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Original Research

Correlations between sleep disturbance and brain structures associated with neurodegeneration in the National Alzheimer's Coordinating Center Uniform Data Set

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ABSTRACT

This study aimed to 1) determine the association between sleep disturbance and brain structure volumes, 2) the moderation effect of apolipoprotein ε4 genotype on sleep disturbance and brain structures, and 3) the moderation effect of sleep disturbance on cognitive status and regional brain volumes.

Using the National Alzheimer's Coordinating Center Uniform Data Set (n = 1,533), multiple linear regressions were used to evaluate the association between sleep disturbance and brain volumes. Sleep disturbance was measured using one question from the NPI-Q.

After controlling for intracranial volume, age, sex, years of education, race, ethnicity, and applying the FDR correction, total cerebrospinal fluid volume, left lateral ventricle volume, total lateral ventricle volume, and total third ventricle volume demonstrated significantly higher means for those with sleep disturbance. Total brain volume, total white and gray matter volume, total cerebrum brain volume (including gray but not white matter), left hippocampus volume, total hippocampal volume, the left, right, and total frontal lobe cortical gray matter volume, and the left, right, and total temporal lobe cortical gray matter volume demonstrated significantly lower mean volumes for those with sleep disturbance. Sleep disturbance moderated the association between cognitive status and lateral ventricular volumes. These findings suggest that disrupted sleep is associated with atrophy across multiple brain regions and ventricular hydrocephalus ex vacuo.

1. Background and introduction

The contribution of sleep disturbance to Alzheimer's disease (AD) risk is an emerging area of research. Advances in the understanding of the glymphatic system have demonstrated that the process of sleeping removes metabolic waste from the brain [1]. Recent research has identified variance in water diffusivity between sleep and wakefulness in human brains, which was correlated with nighttime awakenings by brain region, and further illuminates the glymphatic process [2]. Beta-amyloid is an interstitial protein, and a main constituent in the neuritic plaques found in AD. Sleep disturbance and chronic insomnia may contribute to increased beta-amyloid concentration and

Abbreviations: AD, Alzheimer's Disease; APOE e4, apolipoprotein e4.

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aggregation into plaques due to a slowing of brain interstitial fluid beta-amyloid egress resulting from sleep deprivation [3]. Evidence for the relation between sleep and beta-amyloid has been found such that disrupted sleep has been related to increased levels of beta-amyloid in the brains of older adults.[4–6]. In a study of 27 to 72-year-olds, one night of sleep deprivation resulted in a significant increase of beta-amyloid in the hippocampus and thalamus [7]. Empirical studies indicate that sleep disturbance may subsequently result in neurodegeneration [8]. Sleep disturbance has been associated with an elevated risk of AD in individuals who were otherwise cognitively healthy [9–11] though differences between studies examining sleep disturbances and brain-related outcomes may result from the different aspects of sleep measured and the different tools applied to measure them.

The hippocampus is an early site of beta-amyloid and neurofibrilliary tangle accumulation in AD, which disrupts hippocampus-related learning and memory consolidation [12]. The resulting neurotoxicity leads to neural cell death and reductions in gray matter volume, alterations to neurocircuitry, and subsequent cognitive dysfunction [13]. Given the hippocampus' central involvement in AD pathology, researchers have sought to elucidate the influence of sleep disturbance on hippocampal tissue and found that middle-aged adults with insomnia were more likely to have lower bilateral hippocampal volumes [14], which is echoed by research in male rats wherein sleep restriction reduced hippocampal volume [15]. Changes in hippocampal volume have not been observed consistently, however [16–18]. One study observed a negative relationship between hippocampal volume and years of sleep disturbance, although mean hippocampal volumes did not differ between participants with insomnia and controls [1]. Correlations between sleep quality scores and medial frontal cortex atrophy have also been documented [19] and participants with greater difficulty falling and staying asleep were more likely to have increased atrophy in the prefrontal cortex and higher amounts of beta-amyloid deposition [20]. Finally, among late middle-aged cognitively healthy adults, sleep issues have been associated with greater amyloid burden in the medial orbital cortex, cingulate gyrus, precuneus, and the angular gyrus [21]. These brain regions are not only associated with sleep disturbance but are also associated with brain atrophy and structural abnormalities occurring in the neurodegenerative process, thereby providing a theoretical basis for the link between sleep disturbance and Alzheimer's disease.

Apolipoprotein (APOE) ε 4 has been identified as a susceptibility gene for AD [22], but researchers' understanding of its influence within the theorized bidirectional sleep-AD relationship [23] remains limited. Initial data suggests that among ε4 carriers better sleep (sleeping without interruption) may decrease AD risk [24], however, ε4 has been associated with higher levels of REM sleep disturbance [25], especially for those with cognitive concerns [26]. The interaction between APOE and lack of sleep has been found to be significant for ε4 carriers, but not for non–ε4 carriers [27]. It is imperative that future research investigating the association between sleep and disturbance and regional brain volumes account for the influence of APOE ε4 status on AD risk and disease progression.

This study sought to 1) determine the association between sleep disturbance and regional brain volumes, 2) the moderation effect of APOE ε 4 status on the association between sleep disturbance and regional brain volumes, and 3) the moderation effect of sleep disturbance on the association between cognitive status and regional brain volumes.

