RESEARCH ARTICLE

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Differential effects of sleep on brain structure and metabolism at the preclinical stages of AD

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Abstract

INTRODUCTION: Poor sleep quality is associated with cognitive outcomes in Alzheimer's disease (AD). We analyzed the associations between self-reported sleep quality and brain structure and function in cognitively unimpaired (CU) individuals.

METHODS: CU adults ($N = 339$) underwent structural magnetic resonance imaging, lumbar puncture, and the Pittsburgh Sleep Quality Index (PSQI) questionnaire. A subset ($N = 295$) performed [18F] fluorodeoxyglucose positron emission tomography scans. Voxel-wise associations with gray matter volumes (GMv) and cerebral glucose metabolism (CMRGlu) were performed including interactions with cerebrospinal fluid (CSF) AD biomarkers status.

RESULTS: Poorer sleep quality was associated with lower GMv and CMRGlu in the orbitofrontal and cingulate cortices independently of AD pathology. Self-reported sleep quality interacted with altered core AD CSF biomarkers in brain areas known to be affected in preclinical AD stages.

DISCUSSION: Poor sleep quality may impact brain structure and function independently from AD pathology. Alternatively, AD-related neurodegeneration in areas involved in sleep–wake regulation may induce or worsen sleep disturbances.

KEYWORDS

cerebrospinal fluid biomarkers, fluorodeoxyglucose positron emission tomography, preclinical Alzheimer's disease, sleep, structural magnetic resonance imaging

Highlights

- Poor sleep impacts brain structure and function independent of Alzheimer's disease (AD) pathology.
- Poor sleep exacerbates brain changes observed in preclinical AD.
- Sleep is an appealing therapeutic strategy for preventing AD.

1 | BACKGROUND

Sleep disturbances are prevalent in Alzheimer's disease (AD) with sleep quality already being impaired in its earliest stages.[1] A bidirectional relationship between sleep and AD has been postulated, with epidemiological evidence that poor sleep quality is associated with an increased risk of AD.[2,3] Furthermore, both shorter and longer sleep times,[4,5] sleep fragmentation,[6] and excessive daytime sleepiness[7] have been linked to altered cerebral spinal fluid (CSF) AD biomarkers in cognitively unimpaired (CU) individuals.[8]

Accordingly, studies using neuroimaging metrics support the association of different sleep disturbance phenotypes with an increased risk of AD.

Structural imaging data showcase subjective poor sleep quality to be associated with lower gray matter volume (GMv) in frontal, medial-temporal, and parietal regions[9] cross-sectionally, as well as greater fronto-temporal-parietal atrophy longitudinally[10] in CU older adults. Additionally, accelerated cortical thinning in the middle temporal gyrus has been associated with self-reported poor sleep quality and sleep disturbances.[11] Notably, many of the aforementioned regions are known to undergo atrophy in AD, which could be explained by the potential role of sleep deprivation in promoting AD pathology.[2] Alternatively, sleep alterations may impact cerebral structure through other mechanisms, such as neuroinflammation.[12]

Sleep fragmentation has also been associated with lower GMv in the insula,[13] the thalamus,[14] and the orbitofrontal cortex (OFC).[15,16] The latter brain region is crucial for the genesis of slow waves and sleep spindles that stand at the core of sleep-dependent memory consolidation.[17]

Research in insomnia patients has found lower GMv in the OFC and the precuneus/posterior cingulate cortex (PCC) region,[18,19] the latter being particularly vulnerable to cognitive deterioration and AD.[20] Conversely, higher glucose uptake has been discovered in wake-promoting regions (i.e., the ascending reticular activating system, hypothalamus, and thalamus) in insomnia, potentially linking this disorder to an inefficient regulation in these systems.[21]

Obstructive sleep apnea (OSA), a condition associated with aging and increased AD risk,[22] has also shown inconsistent patterns across neuroimaging studies. A meta-analysis reported lower GMv in various regions (including the OFC, anterior cingulate [ACC]/paracingulate gyrus, hippocampus, and cerebellar regions),[23] whereas other studies demonstrated higher volumes or cortical thickness in frontal, parietal, and cingular regions, including AD vulnerable regions, like the precuneus and PCC.[24–26] Regarding functional studies, Fernandes et al.[27] demonstrated lower brain glucose metabolism in patients with OSA involving the precuneus/PCC area, which aligns with previously reported patterns of decreased hypometabolism in OSA patients across frontoparietal and parieto-occipital regions.[28,29] Conversely, André et al.[25] reported heightened brain metabolism and perfusion encompassing the above-mentioned regions, including the bilateral precuneus, PCC, and lingual areas. Importantly, the authors reported increased amyloid deposition and higher GMv in the same regions, suggesting a potential underlying pathway linking OSA and AD via the neuroinflammatory process. Other potential mechanisms potentially driving OSA-induced brain structural and functional changes include intermittent hypoxia, oxidative stress, and sleep fragmentation.[25,30,31]

Last, the apparent heterogeneity among studies' results may stem from (1) the variability between sleep measurement techniques

(i.e., objective vs. subjective) used in different studies, as well as (2) the differences deriving from variability in age groups investigated by different research groups.

Although the current knowledge of the relationship between sleep and AD provides promising and compelling insights, underlying mechanisms remain elusive. Moreover, there is huge heterogeneity in the topography and directionality of brain regional changes in association with various sleep disturbances. Finally, there is a lack of evidence on the relationship among sleep quality, structural brain integrity, and brain glucose metabolism in the preclinical stages of AD.

Such studies could improve our understanding of the underlying causes of the observed associations between sleep quality and brain changes in preclinical AD. Unraveling this bidirectional relationship may pave the way for developing sleep-focused preventive strategies and treatments targeting the early stages of the disease, as well as improving its early diagnosis.

Thus, this study aimed to shed light on this by investigating the relationship between self-reported sleep quality and cerebral structure and glucose metabolism in CU individuals. Our main hypothesis was that poor self-reported sleep quality would be associated with more deleterious neuroimaging phenotypes, mainly denoted by lower GMv and lower cerebral glucose consumption. However, we explored associations in both directions (poor self-reported sleep quality being associated with either higher or lower GMv and cerebral glucose metabolism [CMRGlu]), because patterns of higher GMv, cortical thickness, and brain metabolism have been previously reported in association with different sleep disorders.[19,24,25] Owing to the previously described overlap in neuroimaging findings in the sleep and AD research fields, we expected that the presence of AD pathology would modify the association between self-reported sleep quality and brain structure and function in regions that are known to be affected by AD.

To test these hypotheses, we undertook a multimodal approach using a combination of GMv and glucose metabolism that provides different but complementary information about cerebral integrity together with CSF biomarkers to unravel the potential role of AD pathology markers in these associations.

2 | METHODS

2.1 | Study participants

Participants' data used for this study were acquired from the ALFA+ cohort, a study nested in the ALFA (Alzheimer's and Families project) parent cohort.[32] The ALFA+ participants underwent a comprehensive evaluation including clinical, lifestyle, and cognitive assessments; lumbar puncture; neuroimaging acquisition (including magnetic resonance imaging [MRI], amyloid beta [Aβ], and [18F] fluorodeoxyglucose positron emission tomography [FDG PET]); as well as genetic characterization and medications that may affect central nervous system (CNS) functioning (defined as at least one prescription of psycholeptics, psychoanaleptics, and/or antiepileptics, as classified by the Anatomical Therapeutic Chemical convention). Key exclusion criteria included

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using traditional sources (e.g., PubMed) as well as insights based on the presentations and posters from the annual Alzheimer's Association International Conference. Current findings demonstrate associations with poor sleep quality and altered cerebrospinal fluid Alzheimer's disease (AD) biomarkers, as well as sleep quality abnormalities to be linked with neuroimaging correlates of the disease.

