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Examining the relationship between anxiety and regional brain volumes in the National Alzheimer's Coordinating Center uniform, imaging, and biomarker datasets☆,☆☆,★

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ABSTRACT

Anxiety has been associated with a greater risk of Alzheimer's disease (AD). Existing research has identified structural differences in regional brain tissue in participants with anxiety, but results have been inconsistent. We sought to determine the association between anxiety and regional brain volumes, and the moderation effect of APOE ε4. Using data from participants in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set, with complete imaging (MRI) and biomarker data (n = 1533), multiple linear regression estimated the adjusted effect of anxiety on 30 structural MRI regions. The moderation effect of APOE ε4 on the relation between structural MRI regions and anxiety was assessed as was the moderation effect of cognitive status. False discovery rate was used to adjust for multiple comparisons. After controlling for intracranial volume, age, sex, years of education, race, Hispanic ethnicity, and cognitive status, seven MRI regions demonstrated lower volumes among participants with anxiety: total cerebrum gray matter volume, right hippocampus volume, hippocampal volume (total), right and left frontal lobe cortical gray matter volume, and right and total temporal lobe cortical gray matter volume. Findings suggest that anxiety is associated with significant atrophy in multiple brain regions, with corresponding ventricular enlargement. Future research should investigate if anxiety-related changes to brain morphology contribute to greater AD risk.

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Introduction and background

Research suggests that psychiatric conditions increase the risk for neurodegeneration [1–4]. Differences in brain structure or volume have been observed in both individuals with Alzheimer's disease (AD) and psychiatric patients [5–9] and may serve as disease biomarkers. Given that an estimated 6.2 million Americans are currently diagnosed with AD (in 2023), and this number is expected to reach 13.8 million by 2060 [10], it is critical to clarify possible risk factors and the physiological mechanisms that increase vulnerability. Given that the pathophysiological neurodegenerative process precedes the clinically observable manifestation of AD by potentially a decade or more [11], early diagnosis of dementia-spectrum disorders must incorporate fluid and imaging biomarkers to the extent possible, and also account for an increase in risk due to multiple risk factors [12], which may include neuropsychiatric conditions, such as anxiety.

Individuals with anxiety may be at greater risk of AD, though the causal pathway remains unknown [13]. Palmer et al. [14] found that over 84% of participants diagnosed with anxiety and MCI progressed to AD within three years. When controlling for the effect of cognitive decline and depression, a correlation between anxiety level and progression to AD was observed [15], though results examining the predictive value of anxiety related to AD progression have been inconsistent [16]. Anxiety has also been associated with cognitive decline in individuals with normal cognition. In a group of healthy older adults (n = 178) observed over three years, anxiety levels moderated the relationship between beta-amyloid and episodic and verbal memory loss [17].

Several genetic loci have been associated with Alzheimer's disease [18,19]. The presence of the ε4 allele of the apolipoprotein E (APOE) gene is also a major risk factor for AD [20]. Individuals with APOE ε4 (ε4 carriers) have abnormal metabolic functions in brain regions susceptible to AD pathology even prior to experiencing memory loss [20]. Approximately 20% of individuals in North America and Europe are either heterozygous or homozygous APOE ε4 carriers [20]. Apolipoprotein ε4 has been associated with increased risk of AD, while the apolipoprotein E ε2 allele is considered neuroprotective. Prior studies have demonstrated that ε4 carriers had greater atrophy in the temporal lobes and hippocampus, with the right hippocampus showing greater volume loss than the left [21,22]. Unlike autosomal dominant Alzheimer's disease that is caused by rare genetic mutations in three specific genes, late-onset Alzheimer disease (LOAD) is polygenetic [23].

Studies exploring associations between anxiety, AD, and APOE found that the APOE ε4 allele was associated independently with increased beta-amyloid deposition [24,25], earlier progression to AD [26], and anxiety symptoms [27]. High neuroticism scores were found to predict worse cognitive function and increased progression to AD in ε4 carriers [28]. Given the range of studies suggesting relationships among APOE ε4, anxiety, and AD, Burke et al. [29] explored the impact of anxiolytics on AD risk and found decreased hazard ratios for AD development among APOE ε4 carriers whose anxiety had been treated pharmacologically. These findings indicated that anxiety-related changes to brain structure and/or functioning may impact AD progression, but a need for clarification remains.

Regional brain atrophy, notably in medial temporal regions, has been correlated with the underlying severity of neurodegenerative diseases, such as AD. Atrophy of this region is strongly associated with the severity of memory deficits and overall cognitive impairment [30]. Structural neuroimaging can be used to distinguish among levels of neurodegeneration into classifications such as cognitively normal, MCI, and AD [18,31,32]. Analyzing regional brain atrophy in structural MRI scans is considered an unbiased way of assessing disease severity across different ethnic, linguistic, and demographic groups [33–39]. Studies focused on neurodegenerative conditions frequently use hippocampal volume as a biomarker in both AD and non-AD neurodegenerative conditions [40,41].

