


RESEARCH ARTICLE

Altered brain glucose metabolism and connectivity in young adults with obstructive sleep apnea

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Abstract

INTRODUCTION: Obstructive sleep apnea syndrome (OSAS) is a recognized risk factor for neurodegenerative disorders. However, a causal link between OSAS and brain damage has yet to be established.

METHODS: Thirty cognitively normal patients with moderate-to-severe OSAS, free from systemic or neurological comorbidities, were enrolled and underwent ¹⁸F-fluorodeoxyglucose positron emission tomography imaging. Their scans were compared to those of cognitively normal, OSAS-free controls from the Alzheimer's Disease Neuroimaging Initiative database. Additional analyses included commonality mapping, correlations with polysomnographic parameters, and seed-based metabolic connectivity of major resting-state networks.

RESULTS: Group-level analyses showed fronto-parietal glucose hypometabolism and cerebellar glucose hypermetabolism in patients with OSAS compared to controls. Cerebellar glucose hypermetabolism was associated with reduced rapid eye

Silvia P. Caminiti and Mariana Fernandes contributed equally to this work.

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movement sleep latency and duration. Seed-based connectivity analysis revealed alterations in attentional and limbic networks.

DISCUSSION: Moderate-to-severe OSAS may represent a cause of brain dysfunction, highlighting the importance of its early diagnosis and appropriate treatment to prevent worsening brain damage and possible future neurodegenerative processes.

KEYWORDS

¹⁸F fluorodeoxyglucose positron emission tomography, attentional network, cerebellum, cognition, frontal lobe, limbic network, parietal lobe, polysomnography, rapid eye movement sleep

Highlights

- Moderate-to-severe obstructive sleep apnea syndrome (OSAS) is associated with altered brain glucose metabolism.
- Cerebellar glucose hypermetabolism is associated with rapid eye movement sleep impairment.
- Attentional and limbic networks connectivity is disrupted in moderate-to-severe OSAS.
- Early recognition of patients with moderate-to-severe OSAS has the potential to overcome the risk of worsening brain damage that may lead to neurodegeneration.

1 | BACKGROUND

Obstructive sleep apnea syndrome (OSAS) is the most frequent sleep-disordered breathing (SDB) and is a highly prevalent sleep disorder in adults and the elderly.¹ Resting-state brain glucose metabolism using ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) is a widely used technique providing information on neuronal dysfunction. However, few studies have used cerebral ¹⁸F-FDG PET for investigating neuronal dysfunction in patients with OSAS, and studies have documented both a reduction²⁻⁴ and an increase^{3,5} of glucose metabolism in frontal, temporal, and parietal regions, including the precuneus and posterior cingulate cortex. These heterogeneous results may be due to differences in study designs, to the lack of healthy controls (HCs) as a comparison group, and to the inclusion of small subject groups with different degrees of OSAS severity. Additionally, the frequent presence of other systemic and neurological comorbidities affecting patients with OSAS may further impair cerebral functioning,⁶⁻⁸ contributing to the variability of the findings. Consistently, OSAS is recognized as a risk factor for cognitive impairment due to its direct impact on brain health.⁹ Studies have also linked it to an increased risk of neurodegeneration, particularly dementia and Alzheimer's disease (AD).¹⁰ Both nocturnal intermittent hypoxia and sleep dysregulation can impair synaptic function and brain glucose metabolism, as measured by cerebral ¹⁸F-FDG PET.^{11,12} Moreover, OSAS has been shown to cause both vascular injury, due to sudden sympathetic-mediated pressure spikes, and intermittent hypoxic damage directly linked to apneas and hypop-

neas. These events contribute to neuronal damage, a key driver of neurodegeneration.^{9,11}

Therefore, the present study aimed to analyze the effects of moderate-to-severe OSAS on brain function measured by ¹⁸F-FDG PET in subjects cognitively unimpaired and without other systemic or neurological disorders, who were compared to a group of HCs, cognitively intact and OSAS-free.

2 | METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

Patients provided written informed consent at the time of study entry and at follow-up. This study obtained ethics approval from the ethical committee of the University Hospital of Rome Tor Vergata (RS 189/21).

2.2 | Participants and study procedures

Thirty consecutive patients were recruited from the neurology unit of the University Hospital of Rome Tor Vergata, where they had been referred for the evaluation of OSAS. As part of the standard evaluation, all patients underwent a study protocol including sleep medicine visit, physical and neurological examination, neuropsychological and cognitive testing, polysomnographic (PSG) recording, and brain magnetic resonance imaging (MRI). The criteria for enrollment

RESEARCH IN CONTEXT

- 1. Systematic review:** To date, no study has assessed cerebral glucose metabolism in cognitively unimpaired patients with moderate-to-severe obstructive sleep apnea syndrome (OSAS), free from other neurological or systemic diseases, compared to OSAS-free cognitively normal controls.
- 2. Interpretation:** The significant brain glucose hypometabolism consistently found in the middle fronto-parietal and subcortical regions of patients with OSAS, compared to controls, highlights initial impairment of brain glucose metabolism, proxy of synaptic dysfunction. These findings were confirmed by group-level analyses showing fronto-parietal glucose hypometabolism alongside relative cerebellar glucose hypermetabolism. Notably, cerebellar glucose hypermetabolism was associated with rapid eye movement sleep impairment, characterized by reduced latency and duration. Furthermore, seed-based connectivity analysis revealed alterations in attentional and limbic networks in patients with moderate-to-severe OSAS.
- 3. Future directions:** These results provide a rationale for the early identification of OSAS in clinical settings, as appropriate treatments are available and may mitigate the risk of neurodegeneration characterized by brain glucose metabolism impairment.

