


# Mean Oxygen Saturation during Sleep Is Related to Specific Brain Atrophy Pattern

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**Objective:** There is much controversy about the neurobiological mechanisms underlying the effects of sleep-disordered breathing on the brain. The aim of this study was to investigate the association between markers of sleep-related hypoxemia and brain anatomy.

**Methods:** We used data from a large-scale cohort from the general population ( $n = 775$ , 50.6% males, age range = 45–86 years, mean age =  $60.3 \pm 9.9$ ) that underwent full polysomnography and brain magnetic resonance imaging to correlate respiratory variables with regional brain volume estimates.

**Results:** After adjusting for age, gender, and cardiovascular risk factors, only mean oxygen saturation during sleep was associated with bilateral volume of hippocampus (right:  $p = 0.001$ ; left:  $p < 0.001$ ), thalamus (right:  $p < 0.001$ ; left:  $p < 0.001$ ), putamen (right:  $p = 0.001$ ; left:  $p = 0.001$ ), and angular gyrus (right:  $p = 0.011$ ; left:  $p = 0.001$ ). We observed the same relationship in left hemispheric amygdala ( $p = 0.010$ ), caudate ( $p = 0.008$ ), inferior frontal gyrus ( $p = 0.004$ ), and supramarginal gyrus ( $p = 0.003$ ). The other respiratory variables—lowest oxygen saturation, percentage of sleep time with oxygen saturation  $< 90\%$ , apnea–hypopnea index, and oxygen desaturation index—did not show any significant association with brain volumes.

**Interpretation:** Lower mean oxygen saturation during sleep was associated with atrophy of cortical and subcortical brain areas known for high sensitivity to oxygen supply. Their vulnerability to hypoxemia may contribute to behavioral phenotype and cognitive decline in patients with sleep-disordered breathing.

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Sleep-disordered breathing (SDB) encompasses different conditions associated with nocturnal hypoxemia, of which obstructive sleep apnea is the most common.<sup>1</sup> It is characterized by repeated collapse of the pharyngeal airway during sleep, resulting in hypoxemia, fragmented

sleep, and hemodynamic fluctuations.<sup>2</sup> Besides its association with cardiovascular diseases,<sup>3,4</sup> SDB is also related to depression<sup>5,6</sup> and varying degrees of cognitive deficits.<sup>7,8</sup> Moreover, epidemiological studies suggest that SDB could constitute a modifiable risk factor for dementia.<sup>9,10</sup>

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Imaging studies investigating the effect of nocturnal hypoxemia on brain anatomy have been carried out mostly in selected clinical populations, particularly in middle-aged patients diagnosed with obstructive sleep apnea. Brain structural changes have been observed in pre-frontal, sensorimotor, anterior cingulate, cerebellar, and brainstem areas, but findings showed substantial variability across studies and methods.<sup>11–15</sup> A meta-analysis summarizing the results of 15 structural and functional magnetic resonance imaging (MRI) studies showed alterations in the hippocampus, amygdala, and insula in 290 patients with obstructive sleep apnea compared to 290 healthy controls.<sup>16</sup> However, no studies have investigated the association between nocturnal markers of hypoxemia and brain anatomy in the general population. Therefore, the contribution of nocturnal hypoxemia to brain pathophysiology and its clinical significance remain partly unclear.

The aim of the present study was to investigate the association between polysomnographic (PSG) respiratory variables and estimates of regional gray matter volume across the whole brain in the general population. We hypothesized that brain areas that are oxygen-sensitive would demonstrate atrophy in subjects with more severe SDB.<sup>17–19</sup>

## Subjects and Methods

### Study Participants

The study participants were selected from the longitudinal general population-based CoLaus|PsyCoLaus study that started in 2003 with 6,734 participants aged 35–75 years.<sup>20,21</sup> Participants have been followed up twice, and a third follow-up is currently ongoing. Assessments covered several cardiovascular and psychiatric conditions, using diagnostic interviews, self-rating questionnaires, clinical examinations, and blood tests. During the first follow-up, 2,162 participants agreed to undergo a full-night PSG recording at home (HypnoLaus nested study). During the second follow-up, 1,323 participants underwent a brain MRI (BrainLaus nested study). For this study, we included participants who underwent both PSG and MRI examinations. We excluded participants with incomplete PSG and/or MRI data. The final sample resulted in 775 individual records. Prior to the study, participants signed a written informed consent approved by the local ethics committee.

### PSG Data Acquisition

Recordings were made with a PSG recorder (Titanium, Embla Flaga, Reykjavik, Iceland) as previously described.<sup>5,22</sup> Sleep technicians visually scored PSG recordings using Somnologica software (v5.1.1, Embla Systems). An expert sleep physician reviewed every recording, and a second sleep expert did random quality checks. We scored sleep stages and arousals according to the 2007 American Academy of Sleep Medicine (AASM) recommended criteria. We recorded mean arterial oxygen saturation (SaO<sub>2</sub>) during sleep, lowest SaO<sub>2</sub> (defined as the lowest

saturation reached during sleep), and the percentage of time spent asleep with oxygen saturation < 90% (T90). We defined apnea as a drop of at least 90% of airflow from baseline lasting 10 seconds or longer. We defined hypopnea with the 2012 AASM recommended criteria (≥30% drop of airflow lasting at least 10 seconds with either an arousal or ≥3% oxygen saturation drop). We calculated the average number of apneas and hypopneas per hour of sleep (apnea–hypopnea index [AHI]). The oxygen desaturation index (ODI) represents the number of oxygen drops of ≥3% per hour of sleep.

