Philips Scanner ($n = 20$). 91 participants completed the scanning protocol between December 2012 and July 2016 with the Magneton 3T Trio Tim Siemens Scanner with a 32-channel head coil. The parameters used were those of the Massachusetts General Hospital (Boston, Massachusetts, USA). A three-dimensional (3D-T1) T1-weighted Turbo Flash multi-echo Magnetization-prepared rapid gradient-echo (MPRAGE) sequence was acquired first using the following parameters: repetition time = 2,530 ms/root mean square of four echo times = 1.64 ms, 3.50 ms, 5.36 ms, 7.22 ms; inversion time: 1200 ms; matrix size = 256×256 ; field of view = 256×256 mm; voxel size = 1.0 mm isotropic; flip angle = 7° ; and 176 sagittal orientations. In addition, a pulsed spin echo diffusion-weighted imaging sequence was acquired, as well as a reference image without diffusion ($b = 0$ s/mm²). The following parameters were used: 64 uniformly distributed directions; b value of 1000 s/mm²; repetition time = 9,100 ms; echo time = 89 ms; 72 slices; matrix size = 120×120 mm; field of view = 240×240 mm; voxel size = 2.0 mm isotropic; flip angle = 90° .

The other 45 participants were tested between August 2019 and December 2019 in Montreal and Sherbrooke research sites. For this study, The Canadian Dementia Imaging Protocol (<https://www.cdip-pci.d.ca>) developed by the Canadian Consortium on Neurodegeneration in Aging was used to harmonize acquisition parameters between sites and minimize the impact of using different scanners. Overall, 25 participants were tested with the upgraded scanner, the 3T Prisma Tim Siemen Scanner. First, a T1-weighted MPRAGE sequence was acquired following these parameters: repetition time = 2300 ms; echo time = 2.98 ms; inversion time: 900 ms; matrix size = 256×256 ; field of view = 256×256 mm; voxel size = 1.0 mm isotropic; flip angle = 9° ; and 192 sagittal orientations. The acquisition of a diffusion sequence was done with the following parameters: 32 uniformly distributed directions; b value 1 of 0 s/mm²; b value 2 of 1000 s/mm²; repetition time = 6900 ms; echo time = 64 ms; 70 slices; field of view = 256×256 mm; voxel size = 2.0 mm isotropic. The remaining 20 participants were tested using a 3T Ingenia Philips Scanner. The MPRAGE sequence was acquired with these parameters: repetition time = 7.1 ms; echo time = 3.2 ms; inversion time: 944.55 ms; matrix size = 256×256 ; field of view = 256×256 mm; voxel size = 1.0 mm isotropic; flip angle = 9° ; and 192 sagittal orientations. The acquisition of a diffusion sequence was done with the following parameters: 32 uniformly distributed directions; b value 1 of 0 s/mm²; b value 2 of 1000 s/mm²; repetition time = 10,185 ms; echo time = 109 ms; 70 slices; field of view = 256×256 mm; voxel size = 2.0 mm isotropic.

2.4. MRI analyses

Volumes of regions of interest (ROIs) were obtained using FreeSurfer 7.1 (<https://surfer.nmr.mgh.harvard.edu/>). T1-weighted imaging scans were processed using 'Recon-all' automatic segmentation, which allowed computing volumes of the entorhinal cortex and the parahippocampal gyri. The steps included motion correction, registration, intensity normalisation, removal of non-brain tissues, smoothing and inflating, tracing of white/grey matter boundaries and a cortical parcellation and labelling based on a probabilistic atlas. The 'Segmentation of hippocampal subfields and nuclei of the amygdala module' was used to obtain whole hippocampal volume, as it is expected to provide a more accurate volume estimation than the standard FreeSurfer pipeline by using a statistical atlas constructed with both ex vivo and in vivo MRI data (Iglesias et al., 2015). These volumes were then normalized with the estimated total intracranial volume (TIV) obtained with Computational Anatomy Toolbox version 12.7 (CAT12, Jena University Hospital, Germany; release 1742; <https://www.neuro.uni-jena.de/cat/index.html>), as this estimation is considered superior to the one provided by FreeSurfer in the context of neurodegeneration and when multiple

scanners are used (Malone et al., 2015; Tavares et al., 2019). To obtain TIV values, standard segmentation preprocessing was done using CAT12 for SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; release 6906) (<https://www.fil.ion.ucl.ac.uk/spm/>), under MATLAB R2018b ([MathWorks, Natick, MA, USA]; <https://www.mathworks.com/>).