in this study included moderate-to-severe OSAS (apnea-hypopnea index [AHI] ≥ 15 /hour); no concomitant neurological, psychiatric, and sleep disorders; and no use of drugs active on the central nervous system. Exclusion criteria included hypertension, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, according to the European Society of Cardiology and consistent with previous publications.^{13,14} Additional exclusion criteria were systemic diseases, heavy smoking, bronchial asthma, chronic obstructive pulmonary disorders and/or interstitial lung diseases, mild cognitive impairment or dementia (Clinical Dementia Rating > 0.5 ¹⁵ and Mini-Mental State Examination < 24),¹⁶ any conditions potentially affecting cognitive performance, a history of alcohol or substance abuse, brain atrophy, and white matter hyperintensities (WMHs) documented by a Fazekas score ≥ 2 .¹⁷ Moreover, subjects with a long-lasting symptom history of OSAS were excluded.

3 | DATA COLLECTION AND STATISTICAL ANALYSIS

3.1 | PSG

All patients underwent PSG recording to evaluate nocturnal sleep (SOMNOscreen, SOMNOmedics GmbH). Standard sleep and oxygen

parameters were computed, and sleep stages were calculated as percentages of total sleep time (TST). Apneas were defined as a reduction of $\geq 90\%$ of respiratory airflow for ≥ 10 seconds, while hypopneas were determined as the reduction of $\geq 30\%$ of respiratory airflow for ≥ 10 seconds associated with an oxygen desaturation of $\geq 3\%$. The sum of all apnea and hypopnea events were then distributed on the TST and the AHI was calculated. Only patients with an AHI ≥ 15 /hours of sleep were included in this study. Based on sleep stages, AHI was distinguished in AHI-REM (events in rapid eye movement sleep) and AHI-NREM (events in non-REM sleep). PSG recordings were scored by experts in sleep medicine (C.L., N.M.) based on the international standard criteria of the American Academy of Sleep Medicine.¹⁸

3.2 | Brain MRI

All patients with OSAS had a baseline brain MRI assessment for clinical purposes. The MRI exam was performed using a 3T super-conductive system (Achieva 3T, Philips Healthcare) equipped with a dedicated 32-channel sensitivity encoding head coil. The acquisition protocol included three-dimensional T1-weighted, magnetization prepared rapid gradient echo (MPRAGE) images. MPRAGE images were acquired using the following parameters: field of view (FOV) 256×256 mm², repetition time (TR) 6.5 ms, echo time (TE) 2.9 ms, flip angle 9° , and voxel size $1 \times 1 \times 1$ mm³ and axial T2-weighted turbo spin echo images (TR = 3000 ms, TE = 80 ms, and thickness/gap = 4/1 mm), fluid attenuation inversion recovery (FLAIR) 3D (voxel size = $1.12 \times 1.12 \times 1.12$ mm³, TR = 4800 ms, TE = 340 ms, flip angle = 40° , FOV = 250×250 mm²).

Additionally, axial T2-weighted turbo spin echo images (TR = 3000 ms, TE = 80 ms, and thickness/gap = 4/1 mm) and diffusion weighted imaging were acquired and evaluated by an expert neuroradiologist to exclude the presence of pathological findings. The participants were categorized based on the severity of white matter lesions (WMLs) according to the Fazekas scale.¹⁷ Two neurologists (C.L., N.M.) and a neuroradiologist (F.D.G.), blinded to the clinical characteristics of the study participants, independently performed the visual grading of WMLs using the Fazekas scale. The severity of the WMLs was visually rated on T2-weighted and FLAIR images according to the Fazekas scale: absence (grade 0), punctuate (grade 1), early-confluent (grade 2), confluent (grade 3). Only patients with Fazekas score < 2 were included in the study.

3.3 | ¹⁸F-FDG PET

3.3.1 | ¹⁸F-FDG PET single-subject procedure

The patients enrolled performed ¹⁸F-FDG PET to assess brain glucose metabolism. The single-subject ¹⁸F-FDG PET procedure was performed through Statistical Parametric Mapping (SPM) 12 software (MATLAB).

Each ¹⁸F-FDG PET image was spatially normalized using a ¹⁸F-FDG PET template.¹⁹ The normalized image underwent smoothing with a

3D Gaussian kernel (full width half-maximum: 8–8–8 mm), and global mean scaling was applied to account for intersubject uptake variability, yielding standardized uptake value ratio (SUVR) values. Subsequently, the normalized and smoothed image underwent testing for relative brain hypometabolism using a SPM two-sample *t* test. This involved comparing the individual subject's image to a large ¹⁸F-FDG PET dataset of HCs, considering age as a nuisance covariate.²⁰ The resulting SPM maps (*t* maps) were thresholded at peak-level *P* value < 0.05 (minimum cluster extent of 100 voxels).²⁰