### MRI Data Acquisition and Processing

Data were acquired on a 3T whole-body system (Magnetom Prisma; Siemens Medical Systems, Erlangen, Germany), using a 64-channel radiofrequency receive head coil and body coil for

**TABLE 1. Clinical Characteristics of the Sample**

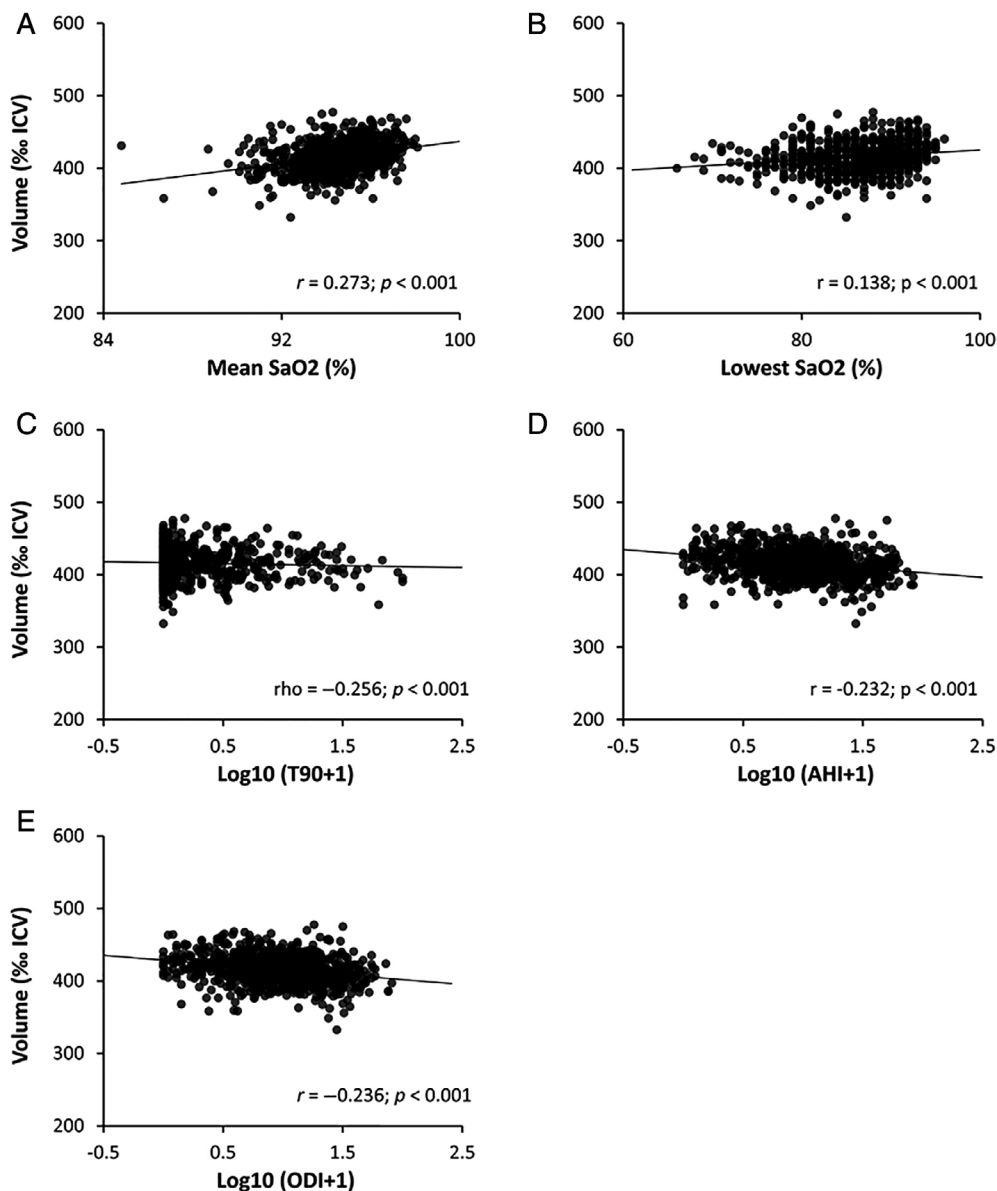
Clinical Characteristics	PSG Visit	MRI Visit
Age, yr	55.9 ± 10.3 (40–84)	60.3 ± 9.9 (45–86)
Male, %	50.6	50.6
BMI, kg/m <sup>2</sup>	25.6 ± 4.0 (14.2–41.9)	26.0 ± 4.3 (13.9–43.3)
Diabetes, %	6.6	7.3
Dyslipidemia, %	37.5	36.6
Hypertension, %	31.8	36.0
Smoking, %	55.3	55.7
Alcohol use, %	84.0	85.3
CPAP, %	0.0	4.0
COPD, %	—	2.7
Mean SaO <sub>2</sub> , %	94.5 ± 1.6 (84.8–98.1)	—
Lowest SaO <sub>2</sub> , %	86.4 ± 5.4 (66.0–96.0)	—
T90, %	2.4 ± 0.1 (0.0–100.0)	—
ODI, events/h	12.1 ± 11.8 (0.0–79.6)	—
AHI, events/h	13.0 ± 13.2 (0.0–82.9)	—
AHI ≥ 15, %	31.7	—
AHI ≥ 30, %	10.6	—

Values are presented as percentage or mean ± standard deviation and range.