2. **Interpretation**: Poor sleep is associated with brain structural and functional alterations in regions commonly affected by AD, independently from AD pathology. Furthermore, it suggests that paradoxical patterns present in AD preclinical stages (i.e., increases in gray matter and cerebral glucose metabolism) may be exacerbated by poor sleep quality.

3. **Future Directions**: This study sheds light on the potential of sleep-based therapeutic and preventative strategies in the preclinical stages of AD and encourages further investigation of the sleep role in AD with objective measures and longitudinal follow-up of individuals.

severe medical co-morbidity or major neurological disorders and contraindications for magnetic resonance (for full criteria see Table S1 in supporting information). All ALFA+ participants were CU at baseline (Mini-Mental State Examination score >26 points, Clinical Dementia Rating = 0). In this study, we included 339 individuals with available subjective sleep data, T1w images, and CSF biomarker data. Of these, 295 also had available [18F] FDG PET scans.

2.2 | Sleep assessment

Sleep quality was measured using the total score of the Pittsburgh Sleep Quality Index (PSQI), a 19-item self-rated questionnaire assessing sleep quality over the preceding month. The total PSQI score ranges from 0 to 21, with higher values indicating poorer sleep quality and a total score above 5 indicating poor quality of sleep.[33]

2.3 | Image data acquisition and preprocessing

MRI scans, performed in a 3T Philips Ingenia CX scanner, included a high-resolution 3D T1-weighted sequence (time to echo /repetition time/inversion time = 4.6/9.9/900 ms, flip angle = 8°; voxel size = 0.75 × 0.75 × 0.75 mm³). PET scans were acquired using a Siemens Biograph mCT scanner, after a cranial computed tomography scan for attenuation correction. [18F] FDG PET scans were acquired

for 20 minutes, 45 minutes after the administration of 185 MBq of [18F] FDG and images were reconstructed using an OSEM3D algorithm (8 iterations, 21 subsets) with point spread function + time-of-flight corrections.

Spatially normalized GMv maps were obtained using the standard procedure for voxel-based morphometry in the Statistical Parametric Mapping software (SPM12) DARTEL toolbox.[34] [18F] FDG PET scans were registered to the corresponding T1-weighted images and normalized to the Montreal Neurological Institute (MNI) space using DARTEL transformations of T1-weighted images.[19] [18F] FDG uptake was normalized to the cerebellar vermis. All images were smoothed with a Gaussian kernel of 8 mm full-width half maximum (FWHM).

2.4 | CSF sampling

CSF levels of Aβ42[35] and Aβ40 were measured with the prototype NeuroToolKit (Roche Diagnostics International Ltd.) on a cobas e 411 instrument. Phosphorylated tau at threonine 181 (p-tau)[36] were measured using Elecsys electrochemiluminescence immunoassays on a fully automated cobas e 601 instrument (Roche Diagnostics International Ltd.). All measurements were performed at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden.

Individuals were classified into amyloid/tau (AT) groups[37] using cutoffs of CSF Aβ42/40 ratio (A+: <0.071) and p-tau (T+: >24 pg/mL), which have been previously validated for research purposes.[38] We excluded A−T+ participants ($n = 13$) from further analyses due to the low sample size and because this profile is suggestive of non-AD pathophysiology.[37]

The time interval between the PSQI and MRI acquisition was on average 18.05 days (standard deviation [SD] 60.8), between PSQI and CSF sample collection 92.34 days (SD 125.57), and between MRI and CSF measurements 94.29 days (SD 125.39).

2.5 | Mood assessment

Participants' depression and anxiety levels were assessed using the Hospital Anxiety and Depression Scale (HADS), which comprises two subscales with a maximum score of 21.[39] We used the total score, which is the sum of both subscales, as a measure of participants' psychological status.

2.6 | Statistical analyses

Extreme values of each CSF biomarker defined using Tukey's criteria set at three times the interquartile range were removed. CSF p-tau levels did not follow a normal distribution and were thus log10-transformed. Pearson's r values were calculated for associations between the total PSQI score and CSF biomarkers of AD pathology.

To study the relationship between self-reported sleep quality and neuroimaging modalities in a voxel-wise manner, we created separate general linear models (GLM) with GMv and FDG metabolism as dependent variables using SPM12. PSQI total score was the independent variable, while age, sex, APOE ε4 allele status (i.e., carriers: APOE ε4/ε4, APOE ε3/ε4 or APOE ε2/ε4 / non-carriers: APOE ε3/ε3, APOE ε2/ε3 or APOE ε2/ε2), education level, and anxiety and depression (HADS) were confounders in both sets of analyses. Despite PSQI already accounting for sleep medication we additionally adjusted our analyses by use of other CNS medications as they may affect brain structure and metabolism. All GMv analyses were corrected for total intracranial volume (TIV).

To determine the extent to which the effect of self-reported sleep quality on neuroimaging modalities was dependent on core AD biomarkers, we set up separate models additionally adjusted for CSF Aβ42/40 and p-tau. Finally, we tested the interactions between PSQI and AT grouping (i.e., A−T−, A+T−, and A+T+). Each of the three dummy regressors coding the AT stages was multiplied by the PSQI score, resulting in three separate interaction terms. For completeness, we also analyzed differences in GMv and FDG metabolism among AT groups, without including the interaction with the PSQI score, and reported them as supplementary material (Figure S1). Contrasts were designed to test all pairwise comparisons in both directions. The statistical threshold was set to a P-value of <0.005 uncorrected for multiple comparisons as this was found to optimally balance sensitivity and specificity,[40] with a cluster-extent threshold (k) of 50 voxels.

2.7 | Post hoc analyses

To examine which of the PSQI items is most related to the effect observed on the brain structure and glucose metabolism, we conducted separate linear regression models investigating the effect of each of the seven PSQI items as an independent predictor (i.e., sleep quality, sleep latency, sleep efficiency, sleep disturbances, sleep medication, and daytime dysfunction) on GMv and glucose metabolism in a composite region (extracted based on the main effect of PSQI total score), for each of the neuroimaging modalities separately.

Also, to ensure that our results are not affected by the multicollinearity between the PSQI total score (which encompasses sleep medication use) and CNS medications we performed sensitivity analyses testing the main effect of PSQI total score on the brain structure and glucose metabolism without including the CNS medication in the models.

3 | RESULTS

3.1 | Sample characteristics

The mean age was 61.2 (SD = 4.66) for the entire sample ($N = 339$), with 59.6% females, 51.9% APOE ε4 carriers, and 44.8% characterized as poor sleepers (PSQI total score > 5; Table 1). There were no significant differences in the PSQI total score or percentage of poor sleepers

TABLE 1 Sample characteristics.

	All (N = 339)	A−T− (N = 223)	A+T− (N = 90)	A+T+ (N = 26)	P-value
Age, mean (SD)	61.2 (4.66)	60.5 (4.46)	62.2 (4.93)	63.4 (4.15)	<0.001
Sex: female, n (%)	202 (59.6%)	137 (61.4%)	48 (53.3%)	17 (65.4%)	0.343
Education, mean (SD)	13.4 (3.45)	13.5 (3.42)	13.7 (3.43)	11.6 (3.40)	0.022
Medication: use of medication, n (%)	49 (14.5%)	28 (12.6%)	12 (13.3%)	9 (34.6%)	0.018
APOE ε4 carriers, n (%)	176 (51.9%)	88 (39.5%)	73 (81.1%)	15 (57.7%)	<0.001
CSF Aβ42/40, mean (SD)	0.07 (0.02)	0.09 (0.01)	0.05 (0.01)	0.05 (0.01)	<0.001
CSF p-tau, pg/mL, mean (SD)	1.16 (0.16)	1.12 (0.13)	1.17 (0.12)	1.46 (0.06)	<0.001
Sleep characteristics					
PSQI total score, mean (SD)	4.88 (3.17)	4.71 (3.12)	5.29 (3.27)	4.96 (3.24)	0.346
Poor sleepers, n (%)	152 (44.8%)	96 (43.0%)	45 (50.0%)	11 (42.3%)	0.515
HADS total score, mean (SD)	6.96 (5.06)	6.94 (5.21)	6.68 (5.07)	8.04 (3.58)	0.483
MMSE, mean (SD)	29.1 (0.95)	29.1 (0.91)	29.2 (0.96)	28.8 (1.17)	0.145

Notes: Aβ-positive (A+) was defined by a CSF Aβ42/40 < 0.071, whereas tau-positive (T+) was defined by p-tau > 24 pg/mL. Poor sleep quality was defined based on PSQI total >5. P-values from a two-sample t-test (continuous variables) or two-sample test of proportions (categorical variables).
Abbreviations: Aβ, amyloid beta; AT, amyloid tau staging model; CSF, cerebrospinal fluid; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini-Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; p-tau, phosphorylated tau at threonine 181; SD, standard deviation.