Structural brain changes have been associated with various anxiety disorders. Impaired hippocampal neurogenesis has been found in rodents exposed to stressful experimental conditions [42,43], while human research exploring anxiety disorders and brain morphology found an association between hippocampal volume and generalized anxiety disorder (GAD) [44,45], but this was not always a consistent finding [46]. A systematic review of existing structural neuroimaging studies with participants diagnosed with GAD found varied results that differed by age: greater amygdala volumes were observed in anxious children, adolescents, and adults, but not older adults when compared to healthy controls, while larger prefrontal volumes were observed in anxious adults compared to controls, but not children or older adults [47,48]. The field's examination of the influence of late-life GAD on regional brain volumes is very limited. In their systematic review and meta-analysis, Hilbert and colleagues [47] found that only one of 15 studies, by Mohlman et al. [48] examined older brains. Focusing on three regions of interest (ROI), the amygdala, medial orbital prefrontal cortex, and dorsolateral prefrontal cortex in 30 adults aged 60 and older. Similarly, Andreescu et al. [49] investigated global and regional volumes in 59 GAD-diagnosed and otherwise healthy older (aged 60+) adults. While both studies found that anxiety influenced regional brain volumes, they produced different results, likely related to methodological differences. Recent research has reported functional salience and executive network connectivity pathologies in participants diagnosed with GAD compared to healthy controls; GAD patients exhibited greater connectivity between regions involved in the prediction of an affective response to negative future events, and less varied connectivity between regions involved in reappraisal activity [50]. Pharmacologic treatment improved salience network-orbitofrontal cortex functional connectivity, but the study did not measure brain tissue atrophy or structural integrity, so the relationship between functional connectivity and ROI volumes in the context of late-life anxiety remains unclear. A recent study of cognitively healthy young and older adults that examined brain atrophy and structural integrity suggested that measures of structural integrity and "gray matter structure, such as cortical volume and thickness, are related to the aging brain's ability to engage and coordinate large-scale functional networks that are central to efficient cognitive functioning and might underlie age-related cognitive decline[51]." However, a strong association between two brain regions may not represent a functional connection of the neurons [52].

Additional research using considerably larger and better powered samples is necessary to evaluate the role of late-life anxiety as a risk factor for neurodegeneration/AD and to clarify the mechanism(s) through which it influences regional and global brain atrophy or hypertrophy. The present study sought to determine the association between anxiety and regional brain volumes and the association between cognitive status and regional brain volumes as moderated by APOE ε4 genotype and anxiety respectively, to identify neuroimaging biomarkers that may correspond with disease severity and stage.

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 1533 participants (mean age: 71.88; SD: 10.3). Initiated in 2005, the NACC UDS is a longitudinal dataset comprised of data collected from yearly assessments of study participants at the NIA-funded Alzheimer's Disease Research Centers (ADRCs) across the country [53]. The UDS and neuroimaging data examined for this study were submitted voluntarily to NACC from 15 different ADRCs. UDS data were collected by trained clinicians and personnel using standardized evaluation and uniform methods for each study subject. Participants were required to have a co-participant or "study partner," typically family members or close friends with significant weekly contact with the subject [53]. The UDS incorporates longitudinal demographics, family and health history, clinical, neuropsychological, and diagnostic data

including medications [54].

Anxiety

Anxiety was measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q;[55]). The NPI-Q is a validated scale, which measures 12 domains: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor activity, night-time behavioral disturbances (sleep disturbance), and appetite and eating abnormalities. This measure is completed by asking the study partner about the presence or absence of each of these behaviors in the participant. For this study, anxiety was measured in a dichotomous fashion using one question from the NPI-Q, "Does {the participant} become upset when separated from you? Does he or she have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?"

Cognitive status

Cognitive status was determined at the ADRC level by a single clinician or a consensus conference. Using the variable naccudsd, participants were classified into one of four groups: normal cognition (n = 832), impaired not MCI (n = 49), mild cognitive impairment (MCI, n = 385), or dementia (n = 217).

Structural MRI regions

Each structural MRI region was examined in relation to the NPI-Q anxiety item. Thirty regions were evaluated, including total brain 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. The NACC provided volumetric summary data for global and regional measures. Calculations were performed by the IDeA Lab (Director: Charles DeCarli, MD; University of California, Davis; http://idealab.ucdavis.edu), following Alzheimer's Disease Neuroimaging Initiative (ADNI) protocols [56].

APOE genotype

The Alzheimer's Disease Center obtained APOE samples using either a blood draw or a buccal swab to determine APOE genotype. NACC provided data for all six possible genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, or ε4/ε4), and for this study were collapsed into ε4 carriers (ε2/ε4, ε3/ε4, and ε4/ε4) vs. non-ε4 carriers (ε2/ε2, ε2/ε3, ε3/ε3).

Statistical analyses

We calculated the mean and standard deviation for continuous variables and the frequency distribution for categorical variables. We compared the two study groups (anxiety vs. no reported anxiety), using the two-sample t-test for continuous variables and the chi-square test for categorical variables. We compared four cognitive statuses (normal cognition, impaired not MCI, MCI, and dementia) using ANOVA for continuous variables and the chi-square test for categorical variables. We employed multiple linear regressions to estimate the adjusted effect of anxiety on the respective structural MRI regions. The control variables were intracranial volume, age, sex, years of education, race, and Hispanic ethnicity. We also investigated the moderation effect of APOE ε4 carrier status on the association between structural MRI features and anxiety by testing the interaction effect between APOE ε4 and anxiety in the aforementioned multiple linear regressions. The moderation effect of anxiety on the association between the structural MRI regions and cognitive status was also examined by testing the interaction effect between anxiety and cognitive status in a separate regression model. 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. All analyses were conducted in SAS 9.4 [57].