2. Methods

Using data spanning June 2005 to June 2019, we conducted a cross-sectional secondary analysis of the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) using complete structural imaging data from 1,533 participants (mean age: 71.9; SD: 10.30). Initiated in 2005, the NACC UDS is a longitudinal dataset comprised of data collected from approximately yearly assessments from participants at the NIA-funded Alzheimer's Disease Research Centers (ADRCs) across the country. NACC participants are voluntary or the result of referrals and as such, are not a statistically based sample of the U.S. population. UDS data were collected by trained clinicians and personnel using standardized evaluation and uniform methods for each study participant [28]. Participants were required to be accompanied by a co-participant or "study partner," typically family members or close friends with significant weekly contact with the subject. The UDS incorporates longitudinal demographics, family and health history, clinical, neuropsychological, and diagnostic data, including medications [28]. This study was approved by the Florida International University Institutional Review Board (IRB-18-0357-CR01).

2.1. Structural MRI regions

The relations between sleep disturbance and structural MRI regions was examined, including total brain volume, cerebrospinal fluid volume, total gray matter volume, white matter volume excluding white matter hyperintensities, the volume of white matter hyperintensities, hippocampal volume, frontal, occipital, parietal, and temporal lobe volumes, and frontal lobe white matter volume. Volumetric summary data for these regions was obtained from NACC. The calculations for volumetric summary data were performed by the IDeA Lab (Director: Charles DeCarli, MD; University of California, Davis; https://idealab.ucdavis.edu), following Alzheimer's Disease Neuroimaging Initiative (ADNI) protocols, which are described in detail at adni.loni.usc.edu. MRI scans at NACC are a convenience sample of images; voluntarily submitted by a subset of ADRCs. As such, the UDS and neuroimaging data examined for this study were from 15 different ADRCs that had voluntarily submitted the imaging data to NACC (as of 2022, there were 33 NIA-funded ADRCs in the United States). Imaging data collection and acquisition protocols vary by ADRC, and MRI sessions may include T1-weighted, FLAIR, DTI, T2, or other sequence types (and any combination thereof).

Cognitive status is determined by a single clinician or a consensus conference at the ADRC level, which is informed by neuropsychological testing, imaging, and a behavioral and neurological examination. Participants are classified as having normal cognition, impaired but not mild cognitive impairment (MCI), MCI, or dementia.

APOE genotype was determined independently by each ADRC or determined by the Alzheimer's Disease Genetics Consortium (ADGC) or the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD). The samples were obtained using either a buccal swab or blood draw. Data for all six possible genotypes were available from NACC (ε2, ε2/ ε2, ε3/ ε3, ε4/ ε3, ε3/ or ε4/ ε4), and for this study were collapsed into ε 4 carriers (ε2/ ε4, ε3/ ε4, and ε4/ ε4) vs non–ε4 carriers (ε2, ε2/ ε2, ε3/ ε3, ε3).

Sleep disturbance was measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q) [29]. The NPI-Q is a validated scale, which measures 12 domains: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioral disturbances (sleep disturbance), and appetite and eating abnormalities. This measure is completed by asking an informant about the presence or absence of each of these behaviors relative to the participant. For this study, sleep disturbance was measured in a binary fashion using one question from the NPI-Q, "Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?" Sleep disturbance is rated in a binary fashion (yes/no).

2.2. Statistical analyses

Descriptive analyses were conducted to calculate the mean and standard deviation for continuous variables, and frequency distribution for categorical variables. Participants with different cognitive statuses were compared using the ANOVA test for continuous variables and the

chi-square test for categorical variables. Participants with and without sleep disturbance were also compared using the two-sample *t*-test for continuous variables and the chi-square test for categorical variables. We compared four cognitive states (normal, impaired not MCI, MCI, and dementia) using ANOVA for continuous variables and the chi-square test for categorical variables. Multiple linear regressions were used to evaluate the association between sleep disturbance and brain volumes while controlling for intracranial volume, age, sex, years of education, race, and Hispanic ethnicity. The moderation effect of ε4 carrier status was examined on the association between the MRI volumes and sleep disturbance by testing the interaction effect between ε4 carrier status and sleep disturbance in the above multiple linear regressions. The moderation effect of sleep disturbance was also examined on the association between cognitive status and the MRI volumes by testing the interaction effect between sleep disturbance and cognitive status using normal as the reference group. Type III *p* values were reported for each interaction effect, which tested the overall interaction effect including all non-reference levels. False discovery rate (FDR) was employed to adjust the *p* values for multiple comparisons. The 0.05 level of significance was used to determine statistical significance and all analyses were conducted using SAS 9.4.

3. Results

3.1. Demographic overview of the sample

The total sample size was 1,533, of which 209 participants had sleep disturbance. The average age of participants was 71.9 years old (SD = 10.3). Men comprised less than half the sample (n = 649; 42.3 %). Almost 12 % of the sample identified as Black (n = 183), 84.3 % as White (n = 1,288), and 3.7 % were other races (n = 57). The sample was predominantly non-Hispanic (10.8 % Hispanic, n = 140), and the majority of participants who identified as Hispanic also identified as White (n = 128, 91.4 %). In addition, the majority of Hispanic participants identified as Mexican, Chicano, or Mexican-American (75 %, n = 106 out of 140 Hispanic participants). Just over 40 % of the sample were

Table 1
Participant Composition by Sleep Disturbance.