TABLE 2 Associations between subjective sleep quality and GM volumes.

		k	P(FWE-corr)	T	P(FWE-corr)	P(unc)	MNI coordinates		
Anatomical location	Side		Cluster level		Peak level		x	y	z
Orbitofrontal cortex/frontal pole	R	254	0.99	3.2	0.972	0.001	51	40	−15
Occipital pole	L	97	1.00	3.08	0.992	0.001	−15	−99	−20
Posterior cingulate cortex	L	62	1.00	2.99	0.997	0.001	−3	−51	9
Frontal pole	R	99	1.00	2.96	0.998	0.002	46	54	−4

Notes: Results of voxel-based morphometry associations between self-reported sleep quality and GMv. These results correspond to negative associations between PSQI and GMv (i.e., poor sleep being associated with lower GMv). The opposite contrast did not yield any significant results. The base model is corrected for age, sex, APOE ε4 status, education years, use of medication, HADS score, and TIV.
Abbreviations: FWE, family-wise error; GM, gray matter; GMv, gray matter volume; HADS, Hospital Anxiety and Depression Scale; k, the cluster mass; MNI, Montreal Neurological Institute; PSQI, Pittsburgh Sleep Quality Index; P-value; T, t value; TIV, total intracranial volume.

between the AT groups. No significant differences between the entire sample and the subsample with FDG (N = 295) were present, except that education was significantly different between the AT groups in the entire study sample (Table S2 in supporting information). CSF Aβ42/40 was significantly negatively associated with PSQI total score in the whole sample (r = −0.123, P = 0.024) and the FDG subset (r = −0.120, P = 0.040), while p-tau was not (r = −0.028, P = 0.612; FDG [r = −0.046, P = 0.426]).

3.2 | Association between subjective sleep quality and brain structure

Poor self-reported sleep quality (i.e., higher PSQI total score) was significantly associated with lower GMv in the right pars orbitalis of the OFC, left occipital pole extending to the occipital fusiform gyrus, and left PCC extending to the contralateral side (Table 2, Figure 1).

These associations remained significant after including either continuous or categorical measures of CSF Aβ42/40 and $\log_{10}$(CSF p-tau; hereafter CSF p-tau) into the model (Table S3 in supporting information).

3.3 | Association between subjective sleep quality and brain metabolism

Poorer self-reported sleep quality was significantly associated with lower brain glucose metabolism in the right temporal pole, extending to the entorhinal cortex and head of the hippocampus, as well as in the right paracingulate gyrus, right cerebellum exterior, and right frontal orbital cortex (Table 3, Figure 2).
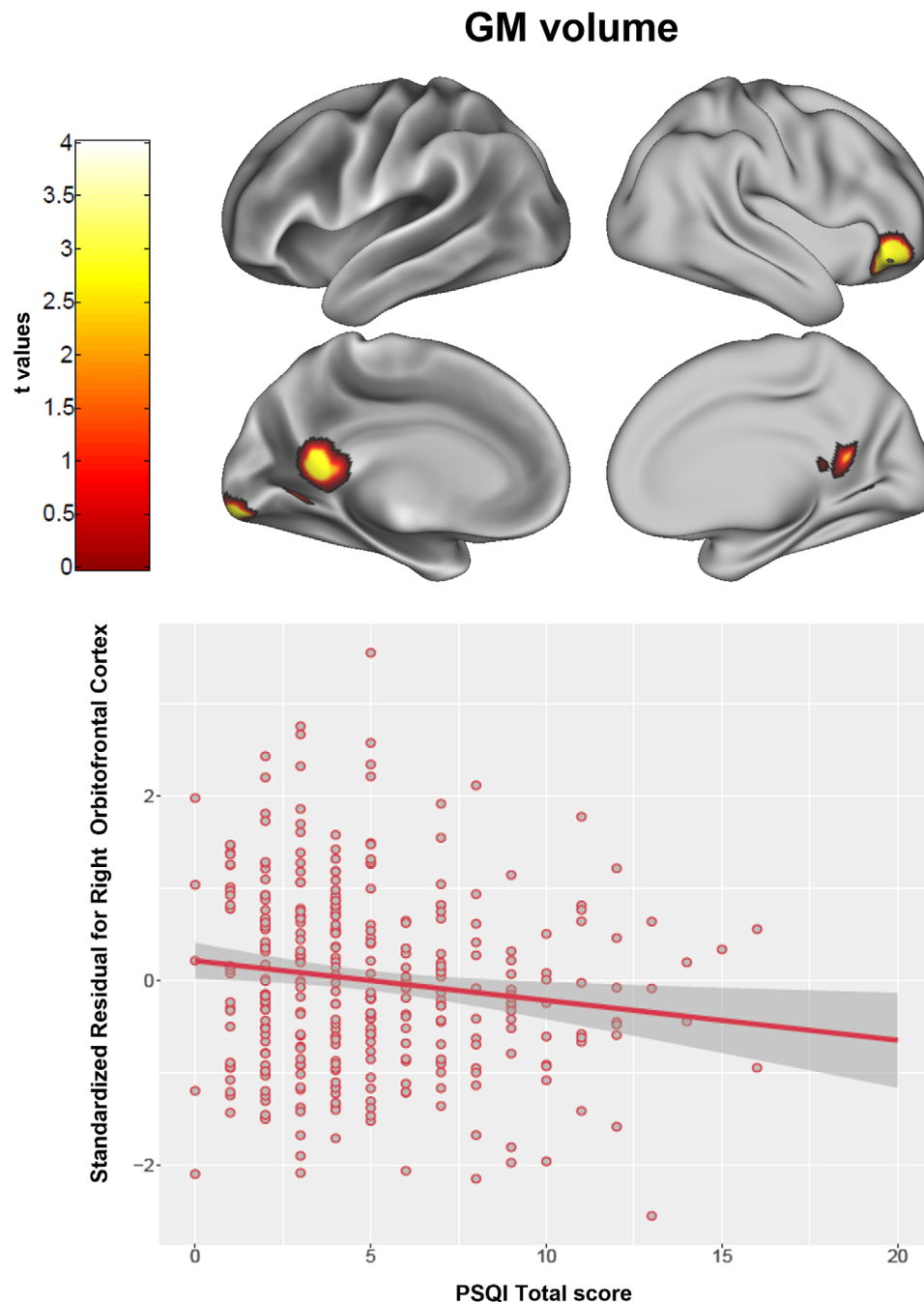
GM volume

FIGURE 1 Associations between subjective sleep quality and gray matter (GM) volume (GMv). Results of voxel-based morphometry associations between self-reported sleep quality and GMv. These results correspond to negative associations between Pittsburgh Sleep Quality Index (PSQI) and GMv (i.e., poor sleep being associated with lower GMv). The opposite contrast did not yield any significant results. Statistical brain maps show regions of GMv in the right orbitofrontal gyrus, left occipital pole, and posterior cingulate cortex, in association with higher PSQI scores, at $P < 0.005$ uncorrected for multiple comparisons, with a cluster-size threshold of 50 voxels. The X-axis represents PSQI Total score, on which higher values indicate poorer sleep quality. Y-axis represents the residuals of significant regions of interest based on statistical parametric mapping analysis, after regressing the effect of age, sex, *APOE* ε4 status, medication, and Hospital Anxiety and Depression Scale score. These results are superimposed with smoothed 8 mm kernel, on the Montreal Neurological Institute template. Scales in the color bar represent *t* statistic values. The left-hand side of the images represents the left hemisphere, right side – the right hemisphere.