Results

The average age of 1533 participants was 71.88 years (SD = 10.30). The sample was majority female (57.66%), and 42.34% male. Most of the sample identified as White (84.29%), almost 12% of the sample identified as Black (11.98%), and 3.73% were other races. Nine percent (9.19%) of the overall sample identified as Hispanic). Less than half of the sample were APOE ε4 carriers (41.88%). The average years of education was 15.01 (SD = 3.55 years); educational obtainment was significantly lower for participants with anxiety (p = 0.004). APOE ε4 carriers comprised a large percentage of participants reporting anxiety (21.65% vs. 14.48% for non-ε4 carriers, $p < 0.001$). Among the four cognitive groups there were statistically significant differences for the following factors: sex ($p < 0.0001$), Hispanic ethnicity ($p < 0.001$), APOE eε4 carrier status ($p < 0.0001$), and race (p = 0.034). (See Table 1 and Supplemental Table 1A).

Five of 30 structural MRI biomarkers demonstrated significantly higher means in participants with anxiety, including total cerebral (CSF) volume, left lateral ventricular volume, right lateral ventricular volume, total lateral ventricular volume, and total third ventricular volume. In contrast, 14 out of 30 structural MRI biomarkers had significantly lower means for participants with anxiety, including total brain gray volume, total cerebrum gray volume, left hippocampal volume, right hippocampal volume, hippocampal volume, left frontal lobe cortical gray volume, right frontal lobe cortical gray volume, total frontal lobe cortical gray volume, left parietal lobe cortical 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 (please see Table 1).

After controlling for intracranial volume, age, sex, years of education, race and Hispanic ethnicity, six MRI biomarkers showed higher volumes among participants with anxiety: total brain CSF volume (B = 9.710, 95% CI = (4.298, 14.0416), FDR corrected $p < 0.001$), total CSF volume (B = 8.848, 95% CI = (4.519, 13.176), FDR corrected $p < 0.0001$), left lateral ventricular volume (B = 1.844, 95% CI = (0.554, 3.133), FDR corrected p = 0.007), right lateral ventricular volume (B = 2.145, 95% CI = (0.906, 3.384), FDR corrected p = 0.001), total lateral ventricular volume (B = 3.989, 95% CI = (1.543, 6.435), FDR corrected p = 0.002), and total third ventricular volume (B = 0.101, 95% CI = (0.041, 0.160), FDR corrected p = 0.001) (please see Table 2).

On the other hand, after controlling the aforementioned covariates, 16 out of 30 structural MRI biomarkers demonstrated lower volumes among participants with anxiety, including total brain gray volume (B = −10.146, 95% CI = (−15.232,−5.059), FDR corrected $p < 0.0001$), total brain gray matter volume (B = −10.583, 95% CI = (−14.074, −7.091), FDR corrected $p < 0.0001$), total cerebrum brain volume (B = −11.011, 95% CI = (−15.632, −6.390), FDR corrected $p < 0.0001$), total cerebrum gray matter volume (B = −12.134, 95% CI = (−15.651, −8.618), FDR corrected $p < 0.0001$), left hippocampus volume (B = −0.159, 95% CI = (−0.212,−0.107), FDR corrected $p < 0.0001$), right hippocampus volume (B = −0.197, 95% CI = (−0.248, −0.146), FDR corrected $p < 0.0001$), hippocampal volume (B = −0.356, 95% CI = (−0.454, −0.258), FDR corrected $p < 0.0001$), left frontal lobe cortical gray matter volume (B = −1.690, 95% CI = (−2.530, −0.850), FDR corrected $p < 0.0001$), right frontal lobe cortical gray matter volume (B = −2.119, 95% CI = (−2.877, −1.361), FDR corrected $p < 0.0001$), total frontal lobe cortical gray matter volume (B = −3.831, 95% CI = (−5.381, −2.280), FDR corrected $p < 0.0001$), left parietal lobe cortical gray matter volume (B = −0.940, 95% CI = (−1.440, −0.441), FDR corrected $p < 0.001$), right parietal lobe cortical gray matter volume (B = −1.229, 95% CI = (−1.747, −0.711), FDR corrected $p < 0.0001$), total parietal lobe cortical gray matter volume (B = −2.160, 95% CI = (−3.104, −1.215), FDR corrected $p < 0.0001$), left temporal lobe cortical gray

Table 1
Participant Composition by Anxiety Status.

Variables	Overall		Anxiety		No Anxiety		
	$N = 1533$		$N = 268$		$N = 1265$		
	N	%	N	%	N	%	p value
Sex							0.065
Male	649	42.34	127	19.57	522	80.43	
Female	884	57.66	141	15.95	743	84.05	
Race[a]							0.722
Black	183	11.98	30	16.39	153	83.61	
Other	57	3.73	12	21.05	45	78.95	
White	1288	84.29	226	17.55	1062	82.45	
Hispanic[b]							0.081
Yes	140	9.19	32	22.86	108	77.14	
No	1384	90.81	235	16.98	1149	83.02	
e4 carrier							**< 0.001**
Yes	642	41.88	139	21.65	503	78.35	
No	891	58.12	129	14.48	762	85.52	