The HC dataset included individuals with normal global cognition from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).²¹ In accordance with a previous study,²² the presence or absence of OSAS was determined from the ADNI medical history item MHDESC during the clinical interview, and individuals with self-reported "sleep apnea", "sleep-disordered breathing", "OSA", or other sleep disorders were excluded from the analysis.²²

3.3.2 | ¹⁸F-FDG PET commonalities

A voxel-wise map of commonalities was computed through one-sample *t* test in SPM12 to evaluate the degree of overlap between the single-subject glucose hypometabolism patterns obtained in the whole OSAS group. The commonality value of each voxel was computed as the proportion of patients in which that specific voxel was found to be hypometabolic. The resulting map was thresholded for cluster-level significance at *P* < 0.05 family wise error (FWE) corrected, with a peak-level *P* value < 0.001 uncorrected and cluster extent > 100 voxels. ¹⁸F-FDG PET standardized uptake values, extracted from the commonalities mask for each patient, were adjusted for age and education by regressing out their effects using a linear model to calculate the residuals. The residuals obtained from patients and HCs were then statistically compared using the Mann–Whitney *U* test.

Moreover, we conducted a sensitivity voxel-wise analysis in SPM12 to identify regions of glucose hypometabolism and glucose hypermetabolism in patients with OSAS compared to the HCs, with age and education included as covariates of non-interest. An exploratory threshold of *P* < 0.01 uncorrected and a cluster extent > 100 voxels was applied.

JuBrain Anatomy Toolbox (<https://github.com/inm7/jubrain-anatomy-toolbox>) was adopted for results anatomical localization.

3.3.3 | ¹⁸F-FDG PET metabolic correlations

For each patient, ¹⁸F-FDG PET SUVR were extracted from the glucose hypometabolism and glucose hypermetabolism masks obtained through the SPM voxel-wise analysis and subsequently correlated offline with PSG sleep parameters using Spearman correlation.

3.3.4 | ¹⁸F-FDG PET metabolic connectivity

Metabolic connectivity analysis was used to extract resting-state networks (RSNs) for both the OSAS and HC groups.

RSN metabolic connectivity was obtained through voxel-wise seed-based interregional correlation analysis.²³ Seed regions were selected for the large-scale networks as previously identified by extensive literature:^{24–26} the ventro-medial frontal cortex for the anterior default mode network (aDMN), the posterior cingulate cortex and precuneus for the posterior DMN (pDMN), the dorsolateral prefrontal cortex for the executive network (EXN), the angular and supramarginal gyri for the attentional network (ATN), and the amygdala for the limbic network (LIN). Seed regions of interest were derived from the Automated Anatomical Labeling atlas²⁷ and functional RSNs atlas,²⁶ using the REX toolbox to extract the mean regional glucose metabolism value from each seed. For each network, the seed uptake was set as the variable of interest in a multiple regression model in SPM12, entering age as a covariate of nuisance to test whole-brain voxel-wise correlations. Statistical significance was set at a voxel-wise threshold of *P* < 0.001 (uncorrected), with a cluster-level correction for multiple comparisons at *P* < 0.05 (FWE corrected). Only clusters extending over a minimum of 100 contiguous voxels were considered significant.²³ Differences in network extension and topography were measured through the Dice similarity coefficient index.²⁸ In addition to the direct comparison to the OSAS-free HC group, the spatial correspondence of RSNs was further evaluated against an independent, validated template to ensure that our findings were not exclusively dependent on the demographics of our HC cohort. Specifically, the Network Correspondence Toolbox (NCT; Python implementation, `cbig_network_correspondence`, 2024) was used to compute Dice similarity coefficients between the RSNs identified in our sample and the canonical Yeo 7-network template.²⁹ This complementary approach allowed us to validate the topographical organization of RSNs using a widely adopted reference atlas, thereby providing a robust benchmark independent of our HC group.

4 | RESULTS

4.1 | Demographic and clinical data

Thirty patients affected by moderate-to-severe OSAS (76.67% male, mean age of 46.87 ± 11.89 years) were recruited for this study. The HC cohort included 68 participants (55.9% males; mean age ± standard deviation: 72.4 ± 5.2 years). Demographic, clinical, and PSG data of patients with moderate-to-severe OSAS and HC are reported in Table 1.

4.2 | ¹⁸F-FDG PET results

4.2.1 | Single-subject and group SPM analysis

At single-subject level, SPM *t* maps revealed in most cases cortical patterns of glucose hypometabolism, mainly involving fronto-parietal cortex (Figure 1A). Consistently, commonalities analysis showed glucose hypometabolism involving precentral gyrus, middle and medial frontal gyri, supplementary motor area, anterior cingulate gyrus,

TABLE 1 Demographic, clinical, and PSG data of patients with OSAS and healthy controls.