Thereafter, a FW fraction ranging from 0 to 1 per voxel was extracted. To obtain these values, a T1 resampled (from FreeSurfer output), a diffusion sequence, as well as bval and bvec files were all imported into TractoFlow Atlas Based Segmentation pipeline (TractoFlow-ABS; (Theaud et al., 2020a,b), running under Compute Canada HPC Beluga node (beluga.computecanada.ca) for initial preprocessing. Adapted parameters were selected for diffusion image preprocessing using TractoFlow-ABS (DTI shells: 0 1000; fODF shells: 0 1000; FRF value: 10, 3, 3; SH order: 6; Algo: prob; Seeding type: npv; Number of seeds: 10; see <https://github.com/scilus/tractoflow-ABS> for more details). These adapted parameters allowed to obtain valid estimations for both the 32 and 64 direction sequences. From these outputs, brain-mask and diffusion-weighted images were analysed with FreeWater Flow (https://github.com/scilus/freewater_flow) using python 3.8 and AMICO wheels module available on HPC. Parameters to run these analyses were as follows: axial diffusivity in the corpus callosum = 0.001; mean diffusivity in ventricles = 0.0025; radial diffusivity minimum = 0.0001; radial diffusivity maximum = 0.0065; first regularization parameter = 0; second regularization parameter = 0.25. The output from this step was a whole brain free-water nifty card for each subject. Next, either the head-body-tail (HBT) or the aseg + aparc atlas from FreeSurfer output for each participant were used to extract FW mean values for each ROI using customized codes from the Sherbrooke Connectivity Lab (<https://scilpy.readthedocs.io/en/latest/scripts>). First, for the hippocampi, the HBT templates from the right and left hemisphere of each subject were registered on their respective T1-warped computed from TractoFlow using the antsApplyTransforms python code with the NearestNeighbor function. Thereafter, these warped images were transformed to the same data type (e.g., uint8), and FW fractions for each ROI were identified (e.g., `scil_split_volume_by_ids.py`) and then extracted (e.g., `scil_compute_metrics_stats_in_ROI.py`). To extract FW values for the remaining regions, the same steps were performed using the aseg + aparc atlas from the right and left hemispheres of the entorhinal cortex (e.g., 1006 ctx-lh-entorhinal; 2006 ctx-rh-entorhinal) and parahippocampal gyrus (e.g., 1016 ctx-lh-parahippocampal; 2016 ctx-rh-parahippocampal). TIV-corrected bilateral volumes were normalized for FW fractions and are referred to as FW-corrected volumes.

2.5. Neuropsychological evaluation and questionnaires

An extensive neuropsychological battery evaluating multiple cognitive domains (i.e., attention, executive functioning, memory, language and visuospatial skills) was implemented. Additionally, global cognition, depressive symptoms, anxiety symptoms, sleep quality, and daily activities were assessed in all participants included in this study. However, specific neuropsychological tests and questionnaires used varied between cohorts (see supplementary table 1). aMCI diagnoses were established when participants had 1) at least two z-scores below -1.5 standard deviations compared to normative data in the memory cognitive domain, or 2) a Montreal Cognitive Assessment score < 26 and at least two z-scores below -1.5 standard deviations, including at least one from the memory cognitive domain. To evaluate the presence or absence of aMCI in participants, we used as many scores per domain as available in the cohorts. We also obtained a self-reported measure of autonomy using the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) for 78 % of our participants (Galasko et al., 1997). Based on previously established cut-offs on the 18-item version (Pedrosa et al., 2010), we considered that participants with a score below 34 might present with dementia. No participant who completed this inventory met this cut-off.

Because questionnaires assessing depressive and anxiety symptoms varied between cohorts, we dichotomized these variables as ‘present’ or ‘absent’. The presence of significant depressive symptoms was concluded using cut-offs of ≥ 14 on the Beck Depression Inventory II, which usually represents mild symptoms of depression (Beck et al., 1996); or ≥ 5 on the Geriatric Depression Scale, which is considered suggestive of depression (Yesavage et al., 1982). For the presence of anxiety symptoms, we used cut-offs of ≥ 8 on the Beck Anxiety Inventory, which is used to assess the presence of mild symptoms of anxiety (Beck et al., 1988); or ≥ 8 on the Geriatric Anxiety Scale, which is suggestive of anxiety symptoms (Johnco et al., 2015; Pachana and Byrne, 2012). Additionally, the Epworth Sleepiness Scale was administered to all participants to assess daytime sleepiness.

2.6. Statistical analysis

Normality was assessed using the Kolmogorov-Smirnov test and variables were log-transformed when necessary. As we did not have a lateralization hypothesis, we combined volumes from both hemispheres analyses to obtain a total bilateral volume for each ROI. To obtain FW-corrected volumes, ROI volumes were extracted from FreeSurfer and divided by FW-fraction and TIV. One-way ANOVAs or chi-square tests were performed to assess differences between controls (AHI < 5), participants with mild OSA (AHI ≥ 5 to < 15) and with moderate-to-severe OSA (≥ 15) on demographic, sleep and clinical variables. Multiple linear regressions were performed with measures of OSA severity (namely hypoxemia and sleep fragmentation components) as independent variables and bilateral volumes of the hippocampi, the entorhinal cortex and parahippocampal gyri as dependent variables, adjusted for age, sex and education. Multiple linear regressions were also performed with FW-corrected ROI volumes. These analyses were performed in the whole sample and according to sex (adjusted for age and education), age (<68 versus ≥ 68 years old; adjusted for sex and education) and cognitive status (aMCI versus cognitively unimpaired; adjusted for sex, age and education). The 68 years old cut-off was chosen as it represented the median in the sample. Analyses were also performed for hippocampal subfields in the whole sample and in each subgroup. *P* was set at < 0.05 with a Family-Wise Error (FWE) correction. In addition, group differences were assessed for FW fraction for subgroups of participants as defined previously using ANCOVAs, with age, sex and education as covariates (when applicable). All statistical analyses were performed using SPSS 27 (IBM SPSS Statistics, New York, USA).