TABLE 3 Associations between subjective sleep quality and brain glucose metabolism.

Anatomical location	Side	K (Cluster level)	P(FWE-corr) (Cluster level)	T	P(FWE-corr) (Peak level)	P(unc)	MNI coordinates x	MNI coordinates y	MNI coordinates z
Temporal pole	R	598	0.423	3.53	0.673	0.001	26	16	−40
Paracingulate gyrus	R	105	0.986	3.09	0.974	0.001	8	28	38
Cerebellum exterior	R	571	0.452	3.09	0.975	0.001	50	−54	−46
Orbitofrontal cortex	R	55	0.997	3.06	0.979	0.001	40	32	−16

Notes: Results of voxel-based morphometry associations between self-reported sleep quality and brain glucose metabolism. These results correspond to negative associations between PSQI and brain glucose metabolism (i.e., poor sleep being associated with lower brain glucose consumption). The opposite contrast did not yield any significant results. The base model is corrected for age, sex, *APOE ε*4 status, education years, use of medication, and HADS score. Abbreviations: FWE, family-wise error; GM, gray matter; GMv, gray matter volume; HADS, Hospital Anxiety and Depression Scale; *k*, the cluster mass; MNI, Montreal Neurological Institute; PSQI, Pittsburgh Sleep Quality Index; *P*-value; T, *t* value.

Significant hypometabolism was observed in the above-mentioned regions after additional adjustment by either continuous or categorical measures of CSF Aβ42/40 and CSF p-tau, except the right frontal orbital cortex (Table 4).

3.4 | Interactions between subjective sleep quality and AT stages on brain structure

Associations between PSQI and GMv differed between A+T+ and A−T−, with higher PSQI scores being associated with higher GMv in the A+T+ group in the following areas: middle temporal gyrus, bilateral caudate, left superior parietal lobule extending to the supramarginal gyrus, postcentral gyrus bilaterally, right occipital pole, right calcarine cortex, left lateral occipital cortex, right inferior temporal gyrus, right precuneus cortex, left putamen, and left temporal fusiform cortex (Table 4, Figure 3).

Another significant interaction was detected comparing the A+T− group to the A−T−, with the first group exhibiting greater volumes associated with higher PSQI scores in the left superior parietal gyrus, extending to the postcentral gyrus, bilateral supramarginal gyri, bilateral middle temporal gyri, bilateral occipital cortices, bilateral inferior temporal gyri, right frontal pole, and left planum temporale extending to the superior temporal gyrus (Table 4, Figure 3).

Finally, the association between PSQI scores and GMv differed between A+T− and A+T+ groups, with higher PSQI scores being associated with lower GMv in the latter group in the middle frontal gyrus, superior temporal gyrus bilaterally, as well as the left middle temporal gyrus.

3.5 | Interactions between subjective sleep quality and AT stages on brain metabolism

Higher PSQI scores were associated with higher metabolism in A+T+ individuals compared to A−T− in the right calcarine cortex extending to the precuneus cortex, right transverse temporal gyrus (Heschl's gyrus), bilateral thalami, left precentral gyrus, right postcentral gyrus, and right cerebellum exterior (Table 5, Figure 4).

Additionally, associations between PSQI and FDG uptake significantly differed between A+T+ and A+T− groups, with A+T+ individuals displaying an association between higher PSQI scores and increased glucose uptake in the bilateral calcarine cortex, bilateral thalami, left precuneus cortex extending to the cingulate gyrus, and the left occipital pole (Table 5, Figure 4).

3.6 | Brain structural and metabolism differences across AT groups

For completeness, and to help in the interpretation of the interactions between AT stages and self-reported sleep quality, we analyzed GMv and FDG metabolism differences between AT groups, without including subjective sleep data in the models (Figure S1 in supporting information). In brief, we observed larger GMv in the A+T− and A+T+ individuals compared to the reference group (A−T−) in bilateral temporal and parietal regions. Conversely, we found lower GMv in bilateral frontal and right temporal regions in A+T+ compared to A+T groups. We also found higher FDG metabolism in A+T+, compared to A+T− and A−T− groups, in widespread bilateral cortical and subcortical regions, involving frontal, temporal, parietal and occipital lobes, and the thalami.

3.7 | Post hoc analyses

We ran separate linear regression models investigating the effect of individual PSQI items as an independent predictor on GMv and glucose metabolism in a composite region (comprised of all significant brain areas from the main effect analyses).

Lower GMv in the composite region was significantly associated with poorer outcomes in the following PSQI items: sleep quality (fairly bad vs. good $\beta = -0.023$, $P = 0.002$); sleep latency between 31 and 60 versus <15 less ($\beta = -0.021$, $P = 0.007$) and sleep latency >60 minutes versus <15 minutes ($\beta = -0.024$, $P = 0.029$); and sleep duration of <5 hours versus >7 hours ($\beta = -0.024$, $P = 0.009$), and sleep efficiency of 75% to 84% versus >85% ($\beta = -0.014$, $P = 0.024$).