AHI = apnea–hypopnea index; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airways pressure; MRI = magnetic resonance imaging; ODI = oxygen desaturation index; PSG = polysomnography; SaO<sub>2</sub> = oxygen saturation; T90 = % of total sleep time with oxygen saturation < 90%.

transmission. The scanning protocol included 3 multiecho 3-dimensional (3D) fast low angle shot acquisitions with magnetization transfer-weighted (repetition time [TR] = 24.5 milliseconds,  $\alpha = 6^\circ$ ), proton density-weighted (TR = 24.5 milliseconds,  $\alpha = 6^\circ$ ), and T1-weighted (TR = 24.5 milliseconds,  $\alpha = 21^\circ$ ) contrasts, with  $1\text{mm}^3$  isotropic resolution.<sup>23,24</sup> B1 mapping data were acquired using the 3D EPI sequence ( $4\text{mm}^3$  resolution, echo time = 39.06 milliseconds, TR = 500 milliseconds).<sup>25,26</sup> We used an automated data processing algorithm within the Statistical Parametric Mapping (SPM12) framework (Wellcome Trust Centre for Neuroimaging, London, UK; [www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). Quantitative MRI maps were computed from the raw MRI data using the histology-MRI toolbox.<sup>27</sup> The quantitative MRI maps were corrected for the effect of spatial inhomogeneities of the

radiofrequency transmit field using the acquired B1 mapping data.<sup>28</sup> The maps of proton density and magnetization transfer saturation were fed into SPM's multichannel segmentation to compute tissue probability maps of gray matter, white matter, and cerebrospinal fluid using the enhanced tissue priors described.<sup>29</sup> This was followed by a diffeomorphic registration procedure using geodesic shooting to estimate spatial registration parameters between individuals' space and standard Montreal Neurological Institute space.<sup>30</sup> The inverse of the estimated parameters is applied to the 134 parcels of the probabilistic Neuroinformatics atlas to register these in individuals' native space (probabilistic and maximum probability tissue labels were derived from the MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labeling; <https://my.vanderbilt.edu/masi/workshops>).



**FIGURE 1:** Bivariate correlation between total gray matter volume and polysomnographic variables. (A) Mean oxygen saturation (SaO2). (B) Lowest SaO2. (C) Percentage of sleep time with oxygen saturation < 90% (T90). (D) Apnea-hypopnea index (AHI). (E) Oxygen desaturation index (ODI). ICV = total intracranial volume.

**TABLE 2. Regression Analysis for Polysomnographic Respiratory Variables Predicting Regional Brain Volumes, after Adjusting for Age, Gender, Body Mass Index, Diabetes, Dyslipidemia, Hypertension, Smoking, and Alcohol Use**

	Mean SaO2		Lowest SaO2		Log10(T90 + 1)		Log10(AHI + 1)		Log10(ODI + 1)	
	<i>B</i>	<i>p</i>	<i>B</i>	<i>p</i>	<i>B</i>	<i>p</i>	<i>B</i>	<i>p</i>	<i>B</i>	<i>p</i>
Total gray matter	1.097	0.031	0.015	0.915	-1.230	0.548	-0.499	0.802	-1.469	0.481
Subcortical structures										
R hippocampus	0.013	0.001 <sup>a</sup>	<0.001	0.910	-0.015	0.379	0.003	0.862	-0.008	0.653
L hippocampus	0.014	<0.001 <sup>a</sup>	<0.001	0.962	-0.013	0.403	<0.001	0.988	-0.009	0.595
R amygdala	0.003	0.036	0.001	0.773	-0.005	0.297	-0.003	0.489	-0.004	0.437
L amygdala	0.003	0.010 <sup>a</sup>	<0.001	0.988	-0.001	0.425	-0.005	0.320	-0.005	0.297
R thalamus	0.030	<0.001 <sup>a</sup>	-0.001	0.755	-0.053	0.093	0.034	0.264	<0.001	0.998
L thalamus	0.032	<0.001 <sup>a</sup>	<0.001	0.999	-0.056	0.086	0.014	0.661	-0.013	0.697
R caudate	0.014	0.014	<0.001	0.802	-0.008	0.713	0.001	0.955	0.001	0.957
L caudate	0.014	0.008 <sup>a</sup>	0.001	0.679	-0.012	0.579	0.005	0.796	0.004	0.861
R putamen	0.022	0.001 <sup>a</sup>	<0.001	0.436	-0.041	0.118	0.012	0.647	-0.002	0.930
L putamen	0.022	0.001 <sup>a</sup>	-0.002	0.276	-0.029	0.295	0.005	0.853	-0.006	0.820
R pallidum	0.004	0.043	<0.001	0.699	-0.013	0.141	0.008	0.340	0.006	0.476
L pallidum	0.002	0.307	<0.001	0.701	-0.009	0.319	0.008	0.364	0.008	0.404
Cortical structures										
R middle frontal gyrus	0.051	0.039	0.002	0.730	-0.126	0.210	-0.029	0.768	-0.102	0.318
L middle frontal gyrus	0.049	0.073	0.002	0.799	-0.086	0.436	-0.039	0.720	-0.123	0.274
R inferior frontal gyrus	0.026	0.035	<0.001	0.930	-0.097	0.053	-0.067	0.175	-0.077	0.133
L inferior frontal gyrus	0.038	0.004 <sup>a</sup>	0.007	0.051	-0.135	0.011	-0.066	0.196	-0.098	0.069
R superior temporal gyrus	0.020	0.057	-0.004	0.128	<0.001	0.998	0.033	0.421	0.001	0.977
L superior temporal gyrus	0.027	0.015	-0.002	0.420	-0.035	0.435	0.041	0.348	0.021	0.518
R middle temporal gyrus	0.035	0.055	<0.001	0.965	-0.020	0.783	0.010	0.884	-0.038	0.609
L middle temporal gyrus	0.038	0.038	-0.007	0.130	-0.014	0.847	0.047	0.518	0.009	0.903
R postcentral gyrus	0.037	0.020	0.002	0.690	-0.039	0.548	0.002	0.968	-0.056	0.395
L postcentral gyrus	0.010	0.556	-0.003	0.541	0.053	0.447	-0.025	0.709	-0.063	0.379
R supramarginal gyrus	0.022	0.082	-0.001	0.657	0.016	0.745	0.015	0.762	0.011	0.834
L supramarginal gyrus	0.041	0.003 <sup>a</sup>	0.004	0.329	-0.031	0.580	0.021	0.705	-0.019	0.746
R angular gyrus	0.039	0.011 <sup>a</sup>	0.001	0.769	-0.043	0.491	0.041	0.502	0.008	0.897
L angular gyrus	0.048	0.001 <sup>a</sup>	<0.001	0.905	-0.047	0.410	0.004	0.942	-0.008	0.891