3. Results

3.1. Study participants

The final sample included 114 participants (68.0 ± 7.9 years old; 40 women) (see Fig. 1; Table 2). Groups did not differ in terms of age, sex, education, sleepiness, depressive and anxiety symptoms, and diagnosis of aMCI. However, moderate-to-severe OSA participants had higher BMI than control and mild OSA participants. We characterized sex, age, and cognitive status subgroups in the supplementary material (see supplementary tables 2-4).

3.2. OSA severity and medial temporal lobe volumes in the whole sample

Positive associations were found between hypoxemia and entorhinal cortex volume (see Table 3A; β (95% CI) = 0.09 (0.02–0.16), *P* = 0.045). No association was found between sleep fragmentation and medial temporal grey matter volumes.

3.3. Analyses by age groups

In older individuals (≥ 68 years old), more severe hypoxemia was associated with higher entorhinal cortex volumes (β (95% CI) = 0.16 (0.06–0.27); *P* = 0.006, see Fig. 2, Table 3B). No association was found in younger participants, except with hippocampal subfields (see below).

3.4. Sex-specific analyses

In women, more severe OSA was associated with larger medial temporal lobe structures (Fig. 3, Table 3C). Higher sleep fragmentation was associated with larger hippocampal volumes (β (95% CI) = 0.39 (0.08–0.70), *P* = 0.048). High hypoxemia levels were also associated with increased entorhinal cortex volumes (β (95% CI) = 0.20 (0.09–0.31); *P* = 0.002). No significant association was found in men.

3.5. Analyses by cognitive status

In aMCI participants, higher hypoxemia levels were associated with increased bilateral hippocampal volumes (Fig. 4, Table 3D): (β (95% CI) = 0.18 (0.05–0.31); *P* = 0.024). No association was found in cognitively healthy participants -.

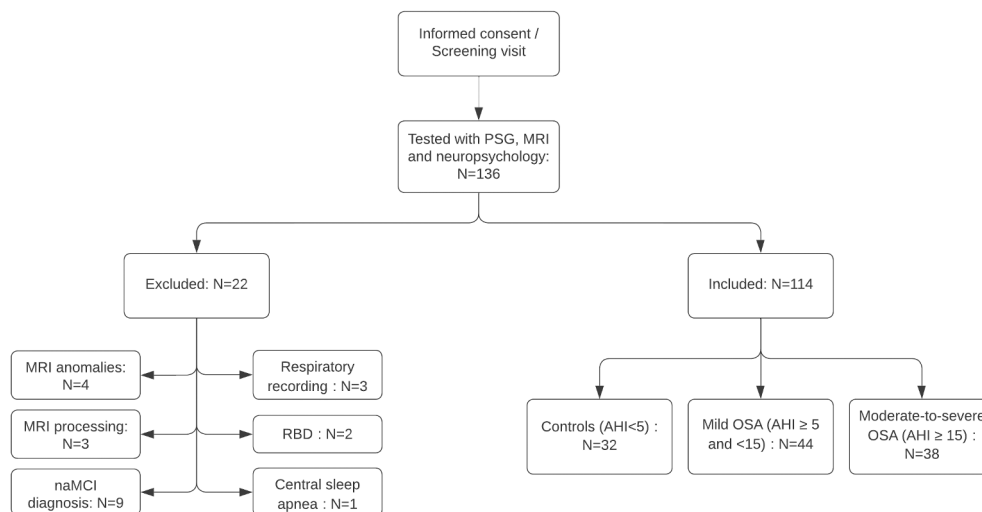


Fig. 1. Study participants flow chart. PSG = Polysomnography; MRI = Magnetic resonance imaging; RBD = Rapid eye movement sleep behavior disorder; OSA = Obstructive sleep apnea. naMCI: non-amnesic mild cognitive impairment.

Table 2
Demographic, clinical and polysomnographic characteristics of participants according to OSA severity.