FDG uptake
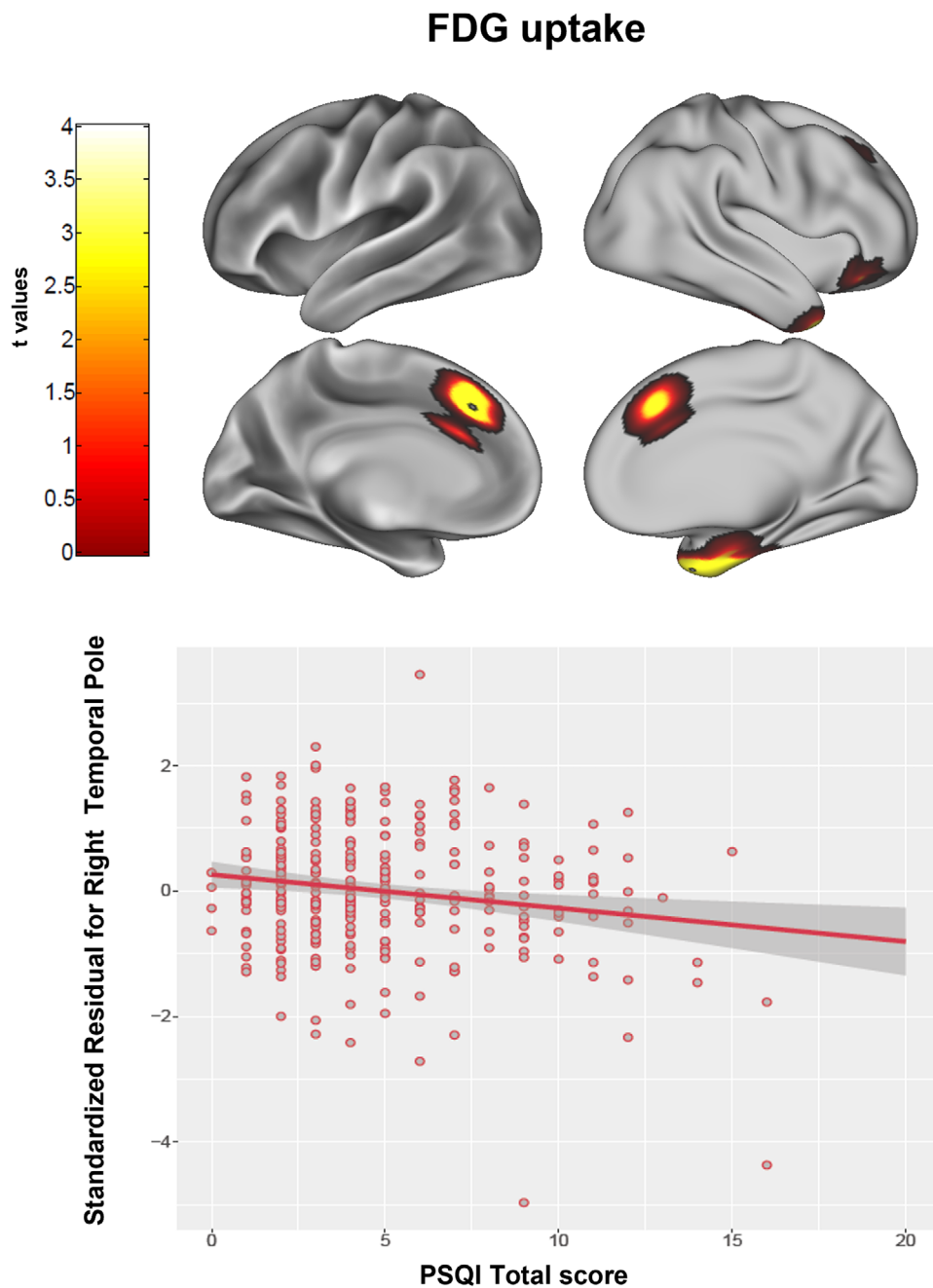
FIGURE 2 Associations between subjective sleep quality and brain glucose metabolism. Results of voxel-based morphometry associations between self-reported sleep quality and brain glucose metabolism. These results correspond to negative associations between Pittsburgh Sleep Quality Index (PSQI) and brain glucose metabolism (i.e., poor sleep being associated with lower brain glucose consumption). Statistical brain maps show lower glucose consumption in brain regions of the right middle temporal pole and right middle cingulate gyrus, in association with higher PSQI scores, at $P < 0.005$ uncorrected for multiple comparisons, with a cluster-size threshold of 50 voxels. The X-axis represents PSQI Total score, with higher values indicating poorer sleep quality. Y-axis represents the residuals of significant regions of interest based on statistical parametric mapping analysis, after regressing the effect of age, sex, *APOE* ε4 status, use of medication, and Hospital Anxiety and Depression Scale score. These results are superimposed with smoothed 8 mm kernel, on the Montreal Neurological Institute template. Scales in the color bar represent t-statistic values. The left-hand side of the images represents the left hemisphere, right side – the right hemisphere. FDG, fluorodeoxyglucose.

TABLE 4 Interactions between subjective sleep quality and AT stages on gray matter volumes.

Contrast	Anatomical location	Side	k	P(FWE-corr)	T	P(FWE-corr)	P(unc)	x	y	z
				Cluster level		Peak level		MNI coordinates		
A−T− < A+T+	Middle temporal gyrus	R	1233	0.426	3.99	.28	<0.001	64.00	−56.00	−4.00
	Caudate	L	74	1.000	3.91	.35	<0.001	−18.00	−12.00	28.00
	Angular gyrus	L	265	0.987	3.62	.66	<0.001	−44.00	−52.00	57.00
	Middle temporal gyrus	L	296	0.981	3.37	.89	<0.001	−62.00	−62.00	0.00
	Precuneus cortex	R	94	1.000	3.37	.89	<0.001	6.00	−78.00	42.00
	Postcentral gyrus	R	444	0.933	3.36	.89	<0.001	64.00	−14.00	28.00
	Occipital pole	R	127	0.999	3.19	.97	0.001	12.00	−104.00	3.00
	Calcarine cortex	R	51	1.000	3.18	.97	0.001	15.00	−78.00	15.00
	Postcentral gyrus	R	105	0.999	3.17	.98	0.001	38.00	−24.00	39.00
	Inferior temporal gyrus	R	380	0.958	3.08	.99	0.001	46.00	−14.00	−33.00
	Lateral occipital cortex	L	51	1.000	3.06	.99	0.001	−34.00	−81.00	21.00
	Precuneus cortex	R	54	1.000	3.05	.99	0.001	14.00	−51.00	45.00
	Putamen	L	133	0.999	3.02	1.00	0.001	−28.00	−12.00	8.00
	Postcentral gyrus	L	72	1.000	2.97	1.00	0.002	−66.00	−18.00	18.00
	Angular gyrus	R	91	1.000	2.81	1.00	0.003	45.00	−51.00	48.00
	Temporal fusiform cortex	L	106	0.999	2.72	1.00	0.003	−42.00	−28.00	−21.00

Contrast	Anatomical location	Side	k	P(FWE-corr)	T	P(FWE-corr)	P(unc)	x	y	z
				Cluster level		Peak level		MNI coordinates		
A−T− < A+T−	Superior parietal lobule/post central gyrus	L	433	0.937	4.04	0.24	<0.001	−15.00	−52.00	74.00
	Supramarginal gyrus	L	3227	0.031	3.95	0.31	<0.001	−52.00	−26.00	30.00
	Lateral occipital cortex	R	1295	0.392	3.82	0.44	<0.001	39.00	−70.00	10.00
	Supramarginal gyrus	R	278	0.984	3.80	0.46	<0.001	68.00	−33.00	28.00
	Cuneal cortex	R	631	0.828	3.59	0.69	<0.001	3.00	−84.00	36.00
	Middle temporal gyrus	R	148	0.998	3.58	0.70	<0.001	57.00	−10.00	−21.00
	Inferior temporal gyrus	L	106	0.864	3.44	0.84	0.00	−54.00	−14.00	−42.00
	Planum temporale/superior temporal gyrus	L	172	0.997	3.41	0.86	<0.001	−63.00	−8.00	4.00
	Inferior temporal gyrus	L	469	0.921	3.37	0.89	<0.001	−48.00	−39.00	−15.00
	Temporal occipital fusiform cortex	R	80	1.000	3.31	0.92	<0.001	30.00	−48.00	−14.00
	Supramarginal gyrus	R	56	1.000	3.17	0.98	<0.001	48.00	−34.00	48.00
	Lateral occipital cortex	L	154	0.998	3.11	0.99	<0.001	−15.00	−80.00	51.00
	Frontal pole	R	129	0.999	3.06	0.99	<0.001	27.00	62.00	21.00
	Superior parietal lobule/post central gyrus	R	57	1.000	3.04	1.00	<0.001	28.00	−56.00	58.00
	Middle frontal gyrus	L	133	0.999	3.03	1.00	<0.001	−39.00	18.00	34.00
	Frontal pole	R	195	0.995	3.00	1.00	<0.001	22.00	50.00	8.00
	Lingual gyrus	R	119	0.999	3.00	1.00	<0.001	14.00	−76.00	−10.00
	Middle frontal gyrus	L	58	1.000	2.95	1.00	<0.001	−38.00	32.00	28.00
	Inferior temporal gyrus	L	74	1.000	2.82	1.00	<0.001	−58.00	−28.00	−22.00

(Continues)

TABLE 4 (Continued)

Contrast	Anatomical location	Side	k	P(FWE-corr)	T	P(FWE-corr)	P(unc)	x	y	z
			Cluster level			Peak level		MNI coordinates		
A+T− > A+T+	Middle frontal gyrus	L	709	0.77	4.06	0.23	<0.001	−44.00	15.00	38.00
	Superior temporal gyrus	L	116	1.00	3.24	0.96	0.001	−66.00	−9.00	0.00
	Middle frontal gyrus	R	96	1.00	3.14	0.98	0.001	34.00	33.00	48.00
	Post central gyrus	L	152	1.00	3.09	0.99	0.001	−18.00	−45.00	72.00
	Middle frontal gyrus	R	67	1.00	3.07	0.99	0.001	34.00	8.00	39.00
	Post central gyrus	L	190	1.00	3.03	1.00	0.001	56.00	−44.00	21.00
	Superior temporal gyrus	R	95	1.00	2.85	1.00	0.002	69.00	−33.00	15.00

Notes: Results of voxel-based morphometry interactions between self-reported sleep quality and AT stages on GMv. Results from three different contrasts are shown (1: A−T + < A+T+, 2: A−T− < A+T−, 3: A+T− > A+T+). Each contrast is corrected for age, sex, *APOE ε*4 status, education years, use of medication, HADS score, and TIV. Aβ-positive (A+) was defined by a CSF Aβ42/40 < 0.071, whereas tau-positive (T+) was defined by p-tau > 24 pg/mL.