	Mean	SD	Mean	SD	Mean	SD	p value	FDR p value
Age	71.881	10.295	71.918	9.621	71.873	10.436	0.948	N/A
Education[c]	15.010	3.553	14.445	3.825	15.129	3.483	**0.004**	N/A
Total intracranial volume	1363.870	142.438	1363.400	138.700	1364.000	143.300	0.947	0.947
Total white matter volume	450.727	60.540	452.600	58.387	450.300	61.002	0.585	0.698
Total brain volume	1015.060	114.370	1006.700	109.600	1016.800	115.300	0.186	0.250
Total brain CSF volume	340.657	63.348	347.800	61.571	339.200	63.641	**0.043**	0.067
Total brain gray matter volume	572.491	62.624	563.000	60.850	574.500	62.834	**0.007**	**0.013**
Total brain white matter volume	442.572	62.284	443.600	60.306	442.300	62.716	0.760	0.803
Total brain white matter hyperintensity volume	8.155	11.788	8.935	12.759	7.990	11.570	0.233	0.301
Total cerebrum cranial volume	1175.640	128.457	1173.600	125.000	1176.100	129.200	0.777	0.803
Total cerebrum brain volume	888.338	101.821	879.300	97.420	890.300	102.700	0.109	0.161
Total cerebrum CSF volume	287.303	55.647	294.300	54.866	285.800	55.719	**0.023**	**0.037**
Total cerebrum gray matter volume	475.613	57.863	464.600	56.786	477.900	57.843	**0.001**	**0.003**
Total cerebrum white matter volume	404.595	57.261	405.700	55.766	404.400	57.592	0.723	0.803
Left hippocampus volume	3.006	0.478	2.871	0.491	3.034	0.470	**<0.0001**	**<0.001**

	Overall Mean	SD	Anxiety Mean	SD	No Anxiety Mean	SD	p value	FDR p value
Right hippocampus volume	3.073	0.475	2.910	0.503	3.108	0.462	**<0.0001**	**<0.001**
Hippocampal volume	6.079	0.920	5.781	0.959	6.142	0.900	**<0.0001**	**<0.001**
Left lateral ventricle volume	18.862	11.753	20.497	12.552	18.516	11.552	**0.012**	**0.022**
Right lateral ventricle volume	17.485	11.151	19.430	11.660	17.073	11.001	**0.002**	**0.005**
Total lateral ventricle volume	36.351	22.400	39.930	23.622	35.592	22.068	**0.004**	**0.009**
Total third ventricle volume	1.378	0.581	1.473	0.585	1.358	0.578	**0.003**	**0.009**
Left frontal lobe cortical gray matter volume	82.621	11.854	81.001	11.755	82.964	11.851	**0.014**	**0.024**
Right frontal lobe cortical gray matter volume	82.875	10.997	80.938	11.086	83.285	10.939	**0.002**	**0.005**
Total frontal lobe cortical gray matter volume	166.113	22.776	162.500	22.683	166.900	22.733	**0.005**	**0.010**
Left occipital lobe cortical gray matter volume	28.744	4.544	28.661	4.772	28.761	4.496	0.743	0.803
Right occipital lobe cortical gray matter volume	29.329	4.719	28.919	4.833	29.416	4.692	0.117	0.165
Total occipital lobe cortical gray matter volume	58.178	8.842	57.709	9.152	58.277	8.776	0.339	0.421
Left parietal lobe cortical gray matter volume	45.797	6.169	44.926	6.202	45.981	6.149	**0.011**	**0.021**
Right parietal lobe cortical gray matter volume	46.360	6.270	45.239	6.486	46.598	6.200	**0.001**	**0.005**
Total parietal lobe cortical gray matter volume	92.252	12.126	90.267	12.286	92.673	12.055	**0.003**	**0.009**
Left temporal lobe cortical gray matter volume	58.644	7.182	56.722	7.098	59.051	7.136	**<0.0001**	**<0.001**
Right temporal lobe cortical gray matter volume	56.200	6.943	54.062	7.033	56.653	6.841	**<0.0001**	**<0.001**
Total temporal lobe cortical gray matter volume	115.091	13.831	111.000	13.680	116.000	13.713	**<0.0001**	**<0.001**

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

matter volume ($B = -2.308$, 95% CI = (−2.923, −1.694), FDR corrected $p < 0.0001$), right temporal lobe cortical gray matter volume ($B = -2.601$, 95% CI = (−3.200, −2.001), FDR corrected $p < 0.0001$), and total temporal lobe cortical gray matter volume ($B = -4.921$, 95% CI = (−6.064, −3.778), FDR corrected $p < 0.0001$) (Table 2).

After adding cognitive status to the list of covariates, 7 out of 30 structural MRI biomarkers demonstrated lower volumes among participants with anxiety, including total cerebrum gray matter volume ($B = -4.439$, 95% CI = (−7.810, −1.069), FDR corrected $p = 0.042$), right hippocampus volume ($B = -0.100$, 95% CI = (−0.150, −0.050), FDR corrected $p = 0.001$), hippocampal volume ($B = -0.147$, 95% CI = (−0.242, −0.053), FDR corrected $p = 0.001$), right frontal lobe cortical gray matter volume ($B = -1.050$, 95% CI = (−1.812, −0.289), FDR corrected $p = 0.034$), left temporal lobe cortical gray matter volume ($B = -0.905$, 95% CI = (−1.489, −0.321), FDR corrected $p = 0.014$), right temporal lobe cortical gray matter volume ($B = -1.240$, 95% CI = (−1.811, −0.670), FDR corrected $p = 0.001$), and total temporal lobe cortical gray matter volume ($B = -2.160$, 95% CI = (−3.233, −1.087), FDR corrected $p = 0.001$) (Table 2a).