Variables	Whole group	Controls (A)	Mild OSA (B)	Moderate-to-severe OSA (C)	F/X ²	P values	Post-Hoc Analyses
Total N	114	32	44	38			
Age (years)	68.0 ± 7.9	67.2 ± 8.4	68.6 ± 7.9	68.21 ± 7.7	0.5	0.6	
Women, N (%)	40 (35 %)	13 (41 %)	19 (43 %)	8 (21 %)	2.5	0.1	
Education (years)	15.1 ± 3.6	14.4 ± 3.5	15.4 ± 3.6	15.3 ± 3.8	1.0	0.4	
Body mass index (kg/m ²)	26.5 ± 3.7	25.3 ± 3.6	25.6 ± 3.5	28.4 ± 3.4	8.9	< 0.001	A, B < C
Epworth Sleepiness Scale score	7.1 ± 4.5	6.1 ± 4.0	6.7 ± 4.7	8.5 ± 4.5	2.5	0.1	
Depressive symptoms (% with)	7.3	6.5	4.5	11.4	1.5	0.5	
Anxiety symptoms (% with)	18.2	22.6	13.6	20.0	1.4	0.5	
Montreal Cognitive Assessment score	26.7 ± 2.6	26.7 ± 2.6	26.8 ± 2.5	26.6 ± 2.8	0.02	1.0	
Amnesic mild cognitive impairment, N (%)	46 (40 %)	15 (47 %)	19 (43 %)	12 (32 %)	3.2	0.5	
Apnea-hypopnea index (events/h)	13.9 ± 14.3	2.2 ± 1.5	8.7 ± 2.8	29.7 ± 14.3	92.5	< 0.001	A < B < C
3 % oxygen desaturation index (events/h)	8.6 ± 10.6	1.6 ± 2.2	4.5 ± 3.8	19.2 ± 12.4	57.3	< 0.001	A, B < C
Mean oxygen saturation (%)	94.6 ± 1.3	95.2 ± 0.9	94.8 ± 1.3	93.9 ± 1.3	9.5	< 0.001	A, B < C
Minimal oxygen saturation (%)	85.9 ± 4.9	89.4 ± 2.8	86.8 ± 3.2	81.9 ± 5.2	32.9	< 0.001	A > B > C
Sleep time with oxygen saturation < 90 % (min)	6.9 ± 18.8	0.3 ± 0.5	2.8 ± 5.3	17.0 ± 30.4	9.5	< 0.001	A, B < C
Total sleep time (min)	364.3 ± 58.2	363.7 ± 61.5	368.2 ± 65.6	360.6 ± 46.8	0.2	0.8	
Total wake time after sleep onset (min)	91.9 ± 51.4	94.9 ± 48.2	91.0 ± 56.6	90.4 ± 49.0	0.04	1.0	
Sleep efficiency (%)	79.8 ± 10.9	79.2 ± 10.7	79.8 ± 12.3	80.1 ± 9.7	0.01	1.0	
Micro-arousal index (events/h)	15.0 ± 8.2	10.6 ± 4.6	12.6 ± 5.6	21.4 ± 9.1	24.0	< 0.001	A, B < C
N1 (min)	71.3 ± 37.3	50.4 ± 28.3	64.7 ± 25.6	96.4 ± 41.9	14.9	< 0.001	A, B < C
N2 (min)	204.7 ± 51.5	215.0 ± 45.7	211.3 ± 52.1	185.4 ± 53.3	3.2	0.05	A, B < C
N3 (min)	29.1 ± 31.9	34.1 ± 34.4	30.9 ± 35.7	22.9 ± 24.0	0.8	0.5	
REM sleep (min)	60.2 ± 22.2	64.0 ± 20.5	61.2 ± 24.3	55.9 ± 20.7	2.4	0.1	

OSA = obstructive sleep apnea; REM: rapid-eye movement.

Results for continuous variables are reported as means ± standard deviation. Controls: AHI < 5, Mild OSA: AHI ≥ 5 to < 15, Moderate-to-severe OSA: ≥ 15.