Abbreviations: Aβ, amyloid beta; AT, amyloid/tau; CSF, cerebrospinal fluid; FWE, family-wise error; GM, gray matter; GMv, gray matter volume; HADS, Hospital Anxiety and Depression Scale; *k*, the cluster mass; MNI, Montreal Neurological Institute; PSQI, Pittsburgh Sleep Quality Index; p-tau, phosphorylated tau at threonine 181; P, *P*-value; T, *t* value; TIV, total intracranial volume.

Lower FDG metabolism in the composite region was significantly associated with poorer outcomes in the following PSQI items: sleep latency between 16 and 30 minutes versus <15 minutes ($\beta = -0.038$, $P = 0.019$) and >60 minutes versus <15 minutes ($\beta = -0.095$, $P = 0.011$); sleep duration of <5 hours versus >7 hours ($\beta = -0.091$, $P = 0.002$); sleep efficiency of <65% versus >85% ($\beta = -0.0112$, $P = 0.006$); a higher number of sleep disturbances of 10 to 18 versus 0 ($\beta = -0.091$, $P = 0.002$); and higher frequency of daytime dysfunction versus no dysfunction ($\beta = -0.042$, $P = 0.020$).

Finally, the main effect of the PSQI total score on the brain structure and glucose did not differ after removing the CNS medication from the models.

4 | DISCUSSION

In this study, we examined the relationships between subjective sleep quality and brain structure and metabolism while adjusting for the presence of AD pathology in CU older individuals. Poorer self-reported sleep quality was associated with lower GMv in the orbitofrontal and PCC, and lower brain glucose metabolism in the orbitofrontal and middle cingulate cortices and the temporal pole, after adjusting for AD pathology. Importantly, these associations differed depending on the AD biomarker profile, with poor self-reported sleep quality being mainly associated with higher GMv and brain metabolism in participants within the AD continuum (A+T+ or A+T−).

Our findings in the orbitofrontal regions align with previous results in individuals with insomnia symptoms,[18,23,41] sleep fragmentation,[14–16] and poor subjective sleep quality.[42] The OFC is known for its role in higher executive functions, which are affected by sleep deprivation.[43] Moreover, due to OFC's role in thermal stimuli sensation, its atrophy may lead to altered thermosensation, potentially affecting sleep quality due to suboptimal temperature sensing for comfortable sleep.[18] While reductions in orbitofrontal area volumes

are commonly observed in patients with depression and anxiety[44,45] and are associated with advanced age,[46] we found that lower OFC volume was associated with poorer self-reported sleep quality, even after controlling for these variables, which reinforces the significance of OFC integrity in sleep quality. Lower GMv was also observed in the PCC, in accordance with previous evidence showing lower volume in this region in individuals with insomnia.[19]

We also found an association between poorer self-reported sleep quality and lower CMRGlu in the right temporal pole (including the entorhinal cortex and the head of the hippocampus, key areas affected early in the AD continuum)[47] and the paracingulate gyrus, consistent with previous studies showing lower metabolic activity in similar areas.[14,31,48]

The topography of our results in brain structure and metabolism is clinically relevant, because the PCC, temporal pole, and cingulate cortex are involved in higher-order cognition and highly vulnerable to AD pathology.[49–51] Moreover, the temporal pole and cingulate cortex belong to the resilience signature, which has been associated with successful aging.[52] Importantly, the main effects of self-reported sleep quality on both brain structure and metabolism were independent of the AD pathology markers, suggesting that poorer self-reported sleep quality may lower brain resilience, which in turn potentially leads to increased vulnerability to cognitive impairment.

Regarding the potential contribution of different self-reported sleep quality characteristics, our sensitivity analyses suggested that sleep latency, sleep duration, and sleep efficiency appear to be the most influential sleep traits associated with alterations in both neuroimaging modalities with the latter one potentially being related to nocturnal awakenings causing fragmentation, which may have relevance for the design of sleep-based intervention strategies to prevent cognitive impairment.

We also investigated whether the presence of AD pathology modified these associations. We found that poorer self-reported sleep quality was associated with higher GMv in A+T+ (but not in other
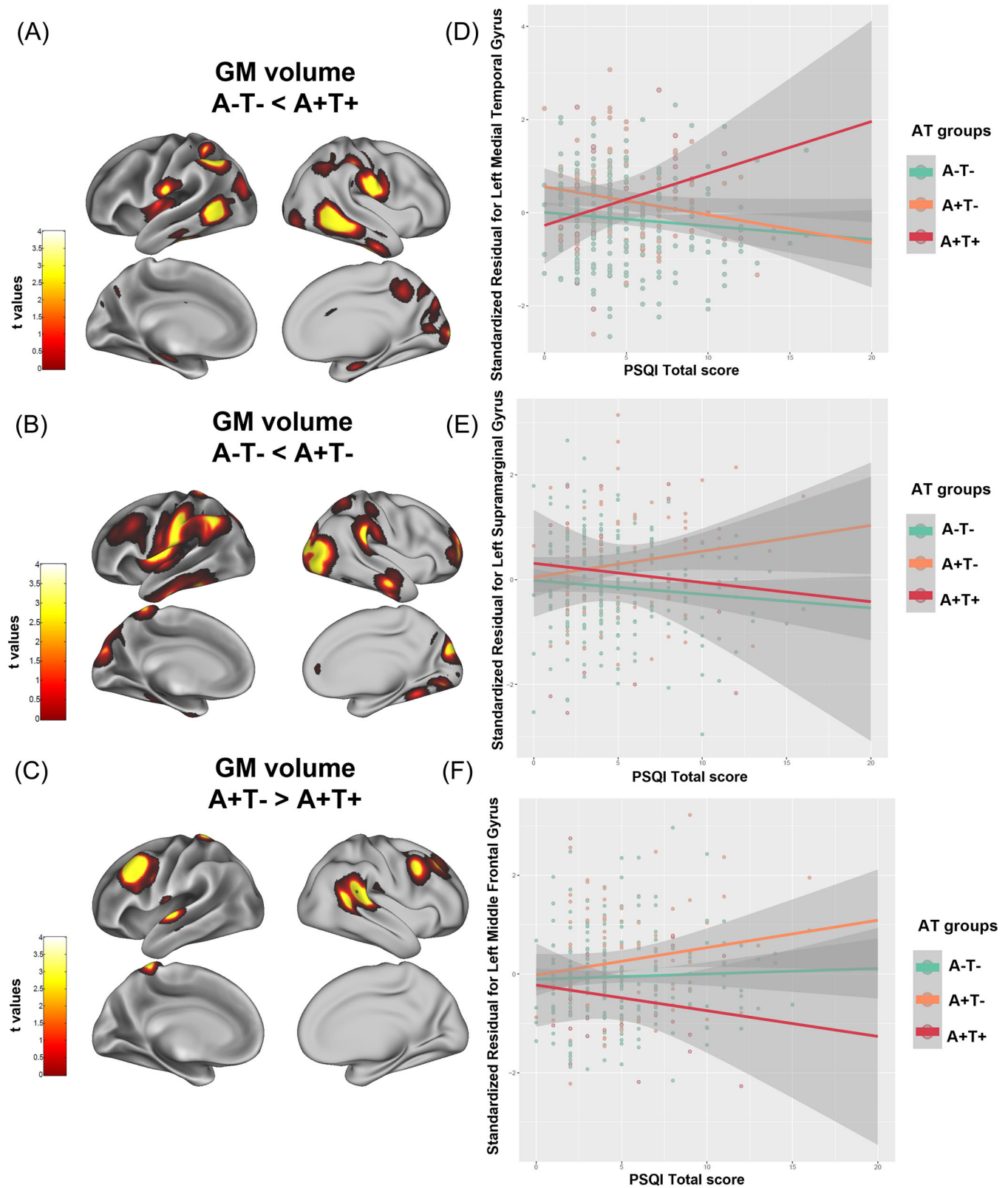
FIGURE 3 Interactions between subjective sleep quality and amyloid/tau (AT) stages with gray matter volumes (GMv). Results of voxel-based morphometry interactions between self-reported sleep quality and AT stages on GMv (panels A, B, C). Panels D, E, and F show representative brain regions where the association between Pittsburgh Sleep Quality Index (PSQI) and GMv differed depending on the AT stage. The X-axis represents PSQI total score, with higher values indicating poorer sleep quality. Y-axis represents the residuals of significant GMv clusters based on statistical parametric mapping analysis, after regressing the effect of age, sex, *APOE* ε4 status, medication, and Hospital Anxiety and Depression Scale score. Scales in the color bar represent *t* statistic values. Each regression line represents a distinct AT stage (A−T−, green; A+T−, orange; and A+T+, red).