'Variables	**Overall**		**Sleep Disturbance – Present**		**Sleep Disturbance - Absent**			
	n = 1533		n = 209		n = 1324			
	N	%	N	%	N	%	*p* value	
Sex							**0.008**	
Male	649	42.34	106	16.33	543	83.67		
Female	884	57.66	103	11.65	781	88.35		
Race[a]							0.553	
Black	183	11.98	25	13.66	158	86.34		
Other	57	3.73	5	8.77	52	91.23		
White	1288	84.29	178	13.82	1110	84.18		
Hispanic[b]							**<0.001**	
Yes	140	10.83	33	23.57	107	76.43		
No	1384	89.17	174	12.57	1210	87.43		
e4 carrier							0.260	
Yes	642	41.88	95	14.8	547	85.2		
No	891	58.12	114	12.79	777	87.21		
	Mean	SD	Mean	SD	Mean	SD	*p* value	Adjusted *p* value[d]
Age	71.88	10.30	73.11	9.44	71.69	10.41	0.063	N/A
Education[c]	15.01	3.55	14.25	3.96	15.13	3.47	**0.003**	N/A
Total intracranial volume	1363.87	142.44	1357.60	151.90	1364.90	140.90	0.497	0.513
Total white matter volume	450.73	60.54	448.40	63.75	451.10	60.04	0.551	0.551
Total brain volume	1015.06	114.37	999.20	117.60	1017.60	113.70	**0.031**	**0.048**
Total brain cerebrospinal fluid volume	340.66	63.35	347.30	66.84	339.60	62.74	0.102	0.132
Total brain gray matter volume	572.49	62.62	561.90	64.06	574.20	62.26	**0.009**	**0.019**
Total brain white matter volume	442.57	62.28	437.30	64.88	443.40	61.85	0.185	0.212
Total brain white matter hyperintensity volume	8.15	11.79	11.15	14.64	7.68	11.21	**<0.001**	**<0.001**
Total cerebrum cranial volume	1175.64	128.46	1169.90	135.20	1176.50	127.40	0.489	0.513
Total cerebrum brain volume	888.34	101.82	876.00	104.70	890.30	101.30	0.059	0.088
Total cerebrum cerebrospinal fluid volume	287.30	55.65	293.90	59.49	286.30	54.97	0.064	0.090
Total cerebrum gray matter volume	475.61	57.86	465.40	58.01	477.20	57.70	**0.006**	**0.014**
Total cerebrum white matter volume	404.60	57.26	399.50	60.25	405.40	56.76	0.167	0.199
Left hippocampus volume	3.01	0.48	2.91	0.47	3.02	0.48	**0.003**	**0.011**
Right hippocampus volume	3.07	0.47	3.00	0.48	3.08	0.47	**0.017**	**0.028**
Hippocampal volume	6.08	0.92	5.91	0.92	6.11	0.92	**0.005**	**0.014**
Left lateral ventricle volume	18.86	11.75	21.73	13.24	18.41	11.44	**<0.001**	**0.002**
Right lateral ventricle volume	17.49	11.15	19.89	12.12	17.11	10.95	**0.001**	**0.005**
Total lateral ventricle volume	36.35	22.40	41.62	24.76	35.52	21.90	**<0.001**	**0.003**
Total third ventricle volume	1.38	0.58	1.51	0.59	1.36	0.58	**0.001**	**0.004**
Left frontal lobe cortical gray matter volume	82.62	11.85	80.42	11.46	82.97	11.88	**0.004**	**0.012**
Right frontal lobe cortical gray matter volume	82.87	11.00	80.79	11.03	83.20	10.96	**0.003**	**0.011**
Total frontal lobe cortical gray matter volume	166.11	22.78	161.80	22.34	166.80	22.78	**0.003**	**0.011**
Left occipital lobe cortical gray matter volume	28.74	4.54	28.37	4.81	28.80	4.50	0.204	0.225
Right occipital lobe cortical gray matter volume	29.33	4.72	28.82	4.59	29.41	4.74	0.094	0.126
Total occipital lobe cortical gray matter volume	58.18	8.84	57.30	8.93	58.32	8.82	0.123	0.152
Left parietal lobe cortical gray matter volume	45.80	6.17	44.85	6.18	45.95	6.16	**0.017**	**0.028**
Right parietal lobe cortical gray matter volume	46.36	6.27	45.39	6.48	46.51	6.22	**0.016**	**0.028**
Total parietal lobe cortical gray matter volume	92.25	12.13	90.34	12.41	92.55	12.06	**0.014**	**0.028**
Left temporal lobe cortical gray matter volume	58.64	7.18	57.21	7.84	58.87	7.05	**0.002**	**0.010**
Right temporal lobe cortical gray matter volume	56.20	6.94	55.13	7.32	56.37	6.87	**0.017**	**0.028**
Total temporal lobe cortical gray matter volume	115.09	13.83	112.60	14.85	115.50	13.63	**0.005**	**0.014**

[a]5 missing cases, [b] 9 missing cases, [c] 8 missing cases, [d] *p* values adjusted by FDR.

APOE ε4 carriers (n = 642; 41.9 %). Participants were generally highly educated (mean 15.01; SD = 3.5 years). There was a statistically significant difference in the distribution of cognitive diagnostic groups (normal, impaired not MCI, MCI, and dementia) between males and females ($p < 0.001$), Hispanic and non-Hispanic ethnicity ($p < 0.001$), ε4 carriers and non-carriers ($p < 0.001$), and between White, Black, and other racial groups ($p = 0.034$). (Tables 1 and 2).

3.2. Demographic factors associated with sleep disturbance

The results of the chi-square analyses indicate that educational obtainment was significantly lower for the participants with sleep disturbance ($p = 0.003$), which is consistent with previous research [30]. Males (16.3 % vs females, 11.6 %, $p = 0.008$) and Hispanic participants (23.57 % vs non-Hispanic participants, 12.57 %, $p < 0.001$) had significantly higher rates of sleep disturbance. (Table 1).