Only the brain regions with right and/or left side uncorrected  $p < 0.05$  are presented in this table.

<sup>a</sup>Significant  $p$  value after correcting for false discovery rate  $< 0.05$ .

AHI = apnea-hypopnea index; *B* = unstandardized beta coefficient; L = left; ODI = oxygen desaturation index;  $p$  = uncorrected probability value; R = right; SaO2 = oxygen saturation; T90 = % of total sleep time with oxygen saturation  $< 90\%$ .

The value in each region of interest is defined as the average of values in all voxels that compose it. Aiming to adjust for the global decrease in gray matter volume with aging, we apply proportional scaling such that gray matter volume (adjusted) = gray matter volume (observed) / total gray matter volume in the brain.<sup>31</sup> In the present study, we investigated 59 regions of interest covering all cortical and subcortical brain areas. Volume findings were reported as % of total intracranial volume (ICV).

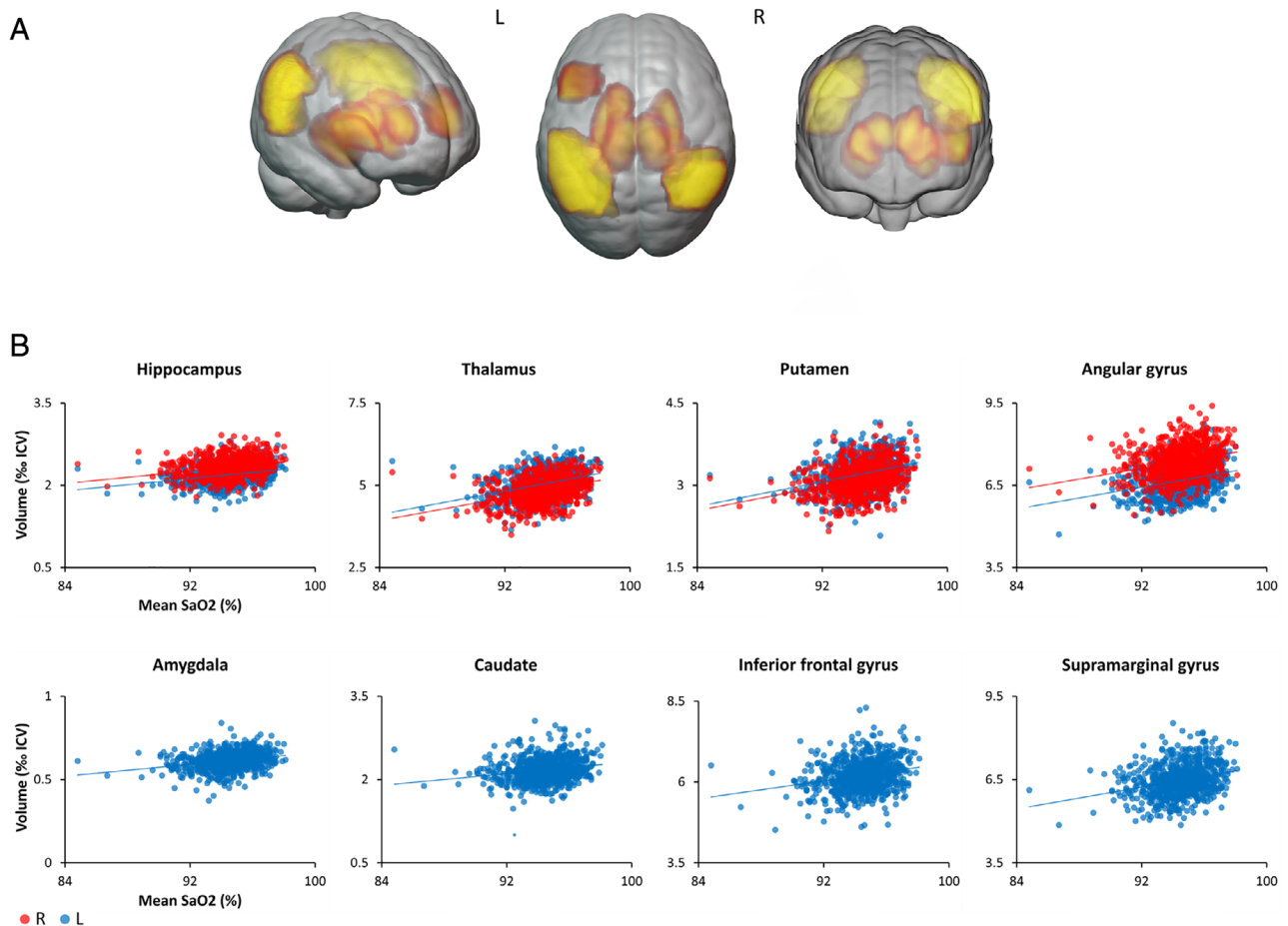
### Clinical Variables

Clinical variables were recorded twice, at the time of PSG and at the time of MRI. We calculated the body mass index (BMI) as weight/height.<sup>2</sup> Diabetes was diagnosed if the fasting blood glucose levels were  $\geq 7\text{mmol/l}$  and/or when antidiabetic drugs were used. Presence of arterial hypertension was defined as a systolic blood pressure  $\geq 140\text{mmHg}$  and/or diastolic blood pressure  $\geq 90\text{mmHg}$  and/or use of antihypertensive drugs. We considered dyslipidemia in cases with low high-density lipoprotein cholesterol  $< 1.0\text{mmol/l}$  and/or high triglyceride  $\geq 4.1\text{mmol/l}$  and/or high low-density lipoprotein cholesterol  $\geq 4.1\text{mmol/l}$  (threshold was lowered at  $\geq 2.6\text{mmol/l}$  in presence of self-reported history of myocardial infarction, stroke, coronary artery disease, or diabetes), or if the participants reported having a

lipid-lowering treatment. Smoking habits were categorized as (ex-) smoker or never smoked. Alcohol consumption was dichotomized as current drinking or no alcohol consumption. Use of continuous positive airways pressure (CPAP) was recorded. Presence of chronic obstructive pulmonary disease (COPD) was investigated using spirometry in a nested study of CoLaus|PsyCoLaus labeled PneumoLaus in 685 of 775 participants representing 88.4% of the sample (this variable was recorded only at the time of MRI).<sup>32</sup>