APOE ε4 carrier status had a significant moderating effect on the association between anxiety and 10 structural MRI features, but while numerically different, these results were no longer significant after the FDR correction for multiple comparisons. These biomarkers included total white volume ($p = 0.024$), total brain gray volume ($p = 0.009$), total brain white matter hyperintensity volume ($p = 0.031$), total cerebrum gray volume ($p = 0.025$), total third ventricular volume ($p = 0.042$), left parietal lobe cortical gray volume ($p = 0.002$), right parietal lobe cortical gray volume ($p = 0.038$), total parietal lobe cortical gray

Table 2
Adjusted Effect of Anxiety on Regional Brain Volumes.

MRI volumetric variables (all continuous)	Anxiety - Yes vs. No (N = 1512)				
	B	SE	95% CI	*p* value	FDR corrected *p* value
Total white matter volume	1.413	2.283	(−3.065,5.892)	0.536	0.590
Total brain volume	−10.146	2.593	(−15.232,−5.059)	**<0.0001**	**<0.0001**
Total brain CSF volume	9.170	2.484	(4.298,14.0416)	**<0.001**	**<0.001**
Total brain gray matter volume	−10.583	1.780	(−14.074,−7.091)	**<0.0001**	**<0.0001**
Total brain white matter volume	0.437	2.319	(−4.111,4.986)	0.850	0.880
Total brain white matter hyperintensity volume	0.976	0.730	(−0.455,2.408)	0.181	0.209
Total cerebrum cranial volume	−2.164	1.107	(−4.336,0.008)	0.051	0.064
Total cerebrum brain volume	−11.011	2.356	(−15.632,−6.390)	**<0.0001**	**<0.0001**
Total cerebrum CSF volume	8.848	2.207	(4.519,13.176)	**<0.0001**	**<0.0001**
Total cerebrum gray matter volume	−12.134	1.793	(−15.651,−8.618)	**<0.0001**	**<0.0001**
Total cerebrum white matter volume	0.125	2.234	(−4.258,4.507)	0.955	0.955
Left hippocampus volume	−0.159	0.027	(−0.212,−0.107)	**<0.0001**	**<0.0001**
Right hippocampus volume	−0.197	0.026	(−0.248,−0.146)	**<0.0001**	**<0.0001**
Hippocampal volume	−0.356	0.050	(−0.454,−0.258)	**<0.0001**	**<0.0001**
Left lateral ventricle volume	1.844	0.657	(0.554,3.133)	**0.005**	**0.007**
Right lateral ventricle volume	2.145	0.632	(0.906,3.384)	**0.001**	**0.001**
Total lateral ventricle volume	3.989	1.247	(1.543,6.435)	**0.001**	**0.002**
Total third ventricle volume	0.101	0.030	(0.041,0.1601)	**0.001**	**0.001**
Left frontal lobe cortical gray matter volume	−1.690	0.428	(−2.530,−0.850)	**<0.0001**	**<0.0001**
Right frontal lobe cortical gray matter volume	−2.119	0.386	(−2.877,−1.361)	**<0.0001**	**<0.0001**
Total frontal lobe cortical gray matter volume	−3.831	0.790	(−5.381,−2.280)	**<0.0001**	**<0.0001**
Left occipital lobe cortical gray matter volume	−0.117	0.229	(−0.566,0.332)	0.608	0.652
Right occipital lobe cortical gray matter volume	−0.476	0.230	(−0.926,−0.025)	**0.039**	0.051
Total occipital lobe cortical gray matter volume	−0.564	0.420	(−1.389,0.260)	0.180	0.209
Left parietal lobe cortical gray matter volume	−0.940	0.255	(−1.440,−0.441)	**0.000**	**<0.001**
Right parietal lobe cortical gray matter volume	−1.229	0.264	(−1.747,−0.711)	**<0.0001**	**<0.0001**
Total parietal lobe cortical gray matter volume	−2.160	0.481	(−3.104,−1.215)	**<0.0001**	**<0.0001**
Left temporal lobe cortical gray matter volume	−2.308	0.313	(−2.923,−1.694)	**<0.0001**	**<0.0001**
Right temporal lobe cortical gray matter volume	−2.601	0.306	(−3.200,−2.001)	**<0.0001**	**<0.0001**
Total temporal lobe cortical gray matter volume	−4.921	0.582	(−6.064,−3.778)	**<0.0001**	**<0.0001**

*adjusted by intracranial volume, sex, age, education, race, and Hispanic ethnicity.

volume (p = 0.005), right temporal lobe cortical gray volume (p = 0.044), and total temporal lobe cortical gray volume (p = 0.048; Table 3)). APOE ε4 carriers with anxiety had higher total white matter volumes (B = = 10.337, 95% CI = (1.351,19.322)), total brain white matter hyperintensity volume (B = 3.155, 95% CI = (0.283,6.027)), and total third ventricular volume (B = 0.124, 95% CI = (0.005,0.242)) compared to non-ε4 carriers with anxiety. APOE ε4 carriers with anxiety had lower total brain gray volume (B = −9.343, 95% CI = (−16.340, −2.346)), total cerebrum gray volume (B = −8.044, 95% CI = (−15.087,−1.001), left parietal lobe cortical gray volume (B = −1.58, 95% CI = (−2.584,−0.583)), right temporal lobe cortical gray volume (B = −1.235, 95% CI = (−2.435,−0.034)), total parietal lobe cortical gray volume (B = −2.687, 95% CI = (−4.580,−0.794)), right temporal lobe cortical gray volume (B = −1.235, 95% CI = (−2.435,−0.034)), and total temporal lobe cortical gray volume (B = −2.308, 95% CI = (−4.596,−0.020)) compared to compared to non-ε4 carriers with anxiety. However, the above results were not significant after the FDR correction for multiple comparisons (Table 3). In Table 3a, we further adjust for cognitive status in addition to the previous covariates, and APOE ε4 carrier status still did not have a significant moderating effect on the association between anxiety and MRI features.