3.3. The association between sleep disturbance and brain regions

Table 1 shows that five out of the 30 MRI regions had significantly higher means for the sleep disturbance group: total brain white matter hyperintensity (WMH) volume, left lateral ventricular volume, right lateral ventricular volume, total lateral ventricular volume, and total third ventricular volume. In contrast, as displayed also in Table 1, 15 out of 30 structural MRI regions had significantly lower volumes in the sleep disturbance group, including total brain volume, total gray matter volume, total cerebral grey volume, left hippocampal volume, right hippocampal volume, total hippocampal volume, left frontal lobe cortical gray volume, right frontal lobe cortical gray volume, total frontal lobe cortical gray volume, left parietal lobe gray volume, right parietal lobe cortical gray volume, total parietal lobe cortical gray volume, left temporal lobe cortical gray volume, right temporal lobe cortical gray volume, and total temporal lobe cortical gray volume. After controlling for intracranial volume, age, sex, years of education, race, ethnicity, and applying the FDR correction, total cerebrospinal fluid volume, left lateral ventricle volume, total lateral ventricle volume, and total third ventricle volume demonstrated significantly higher means for the sleep disturbance group. Total brain volume, total white and gray matter volume, total cerebrum brain volume (including gray but not white matter), left hippocampus volume, total hippocampal volume, the left, right and total frontal lobe cortical gray matter volume, and the left, right, and total temporal lobe cortical gray matter volume demonstrated significantly lower mean volumes for the sleep disturbance group (Table 3).

3.4. The moderation effect of APOE ε4

APOE ε4 had a significant moderation effect on the association between sleep disturbance and left, right, and total parietal lobe cortical gray volume. The decrease in left, right, and total parietal lobe cortical gray volume for those with sleep disturbance was greater for APOE ε4 carriers than non– ε4 carriers. However, these results were not significant after the FDR correction for multiple comparisons (Table 4).

3.5. The moderation effect of sleep disturbance on cognitive status and brain volumes

Sleep disturbance significantly moderated the association between cognitive status and two lateral ventricular volumes. The decrease in right lateral ventricular volume and total lateral volume for participants with dementia was greater for those participants with sleep disturbance compared to those without sleep disturbance and remained so after FDR correction. However, the difference in left lateral volume between people with dementia and sleep disturbance and without sleep disturbance was not significant after FDR correction for multiple comparisons (Table 5).

4. Discussion

This study sought to 1) determine the effect of sleep disturbance on specific regional brain volumes, 2) examine whether APOE ε4 had a significant moderation effect on the association between sleep disturbance and brain volumes, and 3) whether sleep disturbance had a significant moderation effect on the association between cognitive status and regional volumes. Our results replicate previous findings indicating that sleep concerns are correlated with structural differences in adult brains [31]. Fifteen of the 30 structural MRI regions evaluated in this study exhibited lower gray matter volume in older adults who reported sleep disturbance via the NPI while another five exhibited either greater ventricular volume or WMH. Results remained statistically significant for 12 of the 15 MRI regions after accounting for demographic and physiological covariates, and in three additional MRI regions, reduced gray matter was identified.

Our identification of increased WMH volume reflects results similar to Cheng et al. [32], who observed greater numbers of WMHs located primarily in the basal ganglia, but also in the brainstem, thalamus, and hypothalamus, among older adults with sleep disturbance and subcortical ischemic vascular dementia (n = 72) using the Sleep Disturbance Symptom Questionnaire. Investigation of sleep quality (via the

Table 2
Participant Composition by Cognitive Status.

	Normal Cognition		Impaired not MCI		MCI		Dementia		
	n = 882		n = 49		n = 385		n = 217		
	N	%	N	%	N	%	N	%	*p* value
Sex									**<0.001**
Male	307	47.3	21	3.24	203	31.28	118	18.18	
Female	575	65.05	28	3.17	182	20.59	99	11.2	
Race[a]									**0.034**
Black	103	56.28	11	6.01	50	27.32	19	10.38	
Other	29	50.88	3	5.26	20	35.09	5	8.77	
White	748	58.07	34	2.64	314	24.38	192	14.91	
Hispanic[b]									**0.000**
Yes	80	57.14	11	7.86	21	15	28	20	
No	796	57.51	38	2.75	362	26.16	188	13.58	
e4 carrier									**<0.001**
Yes	318	49.53	12	1.87	181	28.19	131	20.4	
No	564	63.3	37	4.15	204	22.9	86	9.65	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p* value
Age	69.63	10.86	72.49	10.76	75.63	8.11	74.26	8.77	**<0.001**
Education[c]	15.36	3.28	13.12	4.12	14.85	3.61	14.27	4.09	**<0.001**

[a]5 missing cases, [b] 9 missing cases, [c] 8 missing cases.

Table 3
Adjusted Effect of Sleep Disturbance.