TABLE 5 Interaction between subjective sleep quality and AT stages on brain glucose metabolism.

| Contrast | Anatomical location | Side | k | P(FWE-corr) | T | P(FWE-corr) | P(unc) | MNI coordinates | | |
			Cluster level			Peak level		x	y	z
A−T− < A+T+	Calcarine cortex/ precuneus cortex	R	814	0.242	3.65	0.542	<0.001	18	−60	8
	Transverse temporal gyrus/Heschl's gyrus	R	222	0.902	3.56	0.642	<0.001	42	−26	14
	Thalamus	R	141	0.969	3.47	0.732	<0.001	12	−16	10
	Thalamus	L	116	0.981	3.36	0.833	<0.001	−14	−20	12
	Precentral gyrus	L	70	0.995	3.19	0.943	0.001	−34	−22	60
	Postcentral gyrus	R	331	0.765	3.17	0.948	0.001	50	−14	46
	Cerebellum exterior	R	77	0.994	3.04	0.983	0.001	34	−66	−30

| Contrast | Anatomical location | Side | k | P(FWE-corr) | T | P(FWE-corr) | P(unc) | MNI coordinates | | |
			Cluster level			Peak level		x	y	z
A+T− < A+T+	Calcarine cortex	R	1171	0.096	3.78	0.404	<0.001	14	−70	14
	Precuneus cortex/ cingulate gyrus	L	63	0.996	3.51	0.694	<0.001	−14	−48	38
	Calcarine cortex	L	129	0.975	3.48	0.73	<0.001	−14	−80	12
	Thalamus	L	75	0.994	3.43	0.777	<0.001	−14	−18	10
	Thalamus	R	111	0.983	3.41	0.794	<0.001	12	−16	10
	Occipital pole	L	66	0.996	3.4	0.799	<0.001	−22	−92	2

Notes: Results of voxel-based morphometry interactions between self-reported sleep quality and AT stages on brain glucose metabolism. Results from two different contrasts are shown (1: A−T− < A+T+, 2: A+T− < A+T+). Each contrast is corrected for age, sex, *APOE ε4* status, education years, use of medication, and HADS score. Aβ-positive (A+) was defined by a CSF Aβ42/40 < 0.071, whereas tau-positive (T+) was defined by p-tau > 24 pg/mL.
Abbreviations: Aβ, amyloid beta; AT, amyloid/tau; CSF, cerebrospinal fluid; FWE, family-wise error; GM, gray matter; GMv, gray matter volume; HADS, Hospital Anxiety and Depression Scale; *k*, the cluster mass; MNI, Montreal Neurological Institute; PSQI, Pittsburgh Sleep Quality Index; p-tau, phosphorylated tau at threonine 181; *P*, *P*-value; T, *t* value.

AT stages) in a subset of temporoparietal, occipital, and subcortical regions, which aligns with previous research in OSA patients.[25] However, because objective or self-reported data related to the presence of OSA were not available for the present study, we could not confirm whether this pattern was driven by underlying sleep-related breathing disorders. Additionally, greater GMv was associated with poorer self-reported sleep quality in a different subset of regions, involving the temporoparietal and occipital areas in the A+T− group but not in the other AT groups. Finally, in the third subset of regions, located in the temporal and frontal lobes, poor self-reported sleep quality was associated with higher GMv in the A+T− group, whereas the opposite pattern was found in the A+T+ group.

Somehow contradicting the common notion that AD pathology is defined by a decrease in neuronal cell count, our observations of bidirectional patterns in GMv are not entirely unusual. Several cross-sectional studies have demonstrated higher GMv/cortical thickness in CU individuals with abnormal AD biomarker profiles.[20,53–56]

We have also reported higher GMv and brain metabolism in A+T− and A+T+ compared to A−T− individuals in the ALFA+ study, and particularly in the subset of participants included in the present study (Figure S1).[54]

Furthermore, this biphasic trajectory of structural changes (initiated by increments in GMv followed by a decline) has also been corroborated by longitudinal results.[57]

Regarding the functional results, poorer self-reported sleep quality was associated with hypermetabolism in A+T+ compared to A−T− in the bilateral thalamus, cerebellum exterior, and different cortical regions involving the right parietal-temporal and occipital areas and the left precentral gyrus, similar to another study.[25] Additionally, A+T+ individuals displayed increased glucose uptake in association with poor self-reported sleep quality in a set of regions, including the bilateral calcarine cortex, bilateral thalamus, left middle cingulum, and left middle occipital gyrus, compared to the A+T− group. The anatomical pattern of our results strengthens previous literature[25] and reinforces the idea of the existence of joint neuronal networks encompassing sleep and AD pathology, which could be tied to the bidirectional relationship governing sleep and AD.