All structural MRI features except total intracranial volume and total cerebral volume demonstrated numerically different means across the four cognitive groups, but the results were not significant after performing FDR correction for multiple comparisons (Supplemental Table 1A). Anxiety significantly moderated the association between cognitive status and two biomarkers, including right (p = 0.017) and total (p = 0.038) temporal lobe cortical gray volume. Participants with anxiety and MCI had lower right temporal lobe cortical gray volume (B = −2.047, 95% CI = (−3.395, −0.700), p = 0.003) or dementia (B = −1.608, 95% CI = (−3.070, −0.145), p = 0.031). Similarly, participants with anxiety and MCI had lower total temporal lobe cortical gray volume (B = −3.649, 95% CI = (−6.185, −1.113), p = 0.005). However, none of the differences were significant after performing FDR correction for multiple comparisons (See Table 4).

Discussion

In this study we sought to determine 1) the effect of anxiety on specific regional brain volumes; 2) the moderation effect of APOE ε4 genotype on the association between anxiety and 30 specific brain structures; and 3) the moderation effect of anxiety on the association between cognitive status and 30 brain-related imaging features. Our investigation addressed a significant gap in the literature, which has almost exclusively assessed middle-aged adult and youth samples to explore the effects of anxiety on regional brain volumes, despite extensive evidence that age is closely associated with gray matter atrophy [58] and white matter hyperintensity (WMH) levels [59]. Our hypothesis that significant structural differences would be identified in the brains of older adults who experience NPI-Q-measured anxiety was supported by these analyses of data from the large, well-characterized NACC database that included over 1500 participants - a considerable expansion from existing studies' small sample sizes [48,49]. Cognitive status and the role of APOE genotype were investigated based on evidence linking neuropsychiatric symptoms to stages of cognitive decline. Our findings indicate that APOE ε4 carrier status influences regional gray matter volumes in healthy cognition, MCI, and AD [60,61] and interacts with anxiety to increase the risk for AD [29].

Our study revealed that after controlling for intracranial volume, age, sex, years of education, race, and Hispanic ethnicity, 16.7% (5/30) of the structural MRI features examined (total CSF volume, left and right lateral ventricular, total lateral ventricular, and third ventricular volumes) were higher in participants with anxiety, while over 50% (16/30) had significantly lower means for participants reporting anxiety (total brain, total cerebrum, and all hippocampal, frontal, parietal, temporal volumes) compared to participants reporting an absence of anxiety (Table 2). After additionally controlling for cognitive status, 23% (7/30) of the MRI features had reduced volumes among individuals with

Table 2a
Adjusted Effect of Anxiety on Regional Brain Volumes.

MRI volumetric variables (all continuous)	Anxiety - Yes vs. No ($N = 1512$)				
	B	SE	95% CI	*p* value	FDR corrected *p* value
Total white matter volume	3.465	2.363	(−1.171, 8.101)	0.143	0.306
Total brain volume	−0.226	2.529	(−5.187, 4.736)	0.929	0.929
Total brain CSF volume	0.392	2.444	(−4.401, 5.186)	0.873	0.929
Total brain gray matter volume	−3.857	1.740	(−7.270, −0.444)	0.027	0.100
Total brain white matter volume	3.631	2.393	(−1.062, 8.325)	0.129	0.298
Total brain white matter hyperintensity volume	−0.166	0.750	(−1.637, 1.305)	0.824	0.929
Total cerebrum cranial volume	−0.197	1.138	(−2.428, 2.035)	0.863	0.929
Total cerebrum brain volume	−0.878	2.255	(−5.301, 3.545)	0.697	0.909
Total cerebrum CSF volume	0.682	2.160	(−3.555, 4.918)	0.752	0.929
Total cerebrum gray matter volume	−4.439	1.718	(−7.810, −1.069)	**0.010**	**0.042**
Total cerebrum white matter volume	3.689	2.297	(−0.817, 8.195)	0.108	0.271
Left hippocampus volume	−0.048	0.026	(−0.098, 0.003)	0.064	0.192
Right hippocampus volume	−0.100	0.025	(−0.150, −0.050)	**<0.0001**	**0.001**
Hippocampal volume	−0.147	0.048	(−0.242, −0.053)	**0.002**	**0.014**
Left lateral ventricle volume	−0.540	0.646	(−1.808, 0.728)	0.404	0.650
Right lateral ventricle volume	−0.064	0.623	(−1.286, 1.159)	0.918	0.929
Total lateral ventricle volume	−0.606	1.223	(−3.006, 1.793)	0.620	0.846
Total third ventricle volume	0.018	0.030	(−0.042, 0.078)	0.557	0.796
Left frontal lobe cortical gray matter volume	−0.499	0.430	(−1.342, 0.345)	0.246	0.462
Right frontal lobe cortical gray matter volume	−1.050	0.388	(−1.812, −0.289)	**0.007**	**0.034**
Total frontal lobe cortical gray matter volume	−1.575	0.792	(−3.129, −0.022)	0.047	0.156
Left occipital lobe cortical gray matter volume	0.264	0.235	(−0.197, 0.725)	0.262	0.462
Right occipital lobe cortical gray matter volume	−0.025	0.235	(−0.486, 0.437)	0.916	0.929
Total occipital lobe cortical gray matter volume	0.261	0.430	(−0.581, 1.104)	0.543	0.796
Left parietal lobe cortical gray matter volume	−0.210	0.256	(−0.711, 0.292)	0.412	0.650
Right parietal lobe cortical gray matter volume	−0.472	0.265	(−0.993, 0.048)	0.075	0.206
Total parietal lobe cortical gray matter volume	−0.681	0.481	(−1.625, 0.263)	0.157	0.315
Left temporal lobe cortical gray matter volume	−0.905	0.298	(−1.489, −0.321)	**<0.0001**	**0.014**
Right temporal lobe cortical gray matter volume	−1.240	0.291	(−1.811, −0.670)	**<0.0001**	**0.001**
Total temporal lobe cortical gray matter volume	−2.160	0.547	(−3.233, −1.087)	**<0.0001**	**0.001**