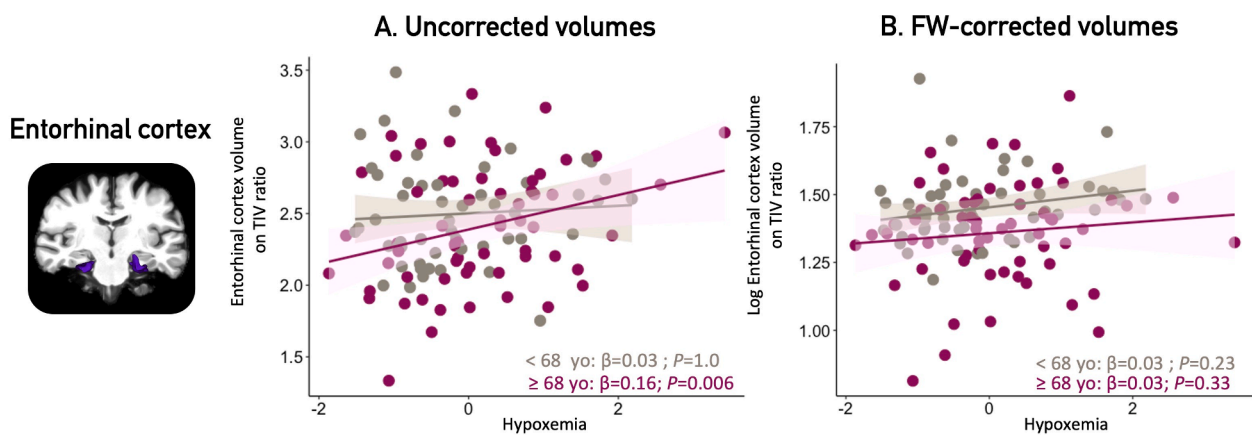


Fig. 2. Associations between hypoxemia severity and entorhinal cortex by age groups. Legend: Panel A presents uncorrected grey matter volumes of the entorhinal cortex in younger (<68 yo) and older participants (≥68 yo) obtained at $p < 0.05$ corrected for multiple comparisons with a family-wise error correction. Panel B presents the FW-corrected volumes. All volumes were corrected for TIV (volume/TIV*1000). Covariates included in the multiple linear regressions were sex and education. OSA = obstructive sleep apnea; FW = free-water; TIV = total intracranial volume; yo = years old.

3.6. Hippocampal subfields

We performed additional analyses on the associations between OSA severity markers and hippocampal subfield volumes extracted from FreeSurfer. In the whole sample, no association was found. When stratifying our sample (by sex, age and cognitive status), we found that increased sleep fragmentation was associated with higher CA2-CA3-CA4-DG volumes (β (95% CI) = 0.06 (0.01–0.1), $P = 0.048$) in younger participants (<68 years old). In aMCI participants, higher hypoxemia levels were associated with higher subiculum volumes (β (95% CI) = 0.01(0.05–0.02), $P = 0.012$). No association was found when stratifying by sex. When using FW-corrected volumes, no association remained significant.

3.7. FW fraction and FW-corrected volumes

FW fraction values were extracted for all ROIs and showed no association with OSA severity in the whole sample and in subgroups.

Regardless of OSA severity, older individuals displayed a higher entorhinal cortex FW fraction than younger participants ($F = 9.4$; $P = 0.009$), men displayed a higher FW fraction than women in parahippocampal gyri ($F = 15.5$; $P = 0.0004$) and aMCI participants had a higher FW fraction in all three medial temporal lobe subregions ($F = 6.9–9.2$; $P = 0.009–0.030$) compared to cognitively healthy participants. Finally, although there were no differences in the medial temporal lobe subregions between aMCI and non-MCI participants when comparing uncorrected volumes, FW-corrected volumes revealed atrophy in all three subregions in aMCI participants ($F = 6.3–9.8$; $P = 0.006–0.039$).

We then investigated the association between OSA severity and FW-corrected grey matter volumes of medial temporal lobe regions. No association between OSA severity markers and medial temporal volumes remained significant, neither in the whole sample nor when stratified for age, sex or cognitive status.