### Statistical Analysis

The association between PSG respiratory variables and regional MRI volumes was tested (1) with bivariate analysis using Pearson or Spearman correlation and (2) with multivariate regression analysis using generalized linear model with adjustment for relevant demographic and clinical factors recorded during MRI study. Given the time lag of 4 years between PSG and MRI, we also included in the regression model the interaction term between PSG variables and age. The reasoning here was that if there is no interaction between age and PSG variables, the impact of the existing time lag on the interpretation of our findings will be negligible. Volume-adjusted means were calculated in quartiles of PSG variables, and the difference between quartiles was evaluated with 1-way analysis of covariance. To facilitate comparison with



**FIGURE 2:** Visual representation of the 12 brain structures associated with mean oxygen saturation. (A) Three-dimensional maps of the brain structures. (B) Bivariate correlation between the volume of these structures and mean oxygen saturation. ICV = total intracranial volume; L = left; R = right; SaO2 = oxygen saturation.

previous studies, we also analyzed volume-adjusted means together with categorical variables according to AHI thresholds of  $\geq 15$  or  $\geq 30$ . T90, AHI, and ODI were parameterized as  $\log_{10}(\text{variable} + 1)$  due to their positive-skewed distribution and occasional zero values.<sup>33</sup> In the setting of bivariate analysis, multivariate regression analysis, and categorical analysis comparing 2 groups according to the AHI threshold, we adjusted the significance threshold using false discovery rate corrected  $p$  value  $< 0.05$  with Benjamini–Hochberg procedure.<sup>34</sup> Statistical significance for categorical analysis comparing findings between quartiles was concluded for  $p$ -trend  $< 0.05$ . We did statistical analyses with SPSS Statistics version 25.0 (IBM, Armonk, NY).

## Results

### Demographic, Clinical, and Sleep Characteristic

The mean age of study participants was  $55.9 \pm 10.3$  years (range = 40–84) at the time of sleep evaluation and  $60.3 \pm 9.9$  years (range = 45–86) at the time of MRI. On average, the participants underwent the MRI  $4.4 \pm 1.0$  years after the PSG. Male prevalence was 50.6%. Mean AHI was  $13.0 \pm 13.2$  events/h (range = 0.0–82.9). The prevalence of moderate-to-severe SDB

(defined as AHI  $\geq 15$ ) was 31.7%. Relevant clinical characteristics are shown in Table 1. Detailed sleep data are presented in Supplementary Table SS1.