*adjusted by intracranial volume, sex, age, education, race, Hispanic ethnicity, and cognitive status.

anxiety (Table 2a). The paucity of geriatric samples in studies of the association between anxiety and brain morphology [62] limits direct comparison of this study's results, however, the outcomes have both similarities with and differences from existing studies. Mohlman and colleagues [48] investigated associations between two prefrontal cortex ROIs (medial orbital prefrontal cortex and dorsolateral prefrontal cortex) and amygdala volumes, and measures of GAD, including the Spielberger State-Trait Anxiety Inventory [63] and the Penn State Worry Questionnaire [64], in adults aged 60 and older. Their methodology allowed for the evaluation of two theories of the effects of GAD on morphology: GAD represents greater activity in the prefrontal region along with negative affect and amygdala hypo-arousal or, alternately, amygdala overactivity with poor frontal control. Mohlman et al. [48] evaluation of three ROIs allowed only a limited view of regional brain volume change, in contrast to the extensive gray matter volume reduction our study observed in participants who endorsed the NPI anxiety item. Mohlman et al. [48] smaller sample ($n = 30$) found that worry, not a GAD diagnosis, was associated with greater mean medial orbital prefrontal cortex volume, although not dorsolateral prefrontal cortex or amygdala volumes. Greater prefrontal volumes have been identified in anxious middle-aged adults [47]. Prefrontal hypertrophy may thus be linked to worry activity that involves the over recruitment of left and frontal regions in an attempt to manage physiological arousal cues rather than the somatic concerns associated with GAD [48]. The NPI-Q anxiety item used in this study (see methods section for exact language of the question) relies heavily on observable behavior rather than reported cognition and may better capture somatic symptoms, which may be more common in older adults due to alterations in brain tissue associated with aging [48].

Using the Hamilton Anxiety rating scale [65], Andreescu and colleagues [49] evaluated regional gray matter volumes in 59 older adults who had been diagnosed with GAD for at least six months (structured clinical interview for DSM-IV Axis I disorders [66]) and healthy controls, as well as white matter integrity measured through mean diffusion tensor imaging and fractional anisotropy. Similar to our study's results, they found no difference in WMH (global or otherwise) between participants with GAD and healthy controls. Their analysis, however, did not investigate the influence of APOE ε4 genotype, which in our study, interacted with anxiety to produce a higher rate of WMH in anxious ε4 carriers. Means for global WMH burden or white matter fractional anisotropy were also similar between groups. Numerical, but statistically insignificant (after FDR correction) differences were observed in mean diffusivity (left frontal middle orbital gyrus and left pallidum), cortical thickness (left rostral anterior cingulate cortex), and gray matter volume between groups (right inferior frontal gyrus pars triangularis and pars opercularis) after adjusting for age. Andreescu et al. [49] found moderate effect sizes in the inferior frontal gyrus, orbitofrontal cortex, and rostral ACC. Age, but not GAD diagnosis in their study, was associated with differences in structural integrity: greater WMH burden globally and in the left interior longitudinal fasciculus and left cingulum bundle, lower mean diffusivity in the left caudate, left orbitofrontal cortex, left lateral orbitofrontal cortex, left interior orbitofrontal cortex

Table 3
Moderation effect of APOE E4 for participants reporting anxiety.