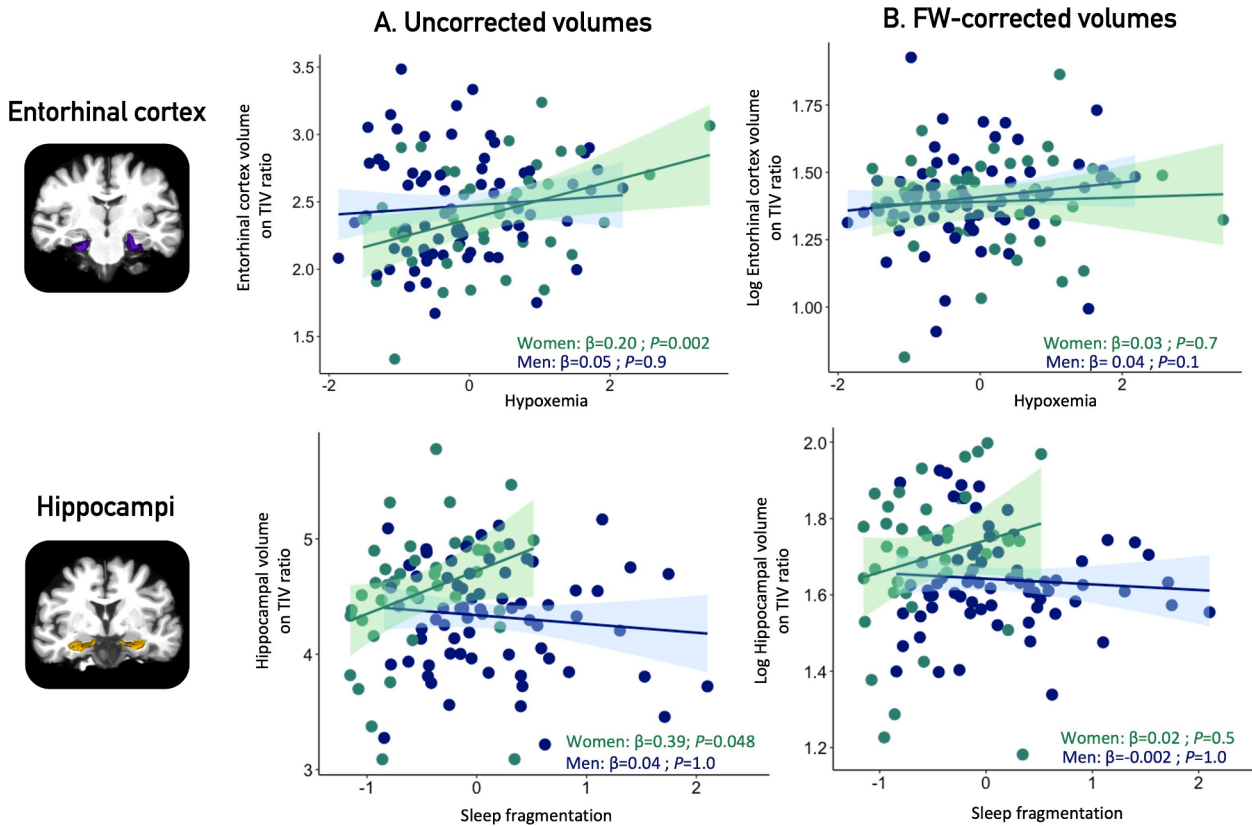


Fig. 3. Associations between OSA severity markers and medial temporal volumes in women and men. Legend: Panel A shows uncorrected grey matter volumes of the hippocampi (upper) and entorhinal cortex (lower) in women and men, obtained at $p < 0.05$ corrected for multiple comparisons with a family-wise error correction. Panel B presents the FW-corrected volumes. All volumes were corrected for TIV (volume/TIV*1000). Covariates included in the multiple linear regressions were age and education. OSA = obstructive sleep apnea; FW = free-water; TIV = total intracranial volume.

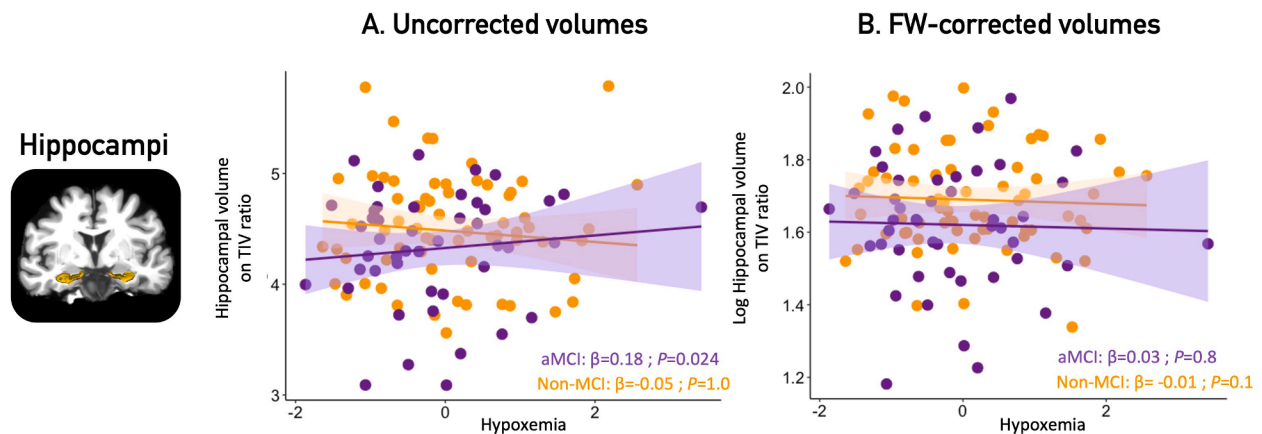


Fig. 4. Associations between hypoxemia and hippocampal volumes in aMCI participants and controls. Legend: Panel A shows uncorrected volumes of the bilateral hippocampus, obtained at $p < 0.05$ corrected for multiple comparisons with a family-wise error correction in participants with aMCI only. No association remained significant between any markers of OSA severity and FW-corrected volumes (panel B). All volumes are TIV-normalized (volume/TIV*1000). Covariates included in the multiple linear regressions were age, education and sex. OSA = obstructive sleep apnea; FW = free-water; aMCI = amnesic mild cognitive impairment, TIV = total intracranial volume.

4. Discussion

Our study showed that increased OSA severity, particularly hypoxemia, was associated with higher volumes in the entorhinal cortex and the hippocampus, and that these associations were mostly observed in women, older participants and those with aMCI. While few neuroimaging studies have investigated the impact of individual characteristics in OSA, these findings represent a significant step toward

personalized medicine and could guide treatment decision for patients who might be at greater risk of pathological changes when OSA is left untreated. In addition, when we applied a FW correction to grey matter volumes, no association between OSA severity and medial temporal subregional volume remained significant, while this correction unveiled atrophy of the medial temporal lobe in participants with aMCI regardless of OSA severity. This suggests that the grey matter hypertrophies were likely due to increased brain water content. To our knowledge, this

Table 3

Significant multiple linear regression results for analyses with OSA severity markers and medial temporal subregional volumes.