	OSAS patients (n = 30)		HC (n = 68)	
	Mean	Standard deviation	Mean	Standard deviation
Demographic and clinical data				
Male, n. (%)	23 (76.67%)		38 (55.9%)	
Age (years)	46.87	11.89	72.40	5.25
Education level (years)	13.67	2.76	16.56	2.52
MMSE	28.56	1.34	28.91	1.46
PSG data				
Time in bed (min)	428.66	72.84	NA	
Total sleep time (min)	359.91	73.59	NA	
Sleep efficiency (%)	84.04	10.16	NA	
Sleep latency (min)	11.90	18.89	NA	
REM latency (min)	86.48	66.49	NA	
% REM	18.26	5.79	NA	
% N1	4.72	2.82	NA	
% N2	56.94	8.93	NA	
% N3	20.09	9.19	NA	
WASO (min)	69.70	47.91	NA	
AHI	41.07	17.42	NA	
AHI-REM	43.38	21.05	NA	
AHI-NREM	37.12	18.10	NA	
ODI	33.28	17.60	NA	
Mean SpO2 (%)	93.67	1.67	NA	
SpO2 nadir (%)	81.80	7.34	NA	
% of time with SpO2 < 90%	7.16	9.96	NA	

Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; HC, healthy control; MMSE, Mini-Mental State Examination; N1, stage 1 of non–rapid eye movement sleep; N2, stage 2 of non–rapid eye movement sleep; N3, stage 3 of non–rapid eye movement sleep; NREM, non–rapid eye movement sleep; ODI, oxygen desaturation index; OSAS, obstructive sleep apnea syndrome; PSG, polysomnography; REM, rapid eye movement; SpO2, oxygen saturation; WASO, wake after sleep onset.

superior parietal gyrus, parietal operculum, supramarginal gyrus, precuneus, fusiform gyrus, hippocampus, and thalamus (Figure 1B). Offline, the Mann–Whitney U test confirmed significant differences in this glucose hypometabolic pattern between patients with moderate-to-severe OSAS and HC ($U = 1227$, $z = 2.22$, $P = 0.027$; Figure 1C).

The voxel-wise group analysis identified fronto-parietal glucose hypometabolism in OSAS compared to HCs. In addition, glucose hypermetabolism voxels were observed in the cerebellum (Figure 2).

4.3 | Correlations between brain glucose metabolism and sleep parameters

Cerebellar glucose hypermetabolism significantly correlated with lower REM latency (minutes; $\rho = -0.41$; $P = 0.03$) and a lower % REM duration ($\rho = -0.48$; $P = 0.01$; Figure 3).

4.4 | Connectivity

Relative to the HC group, patients with moderate-to-severe OSAS exhibited decreased spatial similarity across networks, with the lowest Dice coefficients found in the ATN (Dice = 0.144) and LIN (Dice = 0.282). All other networks showed Dice values > 0.3. In line with these results, the spatial overlap with the Yeo 7-network template revealed that all networks except the ATN and LIN showed significant spatial correspondence (ATN: Dice = 0.109, $P = 0.217$; LIN: Dice = 0.013, $P = 0.244$; Figure 4).

5 | DISCUSSION

The present brain ^{18}F -FDG PET study was performed in relatively young and cognitively normal patients with moderate-to-severe OSAS, without systemic or neurological comorbidities, and compared to OSAS-free and cognitively normal age- and sex-matched HCs. Notably,