### Bivariate Analysis of Volume Findings

Figure 1 illustrates the bivariate correlation between PSG respiratory variables and total gray matter volume. We observed a positive correlation between total gray matter volume and mean SaO<sub>2</sub> ( $r = 0.273$ ,  $p < 0.001$ ) and lowest SaO<sub>2</sub> ( $r = 0.138$ ,  $p < 0.001$ ). We report a negative correlation between total gray matter volume and  $\log_{10}(\text{T90} + 1)$  ( $\rho = -0.256$ ,  $p < 0.001$ ),  $\log_{10}(\text{AHI} + 1)$  ( $r = -0.232$ ,  $p < 0.001$ ), and  $\log_{10}(\text{ODI} + 1)$  ( $r = -0.236$ ,  $p < 0.001$ ). Findings were similar for the majority of regional cortical and subcortical brain volume estimates (data not shown).

### Multivariate Analysis of Volume Findings

We used a generalized linear model to evaluate the independent association of PSG respiratory variables with gray matter regional volumes, after adjustment for age, gender, BMI, diabetes, dyslipidemia, hypertension, smoking, and

**TABLE 3. Expected Changes in Regional Brain Volumes according to Mean Oxygen Saturation or Age Variations**

	Mean Volume	Mean SaO <sub>2</sub> (%)		Age, yr	
		<i>B</i>	Expected Volume Change for Each –1%	<i>B</i>	Expected Volume Change for Each +1 Year
R hippocampus	$2.327 \pm 0.176$	0.013	–0.55%	–0.006	–0.26%
L hippocampus	$2.192 \pm 0.170$	0.014	–0.64%	–0.006	–0.27%
L amygdala	$0.613 \pm 0.053$	0.003	–0.49%	–0.002	–0.33%
R thalamus	$4.837 \pm 0.389$	0.030	–0.68%	–0.020	–0.46%
L thalamus	$5.044 \pm 0.400$	0.032	–0.63%	–0.021	–0.42%
L caudate	$2.174 \pm 0.211$	0.014	–0.64%	–0.003	–0.14%
R putamen	$3.120 \pm 0.279$	0.022	–0.71%	–0.010	–0.32%
L putamen	$3.208 \pm 0.292$	0.022	–0.69%	–0.011	–0.34%
L inferior frontal gyrus	$6.207 \pm 0.530$	0.038	–0.61%	–0.014	–0.23%
L supramarginal gyrus	$6.468 \pm 0.584$	0.041	–0.63%	–0.019	–0.29%
R angular gyrus	$7.360 \pm 0.642$	0.039	–0.53%	–0.022	–0.30%
L angular gyrus	$6.679 \pm 0.592$	0.048	–0.72%	–0.020	–0.30%

Only the brain structures that were associated with mean oxygen saturation in the regression analysis are presented in this table. The unstandardized beta coefficients were calculated in the regression analysis. Mean volume findings are ‰ of total intracranial volume and are presented as mean  $\pm$  standard deviation.

*B* = unstandardized beta coefficient (unit: ‰ of total intracranial volume); L = left; R = right; SaO<sub>2</sub> = oxygen saturation.



alcohol use. The interaction between PSG respiratory variables and age was excluded from the model, given that the results were not significant (data not shown). Among the 5 PSG respiratory variables, only mean SaO<sub>2</sub> was independently associated with volume of hippocampus (right:  $B = 0.013$ ,  $p = 0.001$ ; left:  $B = 0.014$ ,  $p < 0.001$ ), thalamus (right:  $B = 0.030$ ,  $p < 0.001$ ; left:  $B = 0.032$ ,  $p < 0.001$ ), putamen (right:  $B = 0.022$ ,  $p = 0.001$ ; left:  $B = 0.022$ ,  $p = 0.001$ ), and angular gyrus (right:  $B = 0.039$ ,  $p = 0.011$ ; left:  $B = 0.048$ ,  $p = 0.001$ ) bilaterally. The same positive correlation was observed in left hemispheric amygdala ( $B = 0.003$ ,  $p = 0.010$ ), caudate ( $B = 0.014$ ,  $p = 0.008$ ), inferior frontal gyrus ( $B = 0.038$ ,  $p = 0.004$ ), and supramarginal gyrus ( $B = 0.041$ ,  $p = 0.003$ ; Table 2 and Supplementary Table 2). Figure 2 provides a 3D map of these brain structures. Lowest SaO<sub>2</sub>, log<sub>10</sub>(T90 + 1), log<sub>10</sub>(AHI + 1), and log<sub>10</sub>(ODI + 1) were not significantly related to any volume findings after adjustment for the possible confounders. In the 12 brain structures associated with mean SaO<sub>2</sub> in the regression analysis, we calculated the expected volume changes according to mean SaO<sub>2</sub> variation. For example, in the model predicting right hippocampus volume, the unstandardized beta coefficient for mean SaO<sub>2</sub> was 0.013‰ of ICV. Considering that the mean volume of the right hippocampus was  $2.327 \pm 0.176$ ‰ of ICV, this