Brain regions	Unstandardized β coefficient (95% CI)	Standard error	<i>P</i> values, FWE corrected
A. Whole sample ¹			
Entorhinal cortex volume			
Hypoxemia	0.09 (0.02–0.16)	0.04	0.045
B. Older participants ²			
Entorhinal cortex volume			
Hypoxemia	0.16 (0.06–0.27)	0.05	0.006
C. Women ³			
Hippocampal volume			
Sleep fragmentation	0.39 (0.08–0.70)	0.06	0.048
Entorhinal cortex volume			
Hypoxemia	0.20 (0.09–0.31)	0.05	0.002
D. aMCI participants ¹			
Hippocampal volume			
Hypoxemia	0.18 (0.05–0.31)	0.06	0.024

CI = confidence interval, FWE: Family-Wise Error, aMCI = amnesic mild cognitive impairment; OSA = obstructive sleep apnea.

¹ Analyses adjusted for age, sex and education.

² Analyses adjusted for sex and education.

³ Analyses adjusted for age and education.

is the first study investigating the potential impact of edema and neuroinflammation on grey matter volumes using FW-corrected volumes in OSA participants. Applying FW correction on grey matter volumes could therefore lead to more valid neuroimaging results in participants with suspected edema and neuroinflammation.

4.1. Edema as an early response to hypoxia

Medial temporal lobe subregions require a high oxygen supply as demonstrated by their dense vascularity, which makes them especially vulnerable to hypoxemia (Spallazzi et al., 2019). In animal models, regions affected by hypoxemia first show reactive or adaptive mechanisms that include edema, reactive gliosis, oxidative stress, neuroinflammation and ischemic preconditioning (Baril et al., 2021; Gosselin et al., 2019; Rosenzweig et al., 2015). These mechanisms are followed by apoptosis when episodes of hypoxemia are repeated (Fung et al., 2007). We (Baril et al., 2021) and others (Rosenzweig et al., 2015) have suggested that structural neuroimaging changes follow a biphasic evolution in OSA, with a first stage characterized by edema and increased grey matter volume, and a second stage characterized by neuronal death, grey matter loss and cognitive decline. In support of this hypothesis, André et al. (André et al., 2020) tested 127 cognitively unimpaired adults (mean age: 69.1 years old), and found increased amyloid burden and metabolism, but also larger posterior cingulate cortex, cuneus and precuneus volumes in OSA participants compared to controls. Interestingly, a study by Cross et al. included 83 participants (mean age: 67.4 years old) with subjective and/or objective cognitive impairment and found both thicker and thinner cerebral volumes associated with OSA severity (Cross et al., 2018), notably in hippocampal and temporo-parietal areas. Our results further support a biphasic hypothesis in all three medial temporal lobe subregions, in which both atrophy and hypertrophy have been previously underlined (André et al., 2020; Cross et al., 2018; Owen et al., 2019; Shi et al., 2017).

4.2. Effects of age

When stratifying our sample in two age groups (<68 versus \geq 68 years old), we found associations between OSA severity and medial temporal subregional volumes in both groups. We expected to see changes in the younger group, as stronger links between OSA and cognitive function in young and middle-aged adults compared to older adults have been previously reported (Bubu et al., 2020). Accordingly, in the < 68 years old group, we found associations between sleep fragmentation and higher hippocampal subfield (CA2-CA3-CA4-DG) volume. However, we also found that more hypoxemia was associated with larger entorhinal cortex volume in the \geq 68 years old group, which is in line with previous findings in the elderly suggesting that chronic intermittent hypoxemia might be the central mechanism linking OSA to risk of cognitive impairment (Zimmerman and Aloia, 2012). Elderly adults with OSA can present with multiple comorbidities (e.g. obesity, hypertension, diabetes and cardiovascular diseases) (Bonsignore et al., 2019), that are also risk factors for cognitive impairment and dementia. Separating the effects of these conditions from the effects of OSA can thus be challenging, which may explain why some previous studies have observed associations between OSA and cognitive decline in “young elderly” only.

4.3. Sex modulates the association between OSA severity and medial temporal structures

Sex-specific pathophysiology, clinical presentation, and health consequences of OSA have been suggested (Huang et al., 2018). We highlighted noticeable differences on how OSA severity is associated with medial temporal grey matter volumes in men and women, where OSA severity was associated with increased volumes of the hippocampus and entorhinal cortex in women only. In accordance with these observations, epidemiological studies reported that the association between OSA and cognitive decline might be stronger in women compared to men (Thompson et al., 2022; Zhu and Zhao, 2018). This sex effect may however not be specific to OSA. For example, a recent study found that women with aMCI or dementia present higher tau burden measured with positron emission tomography in several regions (e.g., entorhinal cortex) compared to men who had similar cognitive functioning (Edwards et al., 2021). Women may tolerate higher pathology burden with less cognitive consequences; however, this can be followed by marked atrophy and steeper cognitive decline than men. Based on these findings, a particular attention should be paid to women with OSA as they may report being asymptomatic, while their brains may show significant pathological changes.