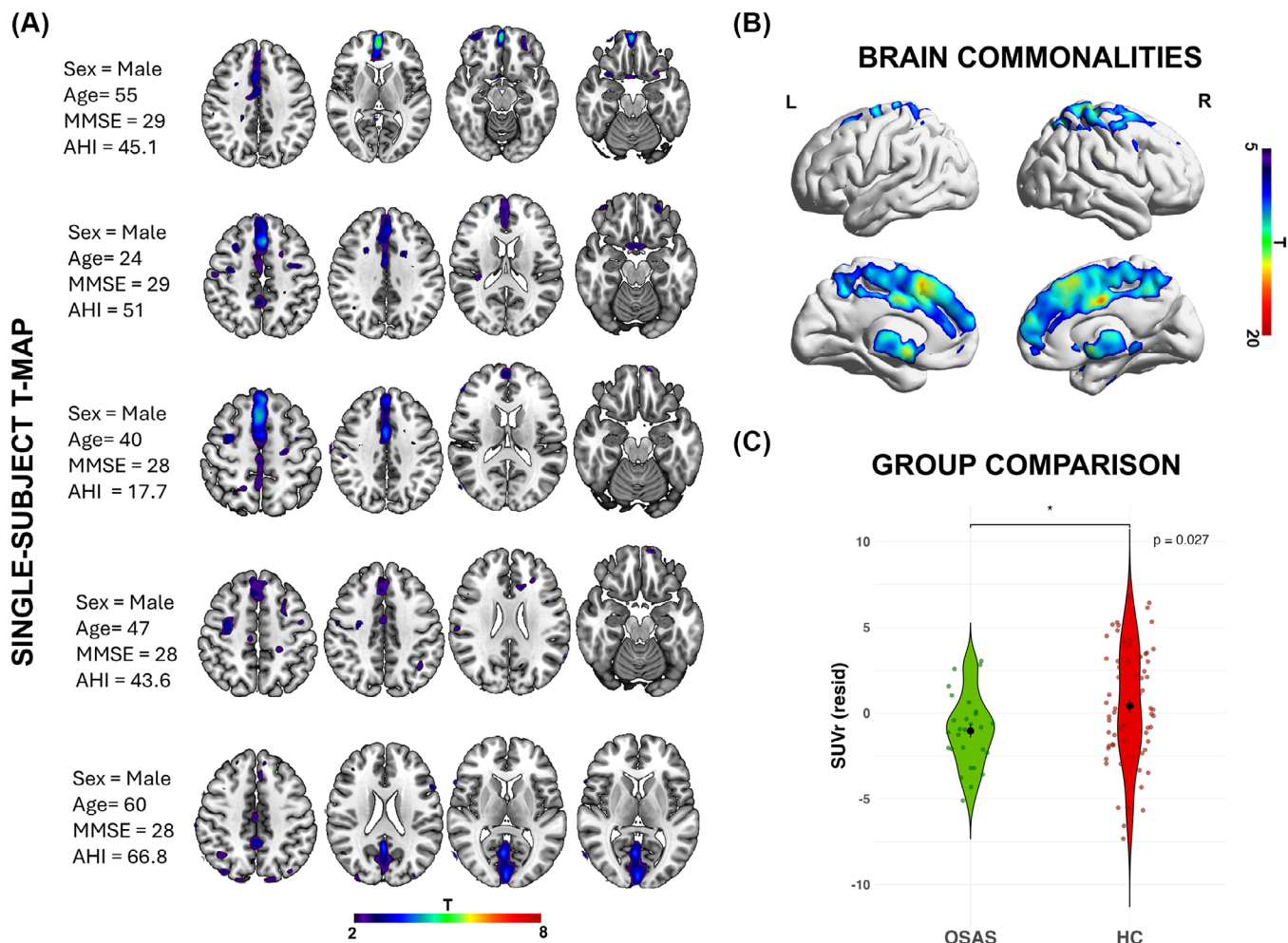


FIGURE 1 Brain glucose hypometabolism in OSAS. A, Examples of single-subject glucose hypometabolic *t* maps. B, Common regions of glucose hypometabolism across subjects. C, Offline statistical comparisons of OSAS cohort with OSAS-free healthy control group. Subject-level SPM *t* maps were obtained using SPM12 voxel-wise comparisons against a pool of 68 HCs, controlling for age. Both the group-level and single-subject analyses revealed predominant middle fronto-parietal glucose hypometabolism in OSAS. The offline comparison, adjusted for age and education, confirmed significantly reduced glucose metabolism in OSAS patients compared to HCs. AHI, apnea-hypopnea index; HCs, healthy controls; MMSE, Mini-Mental State Examination; OSAS, obstructive sleep apnea syndrome; SUVr, standardized uptake value ratio.

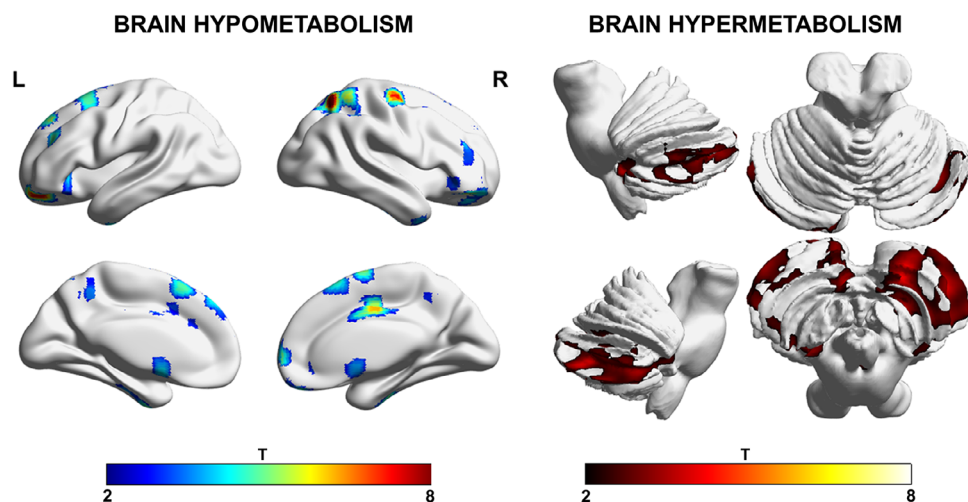


FIGURE 2 Voxel-wise group comparison between patients with OSAS and HCs, with age and education as covariates. OSAS subjects showed significant fronto-parietal glucose hypometabolism along with cerebellar hypermetabolism. Exploratory threshold was set at $P < 0.01$ uncorrected, $ke > 100$. OSAS, obstructive sleep apnea syndrome; HCs, healthy controls.