MRI volumetric variables	Sleep Disturbance (Yes vs No)				
	B	SE	95 % CI	*p* value	FDR corrected *p* value
Total white matter volume	−0.526	2.541	(−5.511,4.460)	0.836	0.865
Total brain volume	−10.241	2.888	(−15.906,−4.575)	**<0.001**	**<0.001**
Total brain cerebrospinal fluid volume	7.332	2.770	(1.898,12.766)	**0.008**	**0.016**
Total brain gray matter volume	−6.806	1.996	(−10.722,−2.891)	**0.001**	**0.005**
Total brain white matter volume	−3.434	2.579	(−8.494,1.625)	0.183	0.220
Total brain white matter hyperintensity volume	2.909	0.809	(1.322,4.496)	**<0.001**	**<0.001**
Total cerebrum cranial volume	−0.155	1.234	(−2.575,2.265)	0.900	0.900
Total cerebrum brain volume	−7.318	2.634	(−12.484,−2.151)	**0.006**	**0.013**
Total cerebrum cerebrospinal fluid volume	7.163	2.462	(2.333,11.992)	**0.004**	**0.009**
Total cerebrum gray matter volume	−6.266	2.019	(−10.226,−2.306)	**0.002**	**0.006**
Total cerebrum white matter volume	−3.956	2.484	(−8.829,0.917)	0.112	0.140
Left hippocampus volume	−0.075	0.030	(−0.134,−0.016)	**0.013**	**0.023**
Right hippocampus volume	−0.055	0.030	(−0.113,0.003)	0.064	0.087
Hippocampal volume	−0.129	0.057	(−0.240,−0.018)	**0.022**	**0.035**
Left lateral ventricle volume	2.743	0.730	(1.310,4.175)	**<0.001**	**<0.001**
Right lateral ventricle volume	2.218	0.703	(0.838,3.598)	**0.002**	0.006
Total lateral ventricle volume	4.962	1.387	(2.242,7.681)	**<0.001**	**<0.001**
Total third ventricle volume	0.107	0.034	(0.041,0.173)	**0.002**	**0.006**
Left frontal lobe cortical gray matter volume	−1.256	0.478	(−2.193,−0.318)	**0.009**	**0.017**
Right frontal lobe cortical gray matter volume	−1.324	0.433	(−2.173,−0.475)	**0.002**	**0.006**
Total frontal lobe cortical gray matter volume	−2.588	0.884	(−4.323,−0.854)	**0.004**	**0.009**
Left occipital lobe cortical gray matter volume	−0.258	0.255	(−0.758,0.241)	0.311	0.333
Right occipital lobe cortical gray matter volume	−0.317	0.256	(−0.820,0.185)	0.215	0.241
Total occipital lobe cortical gray matter volume	−0.578	0.468	(−1.495,0.340)	0.217	0.241
Left parietal lobe cortical gray matter volume	−0.552	0.284	(−1.110,0.005)	0.052	0.074
Right parietal lobe cortical gray matter volume	−0.541	0.296	(−1.121,0.039)	0.067	0.087
Total parietal lobe cortical gray matter volume	−1.083	0.539	(−2.140,−0.027)	**0.045**	0.068
Left temporal lobe cortical gray matter volume	−1.160	0.353	(−1.853,−0.466)	**0.001**	**0.005**
Right temporal lobe cortical gray matter volume	−0.817	0.348	(−1.499,−0.135)	**0.019**	**0.032**
Total temporal lobe cortical gray matter volume	−1.974	0.661	(−3.272, −0.677)	**0.003**	**0.008**

n = 1512; adjusted by intracranial volume, sex, age, education, race, Hispanic ethnicity. All volumes measured in cubic centimeters (cc).

Table 4
Moderation Effect of APOE ε 4.

MRI volumetric variables	Sleep Disturbance*APOE ε 4				
	B	SE	95 % CI	*p* value	FDR corrected *p* value
Total white matter volume	4.522	5.067	(−5.418,14.462)	0.372	0.665
Total brain volume	−3.794	5.758	(−15.088,7.500)	0.510	0.665
Total brain cerebrospinal fluid volume	2.675	5.523	(−8.159,13.509)	0.628	0.725
Total brain gray matter volume	−7.197	3.973	(−14.991,0.597)	0.070	0.525
Total brain white matter volume	3.403	5.144	(−6.687,13.492)	0.508	0.665
Total brain white matter hyperintensity volume	1.119	1.613	(−2.046,4.284)	0.488	0.665
Total cerebrum cranial volume	2.704	2.456	(−2.113,7.522)	0.271	0.665
Total cerebrum brain volume	0.054	5.246	(−10.236,10.344)	0.992	0.992
Total cerebrum cerebrospinal fluid volume	2.651	4.908	(−6.977,12.279)	0.589	0.707
Total cerebrum gray matter volume	−5.631	4.013	(−13.504,2.241)	0.161	0.665
Total cerebrum white matter volume	4.616	4.954	(−5.100,14.333)	0.352	0.665
Left hippocampus volume	0.045	0.060	(−0.072,0.162)	0.448	0.665
Right hippocampus volume	0.069	0.058	(−0.046,0.183)	0.240	0.665
Hippocampal volume	0.114	0.112	(−0.106,0.333)	0.309	0.665
Left lateral ventricle volume	−0.552	1.455	(−3.405,2.302)	0.705	0.755
Right lateral ventricle volume	−1.650	1.401	(−4.399,1.099)	0.239	0.665
Total lateral ventricle volume	−2.199	2.763	(−7.618,3.220)	0.426	0.665
Total third ventricle volume	0.054	0.067	(−0.078,0.186)	0.422	0.665
Left frontal lobe cortical gray matter volume	−0.732	0.952	(−2.599,1.136)	0.442	0.665
Right frontal lobe cortical gray matter volume	0.137	0.861	(−1.553,1.826)	0.874	0.904
Total frontal lobe cortical gray matter volume	−0.694	1.760	(−4.145,2.758)	0.694	0.755
Left occipital lobe cortical gray matter volume	−0.621	0.507	(−1.616,0.375)	0.221	0.665
Right occipital lobe cortical gray matter volume	−0.410	0.510	(−1.411,0.591)	0.422	0.665
Total occipital lobe cortical gray matter volume	−1.046	0.932	(−2.874,0.781)	0.262	0.665
Left parietal lobe cortical gray matter volume	−1.358	0.566	(−2.468,−0.248)	**0.017**	0.170
Right parietal lobe cortical gray matter volume	−1.401	0.588	(−2.555,−0.247)	**0.017**	0.170
Total parietal lobe cortical gray matter volume	−2.762	1.072	(−4.865,−0.660)	**0.010**	0.170
Left temporal lobe cortical gray matter volume	−0.961	0.703	(−2.340,0.418)	0.172	0.665
Right temporal lobe cortical gray matter volume	−0.420	0.691	(−1.775,0.934)	0.543	0.679
Total temporal lobe cortical gray matter volume	−1.427	1.314	(−4.004,1.151)	0.278	0.665