4.4. Mild cognitive impairment, OSA and neuroimaging findings

Regarding the impact of cognitive status, only participants with aMCI showed a link between increased OSA severity and higher hippocampal volumes. These results suggest that the larger volumes observed in relation to OSA severity are not an adaptive process, as they are associated with poorer cognition among participants with OSA. Interestingly, MCI and AD studies (regardless of OSA) report cortical thickening in the early stages of neurodegeneration, which is hypothesized to be linked to edema, as amyloid deposition is a pro-inflammatory process that can lead to changes in water content (Montal et al., 2018). As aMCI participants with increased OSA severity showed significant structural changes in the present study, they likely are at an early stage of neurodegeneration, and the OSA-related sleep disturbances could therefore enhance ongoing neurodegenerative processes and cognitive decline if left untreated (Lucey et al., 2021).

4.5. Hippocampal subfields

Studies have shown that medial temporal lobe subregions are not

homogeneously affected in the first stages of AD. In fact, the entorhinal cortex is the first region affected, followed by specific hippocampal subfields, more specifically the CA1, which is also increasingly sensitive to hypoxia, and the subiculum (Small et al., 2011). Additional analyses on hippocampal subfields (CA1, subiculum, combined CA2-CA3-CA4-DG) showed that the associations between OSA severity and grey matter volumes were more prominent in the subiculum (in aMCI participants) and combined CA2-CA3-CA4-DG (younger participants), but not in the CA1. It was previously shown that CA1 could particularly benefit from ischemic preconditioning (Levchenkova et al., 2021), which could explain the absence of association with OSA. However, due to our MRI resolution, this finding must be interpreted with caution and future studies in OSA should investigate hippocampal subfields with high resolution MRI.

4.6. Using FW fraction to understand medial temporal lobe structure

A gradual increase in FW fraction has been shown in participants with MCI or AD compared to controls (Bergamino et al., 2021; Dumont et al., 2019; Montal et al., 2018). One study also noted a decrease in FW fraction in asymptomatic amyloid-positive but tau-negative patients, and higher FW fraction in further stages (Montal et al., 2018). In this study, we showed that using FW-corrected volumes might allow more precise estimates of grey matter volumes by limiting the impact of artificial hypertrophies caused by water content changes and edema. This is consistent with the atrophy revealed in all three medial temporal lobe regions in our aMCI compared to non-MCI participants, regardless of OSA severity. When investigating associations between OSA and FW-corrected volumes, none remained significant, suggesting that the structural changes in medial temporal lobe subregions could precede future atrophy, thus representing an interesting therapeutic window. Edema could also be due to a combination of many factors, such as ongoing neurodegenerative processes or OSA-related medical comorbidities, as no clear relationship between OSA severity and FW fraction was established.

4.7. Are structural changes reversible in treated OSA?

Another important question to answer is whether structural changes to medial temporal lobe subregions are reversible. Longitudinal studies suggest that treating OSA surgically or using continuous positive airway pressure therapy has a positive impact on medial temporal lobe structure and function by increasing regional cerebral blood flow distribution in the hippocampus and parahippocampal gyri over time (L'Heureux et al., 2021) or decreasing grey matter volumes in the hippocampus (Lin et al., 2016), leading to improved cognitive performance and levels of systemic inflammation markers. These findings highlight the need to follow cohorts of treated and untreated OSA patients over time, and this should be done while considering individual characteristics that might significantly impact outcomes.

4.8. Limitations

The present study has some limitations. Globally, the severity of symptomatology (sleepiness, depression, anxiety and aMCI) was not associated with OSA severity suggesting that the functional consequences of OSA were relatively mild. Although we did follow a protocol aimed at limiting the impact of using multiple scanners, this could still have an impact on neuroimaging analyses. In addition, as FW imaging is a bi-tensor model, it relies on the fact that there is no exchange of liquid between the two compartments (intra/extracellular), and therefore represents a limitation of this model. In the future, FW fraction could be even more robust using a multi-shell diffusion MRI sequence.

4.9. Conclusion

In this study, OSA severity is associated with increased volumes in medial temporal subregions, particularly in women and in participants presenting aMCI. These changes are likely linked to maladaptive processes in the form of extracellular fluid accumulation, which usually precedes or is seen with neuronal death. This study is of clinical importance, as pulmonologists, geriatricians, and family physicians need to know which OSA patients are more vulnerable to cognitive decline and should be treated.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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