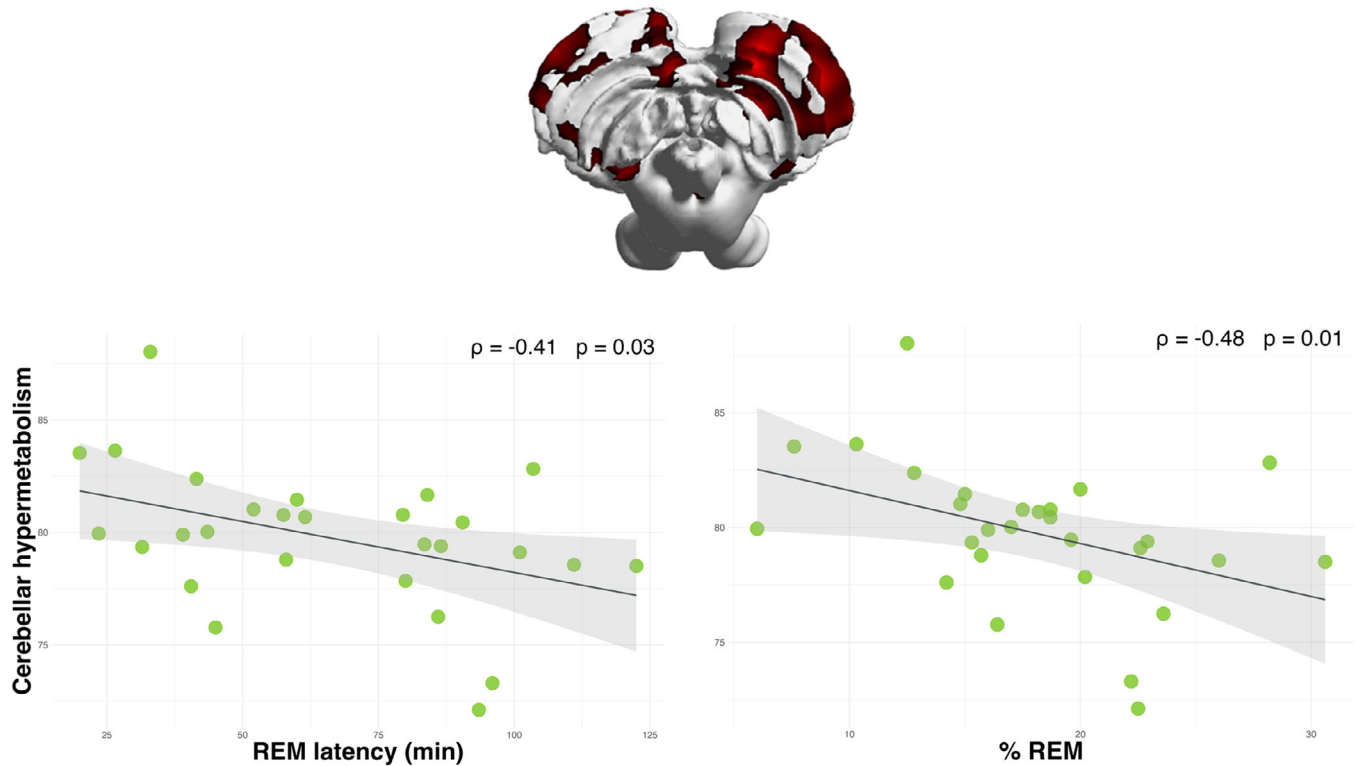


FIGURE 3 Associations between sleep parameters and brain glucose metabolism. Correlation analyses in the OSAS group showed an inverse relationship between REM latency (minutes) and cerebellar glucose hypermetabolism (left), and between percentage of REM sleep (% REM) and cerebellar glucose hypermetabolism (right). OSAS, obstructive sleep apnea syndrome; REM, rapid eye movement.

it demonstrated a common pattern of glucose hypometabolism in fronto-parietal cortex and glucose hypermetabolism in the cerebellum of patients with OSAS compared to HCs. The correlation analysis in the OSAS group between PSG and ^{18}F -FDG PET data showed a significant correlation between higher glucose uptake in the cerebellum and lower REM latency and duration.

OSAS can negatively impact brain glucose metabolism measured by cerebral ^{18}F -FDG PET; however, literature reports non-consistent and disparate results. Here, a reduced ^{18}F -FDG uptake in a large cluster of frontal-parietal brain areas was shown, consistent with a few previous studies aimed at evaluating the brain glucose metabolism in patients with OSAS compared to controls.^{3,4} As a novelty of the present study, a significant glucose hypometabolism was found in the supplementary motor area (SMA) and superior parietal cortex. SMA is neuronally connected to the medial prefrontal cortex, which is also metabolically impaired in patients with OSAS, as found in the present study. The anatomical and functional interaction between these two brain areas may also help explain the simultaneous glucose hypometabolic involvement of these brain regions in moderate-severe OSA.³⁰ In addition, the glucose hypometabolism in the superior parietal cortex may also reflect a regional dysfunction caused by the sleep disorder, which is not clinically manifest at this stage but may further proceed over the disease course.

We also found in patients hippocampal glucose hypometabolism, suggesting the possibility of increased vulnerability of memory circuits to OSAS-related insults, particularly intermittent hypoxia, which

impairs hippocampal neurogenesis and synaptic plasticity.³¹ Moreover, the thalamus, another region showing glucose hypometabolism in patients with OSAS compared to HCs in the present analysis, is among the areas sensitive to oxygen desaturation and plays a central role in regulating arousal and sleep-wake transitions.³²⁻³⁴ Thalamic dysfunction may therefore mediate some of the attentional deficits frequently observed in OSAS. Collectively, these findings support the view that OSAS induces widespread but selective metabolic vulnerability, targeting cortical-subcortical loops crucial for both cognition and sensorimotor function.