n = 1512, adjusted by intracranial volume, sex, age, education, race, and Hispanic ethnicity. All volumes measured in cubic centimeters (cc).

Table 5
Moderation Effect of Sleep Disturbance.

MRI volumetric variables	Dementia*Sleep Disturbance					Cognitive Status* Sleep Disturbance	
	B	SE	95 % CI	p value	FDR*	Type III *p* value	FDR*
Total white matter volume	4.194	6.299	(−8.163,16.550)	0.506	0.660	0.529	0.700
Total brain volume	6.079	6.726	(−7.114,19.273)	0.366	0.606	0.060	0.347
Total brain cerebrospinal fluid volume	−5.659	6.504	(−18.416,7.098)	0.384	0.606	0.176	0.409
Total brain gray matter volume	1.465	4.643	(−7.642,10.572)	0.752	0.868	0.502	0.700
Total brain white matter volume	4.614	6.376	(−7.892,17.120)	0.469	0.640	0.301	0.564
Total brain white matter hyperintensity volume	−0.420	1.991	(−4.325,3.484)	0.833	0.892	0.141	0.385
Total cerebrum cranial volume	5.745	3.024	(−0.187,11.677)	0.058	0.297	0.093	0.347
Total cerebrum brain volume	10.000	5.997	(−1.765,21.764)	0.096	0.297	0.118	0.354
Total cerebrum cerebrospinal fluid volume	−4.255	5.744	(−15.523,7.013)	0.459	0.640	0.073	0.347
Total cerebrum gray matter volume	5.305	4.587	(−3.692,14.301)	0.248	0.496	0.483	0.700
Total cerebrum white matter volume	4.984	6.119	(−7.019,16.987)	0.416	0.624	0.185	0.409
Left hippocampus volume	0.099	0.069	(−0.035,0.233)	0.149	0.355	0.534	0.700
Right hippocampus volume	0.123	0.068	(−0.011,0.256)	0.072	0.297	0.259	0.518
Hippocampal volume	0.222	0.129	(−0.030,0.474)	0.085	0.297	0.382	0.674
Left lateral ventricle volume	−3.177	1.716	(−6.544,0.190)	0.064	0.297	**0.008**	0.080
Right lateral ventricle volume	−5.903	1.647	(−9.133,−2.673)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Total lateral ventricle volume	−9.086	3.240	(−15.442,−2.731)	**0.005**	0.075	**<0.001**	**<0.001**
Total third ventricle volume	−0.119	0.081	(−0.278,0.040)	0.143	0.355	0.089	0.347
Left frontal lobe cortical gray matter volume	1.891	1.145	(−0.355,4.136)	0.099	0.297	0.191	0.409
Right frontal lobe cortical gray matter volume	2.300	1.035	(0.270,4.329)	**0.026**	0.260	0.051	0.347
Total frontal lobe cortical gray matter volume	4.178	2.109	(0.040,8.315)	**0.048**	0.297	0.104	0.347
Left occipital lobe cortical gray matter volume	−0.894	0.626	(−2.121,0.334)	0.154	0.355	0.528	0.700
Right occipital lobe cortical gray matter volume	−0.620	0.627	(−1.849,0.609)	0.322	0.604	0.561	0.701
Total occipital lobe cortical gray matter volume	−1.562	1.144	(−3.806,0.683)	0.173	0.371	0.537	0.700
Left parietal lobe cortical gray matter volume	0.119	0.682	(−1.218,1.456)	0.862	0.892	0.973	0.973
Right parietal lobe cortical gray matter volume	0.621	0.708	(−0.768,2.009)	0.381	0.606	0.798	0.887
Total parietal lobe cortical gray matter volume	0.735	1.283	(−1.782,3.252)	0.567	0.709	0.899	0.930
Left temporal lobe cortical gray matter volume	−0.215	0.796	(−1.775,1.346)	0.787	0.874	0.832	0.891
Right temporal lobe cortical gray matter volume	0.331	0.779	(−1.197,1.859)	0.671	0.805	0.604	0.725
Total temporal lobe cortical gray matter volume	0.115	1.464	(−2.758,2.987)	0.938	0.938	0.710	0.819

n = 1512, adjusted by intracranial volume, sex, age, education, race, Hispanic ethnicity. Reference group = normal cognition. There were no significant results found for MCI*sleep disturbance and impaired, not MCI*sleep disturbance.