means that for each 1% decrease in mean SaO<sub>2</sub>, there was an expected volume change of  $-0.55$ ‰. For comparison, the unstandardized beta coefficient for age was  $-0.006$ ‰ of ICV; this means that for each 1-year increase, there was an expected volume change of  $-0.26$ ‰ in the right hippocampus. The other brain regions showed similar findings; median volume change expected for each 1% decrease in mean SaO<sub>2</sub> was  $-0.63$ ‰, and median volume change expected for each 1-year increase was  $-0.30$ ‰ (Table 3). We also divided our sample into quartiles of mean SaO<sub>2</sub> (Q1,  $\leq 93.5$ %; Q2, 93.6–94.6%; Q3, 94.7–95.6%; Q4,  $\geq 96.7$ %) and compared volume-adjusted means between these groups. Among the 12 regions that were associated with mean SaO<sub>2</sub> in the regression analysis, 9 regions also showed significant differences between quartiles, with lower volumes corresponding to lower quartiles of mean SaO<sub>2</sub> (Table 4). No significant difference was observed between quartiles of the other PSG variables (lowest SaO<sub>2</sub>, log<sub>10</sub>[T90 + 1], log<sub>10</sub>[AHI + 1], log<sub>10</sub>[ODI + 1]; data not shown). No significant difference was observed when the sample was categorized according to AHI threshold of  $\geq 15$  or  $\geq 30$  (Supplementary Tables 3 and 4). The exclusion of participants with CPAP and/or COPD or inclusion of CPAP and/or COPD as covariates in the models did not show any significant impact on our findings (data not shown).

**TABLE 4. Regional Brain Volumes according to Quartiles of Mean Oxygen Saturation, after Adjusting for Age, Gender, Body Mass Index, Diabetes, Dyslipidemia, Hypertension, Smoking, and Alcohol Use**

	Q1, n = 196	Q2, n = 203	Q3, n = 201	Q4, n = 175	p-trend
R hippocampus	2.314 ± 0.012	2.306 ± 0.011	2.335 ± 0.011	2.355 ± 0.013	0.039 <sup>a</sup>
L hippocampus	2.180 ± 0.012	2.167 ± 0.011	2.201 ± 0.011	2.226 ± 0.012	0.004 <sup>a</sup>
L amygdala	0.608 ± 0.004	0.606 ± 0.003	0.617 ± 0.003	0.620 ± 0.004	0.023 <sup>a</sup>
R thalamus	4.787 ± 0.023	4.813 ± 0.021	4.867 ± 0.021	4.887 ± 0.024	0.016 <sup>a</sup>
L thalamus	4.987 ± 0.023	5.015 ± 0.021	5.075 ± 0.021	5.105 ± 0.025	0.005 <sup>a</sup>
L caudate	2.150 ± 0.015	2.145 ± 0.014	2.184 ± 0.014	2.221 ± 0.017	0.006 <sup>a</sup>
R putamen	3.096 ± 0.019	3.087 ± 0.017	3.145 ± 0.017	3.158 ± 0.020	0.022 <sup>a</sup>
L putamen	3.181 ± 0.020	3.183 ± 0.018	3.231 ± 0.018	3.240 ± 0.021	0.091
L inferior frontal gyrus	6.121 ± 0.038	6.246 ± 0.035	6.241 ± 0.035	6.221 ± 0.041	0.061
L supramarginal gyrus	6.403 ± 0.041	6.416 ± 0.037	6.497 ± 0.037	6.566 ± 0.044	0.040 <sup>a</sup>
R angular gyrus	7.286 ± 0.045	7.339 ± 0.041	7.390 ± 0.041	7.433 ± 0.049	0.197
L angular gyrus	6.604 ± 0.041	6.614 ± 0.038	6.747 ± 0.038	6.760 ± 0.045	0.014 <sup>a</sup>

Only the brain structures that were associated with mean oxygen saturation in the regression analysis are presented in this table. Findings are ‰ of total intracranial volume and are presented as adjusted mean ± standard error.

<sup>a</sup>p-trend < 0.05.

L = left; Q1 = mean oxygen saturation  $\leq 93.5$ %; Q2 = 93.6–94.6%; Q3 = 94.7–95.6%; Q4 =  $\geq 96.7$ %; R = right.

## Discussion

To our knowledge, this is the largest study investigating the association between PSG markers of hypoxemia and brain anatomy. Our work, performed in a large cohort of middle-aged and older adults derived from the general population, demonstrates the association between mean SaO<sub>2</sub> during sleep and gray matter volume in specific cortical and subcortical brain regions. We found that a lower mean SaO<sub>2</sub> correlates to reduced volumes in the hippocampus–amygdala complex, thalamus, basal ganglia, and frontoparietal cortex. Given the lack of correlation with other PSG variables—lowest SaO<sub>2</sub>, T90, AHI, and ODI—we provide evidence for the role of mean SaO<sub>2</sub> on brain anatomy in SDB.

Our findings indicate that effects of lower mean SaO<sub>2</sub> on brain anatomy are region-specific and that hippocampus–amygdala complex, thalamus, basal ganglia, and individual cortical regions are particularly sensitive to oxygen supply.<sup>16–19</sup> On the other hand, we extend previous findings by showing a gradient in the relationship between mean SaO<sub>2</sub> level and brain anatomy that goes beyond reported results in obstructive sleep apnea populations.<sup>14,15</sup> One strength of the present study was the sample, which consisted of a large population-based cohort with age span between 45 and 86 years. This could explain some discrepancies with previous publications, which mostly consisted of relatively small samples of clinically selected middle-aged adults. The importance of the age range in the studied population is supported by the notion that cumulative effects of nocturnal hypoxemia may show an age-dependency that explains higher rates of neuropsychological impairment patients of older age.<sup>15,35</sup> Interestingly, recent studies showed that respiratory disturbance could be related to either increased or decreased volume in specific brain structures.<sup>36,37</sup> This may be explained by a distinct time of hypoxemia-related pathological processes leading to gray matter hypertrophy (reflecting inflammation and edema) and/or gray matter atrophy (reflecting neurodegeneration).<sup>38</sup> However, our findings suggest that the overall effect of lower mean SaO<sub>2</sub> is associated with gray matter volume loss.