From a mechanistic perspective, the association between OSAS and brain alterations is bidirectional, with one that can exacerbate the other.³⁵ Indeed, the consequence of disrupted sleep and intermittent hypoxia is to increase the amount of wakefulness during sleep and to decrease the amount of sleep per se. Subsequently, greater neuronal activity and reduced brain clearance function may result in the alteration of brain glucose metabolism. If increased activity and reduced clearance are likely to coexist, their respective contributions are still unclear. In keeping with this evidence, the potential degenerative process triggered by OSAS has been previously highlighted, coupled with the presence of cognitive deficits and alteration of cerebrospinal fluid and neuroimaging markers for amyloid pathology in patients with OSAS.⁹ In particular, disrupted sleep has been demonstrated to induce glutamate-mediated excitotoxicity, altered interstitial clearance mediated by the glymphatic system, and impaired synaptic dysfunction.³⁶ Moreover, intermittent hypoxia has a negative impact on neurons

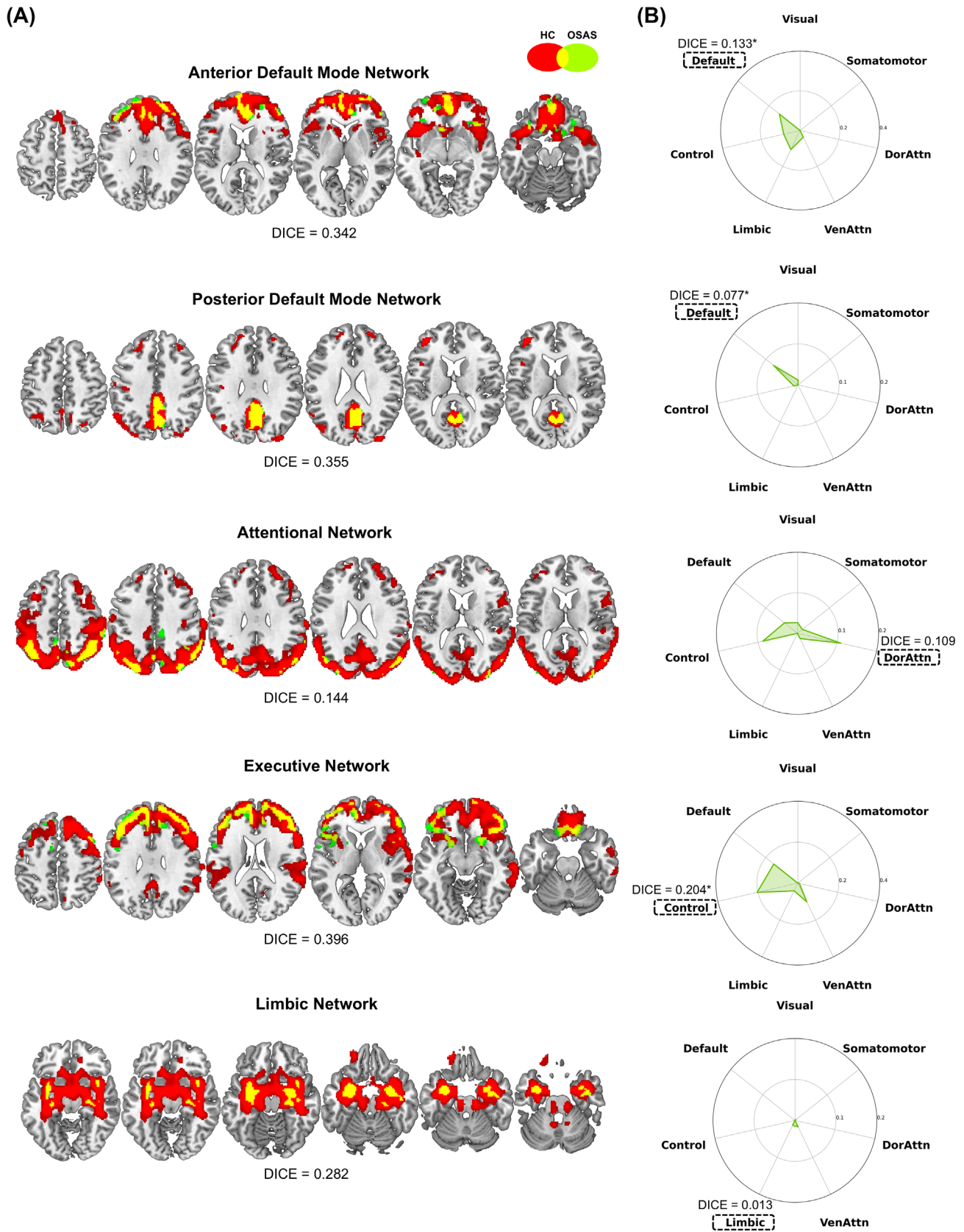


FIGURE 4 Resting-state networks (RSNs) in OSAS and HCs. A, Spatial maps of RSNs in OSAS (green) and HCs (red), overlaid on the anatomical template; voxels of overlap are shown in yellow. B, Radar plots illustrate Dice coefficients quantifying spatial overlap between RSNs. * $P < 0.05$. OSAS, obstructive sleep apnea syndrome; HC, healthy control.

because it increases oxidative stress and neuroinflammation, eventually leading to neuronal death.³⁷ For all these reasons, OSAS can rightly be considered a risk factor for future development of cognitive impairment and dementia, in particular, vascular or AD related.^{9,38}