* FDR corrected *p* values. All volumes measured in cubic centimeters (cc).

Pittsburgh Sleep Quality Index (PSQI) and structural changes also revealed an association among Whitehall II study participants (n = 448): poorer sleep quality correlated with greater WHM volumes [33]. Other studies have yielded similar results when investigating the influence of short sleep and long sleep on WMH levels: Yaffe et al. [34], found greater WMH volume in the parietal region among middle-aged participants (n = 613) while Ramos et al. [35] (n = 1,244) reported greater WMH volume among long sleepers (nine or more hours) with diabetes. Both WMH [36] and sleep disturbance have been associated with poorer cognitive performance [37,38] and a greater risk for dementia [11].

Very little data exist that have captured the influence of sleep duration, sleep disturbance, or insomnia (free of sleep-disordered breathing), on ventricle size. The current study addresses a gap in the literature and documented an association between sleep disturbance and MRI-measured ventricular volume (right, left, total, and total third). Previously, Lo et al., [39] observed that sleep duration correlated positively with ventricle size (n = 66) even after controlling for covariates, and reported that "each 1-h decrease in sleep duration at baseline predicted a 0.59 % increase in the annual ventricular expansion rate" (p. 1171). Global sleep quality as measured by the PSQI did not predict structural changes, however. Lo et al., [39] note that expanded ventricular volume had been observed in response to atrophy associated with neurodegenerative diseases [40], bipolar disorder [41], and schizophrenia [42], suggesting that reductions in gray matter volume contribute to ventricle expansion. Our finding that sleep disturbance moderated the relationship between cognitive status and ventricle volume is consistent with such results.

Our findings that total brain, total gray matter, and total cerebrum gray matter volumes correlated with disrupted sleep are comparable to those reported by Lim and colleagues [43] who found that total cortical gray matter, but not total gray matter volume, was associated with greater actigraphy-measured sleep fragmentation in a sample of 141 cognitively healthy community-dwelling older adults. Regional gray matter volumes in their study were not associated with sleep duration, however. Alternately, among 170 younger and older adults, total gray matter volume was inversely associated with sleep quality, although additional analyses revealed that gray matter volume mediated the relationship between age and sleep [44]. Del Brutto et al. [37] found similar results. Despite identifying total gray matter and total cerebral gray matter differences, we observed no differences in total white matter volume among those with sleep disturbance compared to those who did not report sleep disturbance, replicating results found elsewhere. [43,45].

Investigations of hippocampal gray matter volume in the context of sleep quality have produced varied results using different methodological approaches. We have identified significant atrophy in right, left, and total hippocampal volume in participants with sleep disturbance. Reimann et al.'s [14] MRI pilot (n = 8) identified smaller bilateral hippocampal volumes among insomnia-diagnosed participants (mean age = 45.4) after controlling for covariates. A voxel-based morphometry study (n = 57) also observed smaller hippocampal volumes and reduced hippocampal neurogenesis among middle-aged and older participants with poorer sleep quality [46], similar to observations in animal studies that prolonged sleep deprivation impairs hippocampal neurogenesis in rodents [47]. Associations between sleep concerns and atrophy have not always been identified, however [18,19,48,49].

Other studies produced nuanced results. Noh et al. [48] found that middle-aged adults with primary insomnia did not exhibit smaller hippocampal volumes compared to healthy controls but did observe that the degree of polysomnography-measured arousal and the length of insomnia was related to hippocampal volume. Alternately, Koo et al. [50] identified lower hippocampal volumes among adult participants reporting poorer sleep quality,while in another study, brain volume mediated the relationship between age and sleep quality [44].

Researchers observed an association between sleep and brain volume only in the older adult group. "…on the opposite causal direction, we also found sleep partially mediated age-related gray matter atrophy, only that the mediation effect was smaller than the effect of brain atrophy on poor sleep." [44].

Correlations between smaller mean frontal lobe gray matter volumes and sleep disturbance are well represented in the literature. An initial investigation with a small sample (n = 24) of middle-aged and older adults by Altena et al. [45] using voxel-based morphometry found lower left orbitofrontal region volume among participants with insomnia compared to controls, while Li et al.'s [51] larger sample (n = 113; mean age = 39.9) of primary insomnia patients and matched controls produced differences "in the dorsolateral prefrontal cortices, including middle and inferior frontal regions" (p. 1762). In contrast to other studies, Yu et al.'s [52] study (n = 122) of younger and middle-aged adults found larger volumes in the orbital frontal cortex, and rostral medial and interior frontal gyri among insomnia-diagnosed participants. PSQI results also correlated positively with changes in the orbital frontal cortex region [52].