Another strong point of our study that we investigated the association of brain anatomy and 5 PSG variables used in clinical practice. In this context, our initial hypothesis was only partially confirmed, because we predicted that gray matter volume was associated also with other SDB-related indices such as T90, AHI, or ODI, and not only with mean SaO<sub>2</sub>. This indicates that mean SaO<sub>2</sub> represents a reliable biomarker of sleep-related hypoxemia with higher relevance to brain anatomy. These results are consistent with observations in patients with chronic hypoxemia, such as COPD. COPD patients also

showed reduced gray matter volume<sup>39,40</sup> and had a higher risk of developing mild cognitive impairment or dementia.<sup>41,42</sup> T90 is certainly another reliable marker of hypoxemia severity, but its distribution was very positive-skewed given that most of the participants showed values near to 0%; this lack of variance could explain the absence of significant association with brain volumes. On the other hand, markers of intermittent hypoxemia (AHI and ODI) reflect the number of punctual desaturation events, but not their severity and duration. Thus, these variables may not reflect the overall hypoxic stress affecting the brain during sleep. This may explain why these markers failed to show association with brain anatomy when analyzed as continuous variables.<sup>37</sup> Our findings of absent association between AHI-defined categories and brain anatomy are at odds with previous publications, which we attribute to differences in participant sampling and a broad range of methodological characteristics ranging from data acquisition settings—field strength, spatial resolution, head-coil configuration—to technical details of brain anatomy feature extraction and statistical analysis.<sup>12–15,43</sup> A critical point in this context is the adoption of a quantitative MRI protocol in our study, which minimizes the probability of spurious morphometric findings present when using T1-weighted imaging.<sup>44</sup> Ongoing and future longitudinal studies will help to reveal the causality in the reported association between brain anatomy and hypoxic stress induced by the sum of single apneic and/or desaturation events after considering their depth and duration.

Our study has clinical relevance, particularly in the prospect of preventing neuropsychological decline related to SDB. The presumption here is that SDB-related gray matter atrophy increases the risk of developing neuropsychological impairment and dementia.<sup>9,10</sup> This remains, however, to be confirmed, given the lack of support for this notion from meta-analytic studies, especially on dementia risk factors.<sup>45</sup> Our findings suggest that for each 1% decrease in mean SaO<sub>2</sub> there is an expected volume loss of –0.63% in specific brain structures that are particularly sensitive to oxygen supply. We acknowledge that the clinical correlates of the morphometric alterations reported in this study should be studied. In the present work, we did not include analyses to evaluate the association between volume changes and neuropsychological performances, but already planned studies will focus on a subgroup of individuals older than 65 years who underwent cognitive assessment. One of the important issues here is to define the time course and interindividual variability of hippocampus–amygdala, thalamus, and basal ganglia vulnerability under nocturnal hypoxic stress. Therefore, our finding of a gradient between mean SaO<sub>2</sub> and the volume of these structures offers a window of



opportunity to differentiate early deviations from a “healthy” aging trajectory that could allow efficient and timely intervention. There is empirical evidence from clinical observations and dedicated research that CPAP treatment could improve neurocognitive deficits, probably by limiting the injurious effect of hypoxemia on brain structures.<sup>14,46</sup> However, the cost-effectiveness of large-scale use of CPAP for preventing SDB-related neuropsychological symptoms has not been demonstrated.

We acknowledge some limitations of the current study. There was a delay of  $4.4 \pm 1.0$  years between PSG and MRI evaluation, but SDB is a stable condition that tends to increase slightly with age but rarely shows important severity variations unless in the presence of substantial weight changes. Of note, BMI difference between PSG and MRI visits was negligible ( $0.4 \pm 1.6\text{kg/m}^2$ ); moreover, sensitivity analysis including the change in BMI as a confounder did not show any significant impact on our findings (data not shown). Along these lines, the time lag between PSG and brain MRI could limit the validity of obtained findings in the context of brain aging—ranging from “healthy” aging to subclinical neurodegeneration.<sup>47,48</sup> Given the time ordering of the two investigations and the lack of interaction between age and the tested sleep parameters, we estimate the impact of the time lag as negligible. Another point of discussion is that, aiming for clarity, we focused on objective sleep parameters rather than including subjective measures of sleep quality and daytime sleepiness that were shown to have an association with brain anatomy.<sup>49</sup> Along with our wish to ease the interpretability of findings, we abstained from interaction analyses with demographic factors, although acknowledging potential gender-specific effects of SDB on brain anatomy.<sup>50</sup>

In summary, we demonstrated the association of mean SaO<sub>2</sub> during sleep with a specific pattern of volume changes in hippocampus–amygdala, thalamus, basal ganglia, and frontotemporal cortex across middle-aged and older subjects. Our findings suggest a vulnerability of these regions to nocturnal hypoxemia that might provide a possible explanation for SDB-associated neuropsychological deficits.

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## Author Contributions

Conception and design of the study: N.A.M., J.H.-R., R.H., and B.D. Acquisition and analysis of data: N.A.M., C.R., A.L., F.K., M.P., P.M.-V., P.V., R.H., and B.D. Drafting a significant portion of the manuscript or figures: N.A.M., C.H., J.H.-R., R.H., and B.D.

## Potential Conflicts of Interest

Nothing to report.

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