In the present analysis, cerebellar glucose hypermetabolism was observed in patients with moderate-to-severe OSAS compared to HCs, which was significantly associated with reduced REM latency and duration. This result highlights the potential vulnerability of the cerebellum in OSAS.³⁹⁻⁴¹ Alteration in REM structure was indeed accompanied by an increase in cerebellar glucose metabolism, possibly reflecting a compensatory response maintaining REM-related functions in the context of disrupted sleep. Some preclinical and clinical evidence shows that the cerebellum is sensitive to hypoxia.^{42,43} Intermittent hypoxia, a central mechanism of OSAS, could therefore compromise cerebellar function over time. In line with this, our finding of cerebellar glucose hypermetabolism may represent a preclinical stage of compensation, whereby increased activity is required to preserve the cerebellar functions during sleep. Over time, this maladaptive process may determine metabolic exhaustion, finally resulting in structural degeneration. Moreover, reduced REM latency and duration may trigger enhanced cerebellar recruitment, as the cerebellum contributes to REM-related oculomotor activity and autonomic regulation.³⁹ Conversely, excessive cerebellar activation could disrupt normal REM sleep processes, contributing to the sleep fragmentation observed in OSAS. Finally, considering that REM latency physiologically decreases following prolonged sleep deprivation or disruption,⁴⁴ the association observed between increased cerebellar glucose metabolism and reduced REM latency in OSAS patients further suggests an impairment of cerebellum activity resulting from OSAS-induced chronic sleep disruption.

It is important to note that metabolic connectivity analysis was performed in patients with moderate-severe OSAS to investigate the potential disruption of the interconnection within the major brain networks. Consistently, this analysis showed a reduction in spatial similarity across networks when comparing patients with OSAS and HCs, with the most pronounced alterations in ATN and LIN. Alterations in the ATN and LIN of subjects with OSAS have consistently been reported by other independent research groups.^{45,46} Supporting this evidence, attentional dysfunction, a cognitive domain associated with ATN impairment, has already been documented in subjects with moderate-to-severe OSAS.⁴⁷ A similar alteration has also been observed in patients with early-stage AD, in whom concomitant involvement of the attentional network has been reported.⁴⁸ Likewise, a primary involvement of the limbic system in subjects with OSAS has been demonstrated in association with mild cognitive decline,⁴⁹ further highlighting a potential shared neurobiological substrate between the two nosological entities.

All these brain findings may be considered prodromal to further neuronal damage or possibly neurodegeneration. Accordingly, if the OSAS-induced insult persists, also in conjunction with other factors potentially damaging the brain in predisposed individuals, the cognitive consequences of vascular or AD pathology can become manifest,

initially as subjective cognitive complaints, and then as a mild cognitive impairment, further progressing to dementia. Notably, OSAS can be treated by continuous positive airway pressure (CPAP), which can restore sleep and potentially prevent the risk of future cognitive impairment and dementia. As evidence for this, some studies have shown partial reversibility of clinical, functional, and structural brain changes after CPAP treatment.^{3,6-8} Therefore, an early diagnosis of OSAS is necessary and mandatory at young adult age, as it is possible to take advantage of effective treatments that can not only improve the clinical OSAS-related symptomatology but also possibly delay (or prevent) brain damage.

Our study, however, has some limitations that should be acknowledged. Our data need to be confirmed by other similar controlled investigations, including larger groups of patients, also to corroborate the evidence of the present study, preferably combined with the analysis of other markers, such as the assessment of cerebral amyloid burden. Although brain MRI was performed to exclude signs of brain atrophy and WMHs, a quantitative measure of brain atrophy was missing and only Fazekas classification was reported. Future studies should also consider measuring brain atrophy or white matter damage to better assess the cerebrovascular component in patients with OSAS. Finally, the absence of follow-up, especially without a determination of the effects of CPAP treatment, does not provide a full confirmation of the potential reversibility of the brain functional changes here described, although in a previous study by our group involving another subset of patients, the improvement of brain glucose metabolism after 12 months of CPAP treatment was demonstrated.⁸

Nevertheless, there are some strengths of this study and precisely: selected patients, relatively young without cognitive impairment, in the absence of neurological or systemic comorbidities; ¹⁸F-FDG PET voxel-wise analyses, also in correlation with PSG sleep measures; and, for the first time, a connectivity analysis of the major brain networks, providing quantitative data with high statistical power. Finally, ¹⁸F-FDG PET was performed in all patients close to the diagnosis of OSAS, consequently allowing us to provide a neuroimaging picture reflecting brain metabolism in a narrow time window.

In conclusion, our findings demonstrate that young adults, who are cognitively normal, with moderate-to-severe OSAS and without other systemic comorbidities, can present with alterations of brain glucose metabolism, probably due to neuronal damage induced by intermittent hypoxia and sleep dysregulation. These findings can also be interpreted as the early manifestation of a future neurodegenerative process, mostly coincident with AD-like pathology. This aspect highlights the importance of the early identification of OSAS in clinical settings, as CPAP treatment may correct the cognitive deficit, improve brain glucose metabolism, and possibly prevent neurodegeneration.

AUTHOR CONTRIBUTIONS

C.L.: conceptualization of the study. M.F., A.C., R.C., C.L.: study design and patient selection. M.F. and S.P.C.: data analysis. S.P.C., M.F., C.Z.: preparing the first draft. D.P., C.L.: revising the draft and critical intellectual content. M.D.A., N.B.M.: study supervision.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest or financial disclosures. Any author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

All subjects enrolled provided informed consent.

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