Although AD is typically defined by cerebral hypometabolism,[43] some prior studies have documented similar patterns of increased glucose consumption, as observed here. For instance, Johnson et al.[58] found increased cerebral glucose consumption in the bilateral thalamus and superior temporal gyrus of CU adults with evidence of
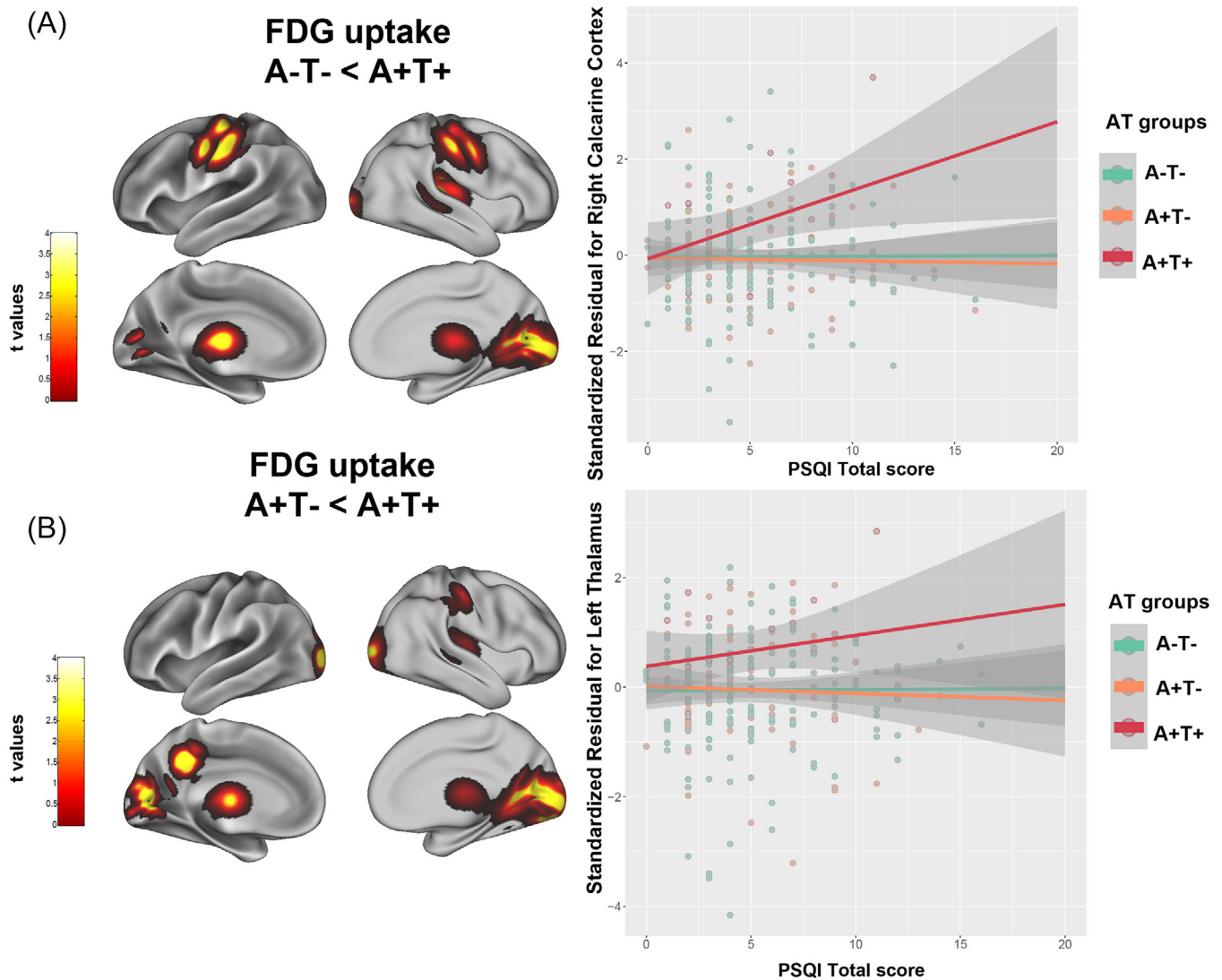
FIGURE 4 Interactions between subjective sleep quality and amyloid/tau (AT) stages with brain glucose metabolism. Results of voxel-based morphometry interactions between self-reported sleep quality and AT stages on brain glucose metabolism (panels A, B). Panels C and D show representative brain regions where the association between Pittsburgh Sleep Quality Index (PSQI) and brain glucose metabolism differed depending on the AT stage. The X-axis represents PSQI total score, with higher values indicating poorer sleep quality. Y-axis represents the residuals of significant clusters based on statistical parametric mapping analysis, after regressing the effect of age, sex, *APOE* ε4 status, medication, and Hospital Anxiety and Depression Scale score. Scales in the color bar represent *t* statistic values. Each regression line represents a distinct AT stage (A−T−, green; A+T−, orange; and A+T+, red). FDG, fluorodeoxyglucose.

amyloid pathology, which also overlaps with our findings. A different group investigating mild cognitively impaired individuals also observed greater glucose metabolism in association with higher amyloid burden in the parietal and posterior temporal lobes.[59] However, none of these studies considered sleep in their models. Our data suggest that poor sleep may potentiate metabolic changes in brain areas affected in preclinical AD, possibly by increasing metabolic demands in these areas. Some support for this hypothesis could be found in the research by Nofzinger et al.,[21] whereby patients with chronic insomnia demonstrated increased glucose metabolism in a wide array of cortical-subcortical structures, ranging from the frontal to superior, temporal-parietal cortices, to the thalamus and brainstem. The dominant theory that stems from these findings advocates for hyperarousal

of the CNS in relation to insomnia, pointing to the altered pattern of glucose consumption during wakefulness that could be related to the compromised functioning of the systems responsible for transitions from the wake-to-sleep stage.[25]

Nonetheless, we cannot exclude the possibility that some of our results are due to a selection bias. More specifically, assuming that poor sleep is a risk factor for dementia, it is possible that, among those individuals with poor self-reported sleep quality and altered AD biomarkers, those with higher brain reserve (i.e., higher GMv and glucose metabolism) would be more likely to fulfill the selection criteria of our study.

Alternatively, such a pattern of increased metabolic demands could be potentially related to the underlying mechanisms observed in OSA

patients such as neuroinflammation or edema caused by intermittent hypoxia.[30]

Albeit the relationship among brain structure, function, and AD biomarkers at the inception of the AD continuum is still dubious, our findings provide a novel insight into interactions between sleep quality and distinct AD profiles. However, the directionality of our findings remains an open question. Further research is warranted to elucidate whether poor sleep quality exacerbates AD-related pathological processes of the disease, and/or early neurodegeneration alters sleep quality in preclinical AD stages.

As major strengths, the present study has been conducted in a large-sized, well-characterized cohort of CU individuals at higher risk of AD, using a multimodal approach that sheds light on how sleep affects brain structure and function, accounting for the presence of AD pathology.

At the same time, several limitations should be considered when interpreting our results. Despite being a validated, stable measure of sleep (even in longitudinal studies[60]) and a highly used instrument in clinical practice, PSQI is a subjective measure of sleep that may be prone to recall bias and could lack sensitivity to detect changes in sleep at different preclinical stages of AD, which would explain the lack of significant differences in PSQI scores among AT groups in our study. Furthermore, it is worth highlighting that the sleep assessment was performed on different occasions to the CSF or neuroimaging data acquisition. Thus, we look forward to replicating these findings with objective methods such as actigraphy or polysomnography, which may strengthen the present conclusions. Another limitation of this study stems from the rather liberal threshold used here for statistical significance ($P < 0.005$) and the lack of corrections for multiplicity. We opted for such a liberal threshold to balance sensitivity and specificity in the expectation of small effect sizes. Still, this threshold was found to optimally balance sensitivity and specificity[40] based on permutation testing in meta-analyses and mega-analyses of comparable data. Also, the observed effects are small in magnitude and need to be replicated in independent datasets. Still, we did not expect to observe large effect sizes in the brain of CU individuals. Moreover, our study's observational cross-sectional design does not allow us to disentangle causality. Finally, because we did not systematically screen participants for the presence of specific sleep disorders, we could not rule out the possibility of our results being driven by specific underlying sleep disorders, such as OSA, insomnia, or restless leg syndrome.

Altogether, this study reports that self-reported sleep quality is associated with alterations in the brain structure and function in CU adults, and these associations differ depending on the presence of AD pathology. Furthermore, the cerebral topography of the effects observed in our study overlaps with AD-sensitive regions,[20,26] further supporting that sleep disturbances may be early and additive elements that make the brain more vulnerable to AD-related neurodegeneration, and that emerging AD pathology, in CU individuals, may influence sleep quality. We hope this research may further accelerate the endeavor to exploit the possibility of sleep-improving treatments as preventive strategies that could potentially lead to delaying the onset of clinical symptoms of the disease.

CONFLICT OF INTEREST STATEMENT

Jose Luis Molinuevo is currently a full-time employee of Lundbeck and previously has served as a consultant or on advisory boards for the following for-profit companies or has given lectures in symposia sponsored by the following for-profit companies: Roche Diagnostics, Genentech, Novartis, Lundbeck, Oryzon, Biogen, Lilly, Janssen, Green Valley, MSD, Eisai, Alector, BioCross, GE Healthcare, and ProMIS Neurosciences. Henrik Zetterberg has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers,

Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). Kaj Blennow has served as a consultant, on advisory boards, or on data monitoring committees for Abcam, Axon, Biogen, and JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Programme. The remaining authors declare that they have no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided informed consent to participate in the present study.

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