The MRI study conducted by Lim et al. [43] MRI study (n = 141) demonstrated lower mean frontal cortex volumes among those with actigraphy-measured sleep fragmentation and volume differences in the inferior frontal gyrus pars orbitalis and lateral orbitofrontal cortex between sample groups, while Sexton et al.'s [19] study (n = 147), which evaluated associations between sleep quality (PSQI) and regional brain volumes, noted that in cross-sectional analysis, atrophy in the right superior frontal cortex was associated with poor sleep quality. The longitudinal analysis produced results correlating sleep quality with areas in both hemispheres. Left and right lateral and medial frontal cortices and rostral cingulate volumes were inversely associated with sleep quality, as was the left caudal cingulate area. Also measuring the influence of sleep quality, Chao and colleagues [53] (n = 144) observed that global sleep quality (PSQI) correlated inversely with total cortical volume and frontal lobe volume in orbitofrontal, superior and middle frontal cortex, frontal pole, and anterior cingulate areas (via MRI), even after models included controls for commonly co-occurring health conditions. Higher levels of beta-amyloid were observed in prefrontal regions and were associated with poorer sleep quality, specifically sleep latency and nocturnal awakenings. Most but not all measures were associated with perceived sleep quality indicating that "sleep quality and other measures of sleepiness and wakefulness may have different effects on different regions of the frontal lobe" (p. 450). The Baltimore Study of Aging study analyzed the relationship of sleep duration to brain atrophy among cognitively normal participants (n = 122); they found that after controlling for APOE ε4 status, those who regularly slept less than seven hours per night in an eight-year study period exhibited greater atrophy in the left inferior frontal gyrus compared to participants sleeping seven hours per night and those who slept more than seven hours per night exhibited greater atrophy in the left superior frontal sulcus [54]. Compared to those who slept less than seven hours per night, those who slept more than seven hours had lower mean right temporal pole volumes.

Similar to our study's results, which documented lower volumes in right, left, and total parietal cortical gray matter volumes among those with sleep disturbance, two other studies noted differences in parietal lobe volumes among those with poorer sleep quality [19] and insomnia severity. Analogous results were identified by Cho [55] who observed greater temporal lobe atrophy among flight attendants employed for five or more years who were exposed to longer periods of jetlag-related circadian rhythm and sleep disturbance. More recent longitudinal data revealed temporal cortex atrophy among those with poorer sleep quality [19]. Van Someren et al. [56], noted medial temporal lobe atrophy among adults aged 50 and older (n = 138) with greater fragmented sleep-wake rhythms; this was greater than that occurring with age. We found no differences in occipital cortex volumes similar to other studies [19,45,54], but like Spira et al., [54] the current study found that APOE ε4 status was associated with gray matter atrophy (specific to the parietal lobe). APOE ε4 correlated with a greater number [57] and length [58] of nighttime awakenings in two actigraphy studies, but interestingly, neither found that the presence of ε4 alleles correlated with subjective sleep quality (PSQI). In the current study, APOE ε4 carrier status significantly moderated the association between sleep disturbance and parietal lobe cortisol gray matter volume, though this effect was no longer significant when adjusted for multiple comparisons. Numerous studies have linked APOE ε4 with greater mean beta-amyloid plaque deposition [5]. APOE also influences beta-amyloid and tau clearance from brain tissues during sleep; [1] higher levels of beta-amyloid deposition have been associated with poorer subjective sleep quality [20]. Additional research is necessary to clarify the relationship between APOE genotype, subjective sleep quality, and beta-amyloid plaque levels given their potential individual influential contributions to AD risk.

5. Limitations

Despite this study's strengths, certain limitations exist. This is a secondary data analysis; the use of NACC data did not allow study authors to select or add additional measures not included in the database. As such, other factors potentially contributing to sleep disorders were not able to be accounted for and the underlying diseases and comorbidities of the cohort are unknown. While the sleep disturbance question was derived from a validated measure, it was based on informant report and does not allow for the collection of data about the nature of the sleep disturbance, which could have provided further information about the relation between sleep concerns and regional brain volumes and allowed for an enhanced comparison with previous studies using other measures, such as the PSQI. This analysis was also cross-sectional and therefore cannot account for change over time. Additionally, the majority of the participants in this study were White non-Hispanic, which is a limitation. Hispanic and Black older adults are diagnosed with AD at 1.5 to twice the rate of WNH adults in the U.S., [59,60] and remain underrepresented in AD research. [61] Moreover, sleep problems have been associated with discrimination in marginalized groups in the U.S. [62] While the dataset utilized for the current study cannot answer whether sleep disturbance causes or is caused by changes in selected brain structures, such data may encourage researchers to further examine this association.

6. Conclusions

Our study replicated some of the findings documented in earlier studies, but the outcomes were not fully consistent. The results were frequently analogous to outcomes from other studies at the frontal, temporal, and parietal region level, but considerable heterogeneity was observed within these regions. In a review of the limited imaging literature examining structural changes in the context of primary insomnia, Dang-Vu [63] suggested that various age ranges and methodological differences likely contribute to the variability of results. This may also apply to literature investigating PSQI-measured sleep quality and brain structural changes, as notable differences in mean sample/age group and imaging methods exist. Sleep disturbance, sleep quality, and sleep duration are different concepts but exist under the larger, 'sleep-concern umbrella;' their overlap may, in part, also contribute to both the similarities and differences observed in the small body of imaging literature. Given the data linking sleep concerns to a greater risk of AD, [8] it is essential to understand the pathways through which sleep affects, and is affected by, brain health. Investigations of structural regions, such as was the case in the current study, inform the development of tools (algorithms, etc.) that will allow researchers to better predict AD risk through the use of biomarkers as well as increase clarity regarding the role of non-modifiable factors such as APOE ε4. Future studies may wish to focus on creating harmonized measures that allow for replication of

studies and pooling of results. [31] The resulting data can then inform the development of targeted interventions that effectively and efficiently reduce AD risk and enhance wellbeing in middle age and older adults through the support of positive sleep outcomes.

The NACC data is publicly available at https://naccdata.org/.

7. Contributorship

SLB, TL, AG, CB, and KH conducted the study, and TL and MA conducted the statistical analyses. All authors contributed to the drafting of this manuscript. MG provided expert consultation on sleep disturbance and SD provided expert consultation on the structural MRI regions.

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Declaration of Competing Interest

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

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