MRI volumetric variables (all continuous)	Anxiety (Yes vs. No)				APOE e4 (Yes vs. No)				Anxiety*APOE e4			
	B	95% CI	*p* value	FDR *p* value	*B*	95% CI	*p* value	FDR *p* value	*B*	95% CI	*p* value	FDR *p* value
Total white matter volume	−3.861	(−10.250, 2.527)	0.236	0.365	−1.469	(−5.310, 2.372)	0.453	0.777	10.337	(1.351, 19.322)	**0.024**	0.144
Total brain volume	−8.843	(−16.108, −1.578)	**0.017**	**0.04**	−1.267	(−5.635, 3.102)	0.57	0.777	−2.161	(−12.380, 8.057)	0.678	0.744
Total brain CSF volume	9.505	(2.545, 16.465)	**0.008**	**0.019**	1.494	(−2.691, 5.678)	0.484	0.777	−0.994	(−10.783, 8.795)	0.842	0.871
Total brain gray matter volume	−5.644	(−10.618, −0.669)	**0.026**	0.056	−0.025	(−3.016, 2.967)	0.987	0.987	−9.343	(−16.340, −2.346)	**0.009**	0.089
Total brain white matter volume	−3.199	(−9.693, 3.295)	0.334	0.418	−1.242	(−5.147, 2.663)	0.533	0.777	7.182	(−1.952, 16.316)	0.123	0.26
Total brain white matter hyperintensity volume	−0.662	(−2.704, 1.380)	0.525	0.583	−0.227	(−1.454, 1.001)	0.717	0.847	3.155	(0.283, 6.027)	**0.031**	0.144
Total cerebrum cranial volume	−2.823	(−5.922, 0.275)	0.074	0.139	−2.094	(−3.957, −0.230)	**0.028**	0.208	1.752	(−2.607, 6.110)	0.431	0.543
Total cerebrum brain volume	−11.549	(−18.145, −4.954)	**0.001**	**0.003**	−3.481	(−7.447, 0.484)	0.085	0.344	1.856	(−7.421, 11.133)	0.695	0.744
Total cerebrum CSF volume	8.726	(2.547, 14.909)	**0.006**	**0.017**	1.388	(−2.330, 5.105)	0.464	0.777	−0.105	(−8.801, 8.592)	0.981	0.981
Total cerebrum gray matter volume	−7.673	(−12.680, −2.665)	**0.003**	**0.009**	−1.656	(−4.667, 1.354)	0.281	0.602	−8.044	(−15.087, −1.001)	**0.025**	0.144
Total cerebrum white matter volume	−3.249	(−9.505, 3.008)	0.309	0.409	−1.604	(−5.366, 2.157)	0.403	0.777	6.771	(−2.029, 15.571)	0.131	0.26
Left hippocampus volume	−0.133	(−0.207, −0.057)	**0.001**	**0.003**	−0.089	(−0.134, −0.044)	**<0.0001**	**<0.001**	−0.029	(−0.133, 0.076)	0.59	0.708
Right hippocampus volume	−0.159	(−0.231, −0.086)	**<0.0001**	**<0.001**	−0.087	(−0.130, −0.043)	**<0.0001**	**<0.001**	−0.051	(−0.153, 0.050)	0.325	0.487
Hippocampal volume	−0.291	(−0.430, −0.151)	**<0.0001**	**<0.001**	−0.176	(−0.260, −0.092)	**<0.0001**	**<0.001**	−0.08	(−0.276, 0.116)	0.424	0.543
Left lateral ventricle volume	0.807	(−1.033, 2.646)	0.39	0.468	0.388	(−0.718, 1.494)	0.492	0.777	1.87	(−0.718, 4.457)	0.157	0.261
Right lateral ventricle volume	1.218	(−0.550, 2.986)	0.177	0.295	0.263	(−0.800, 1.326)	0.628	0.819	1.692	(−0.795, 4.179)	0.182	0.288
Total lateral ventricle volume	2.022	(−1.468, 5.513)	0.256	0.366	0.648	(−1.450, 2.747)	0.545	0.777	3.566	(−1.343, 8.475)	0.154	0.261
Total third ventricle volume	0.036	(−0.048, 0.120)	0.407	0.469	−0.004	(−0.055, 0.046)	0.873	0.903	0.124	(0.005, 0.242)	**0.042**	0.144
Left frontal lobe cortical gray matter volume	−1.209	(−2.408, −0.010)	0.048	0.096	−0.412	(−1.133, 0.309)	0.263	0.602	−0.81	(−2.496, 0.876)	0.346	0.494
Right frontal lobe cortical gray matter volume	−1.848	(−2.929, −0.766)	**0.001**	**0.003**	−0.625	(−1.274, 0.025)	0.06	0.334	−0.363	(−1.883, 1.156)	0.639	0.738
Total frontal lobe cortical gray matter volume	−3.047	(−5.259, −0.835)	**0.007**	**0.019**	−1.011	(−2.341, 0.318)	0.136	0.408	−1.24	(−4.351, 1.871)	0.434	0.543
Left occipital lobe cortical gray matter volume	0.329	(−0.311, 0.969)	0.314	0.409	−0.034	(−0.418, 0.351)	0.864	0.903	−0.837	(−1.737, 0.064)	0.069	0.18
Right occipital lobe cortical gray matter volume	−0.105	(−0.748, 0.538)	0.75	0.75	−0.074	(−0.460, 0.312)	0.708	0.847	−0.684	(−1.589, 0.221)	0.138	0.26
Total occipital lobe cortical gray matter volume	0.251	(−0.924, 1.426)	0.676	0.699	−0.102	(−0.809, 0.604)	0.777	0.863	−1.517	(−3.170, 0.136)	0.072	0.18
Left parietal lobe cortical gray matter volume	−0.154	(−0.865, 0.556)	0.67	0.699	0.4	(−0.027, 0.827)	0.067	0.334	−1.584	(−2.584, −0.583)	**0.002**	0.057
Right parietal lobe cortical gray matter volume	−0.657	(−1.395, 0.082)	0.082	0.144	0.077	(−0.367, 0.521)	0.734	0.847	−1.102	(−2.141, −0.062)	**0.038**	0.144
Total parietal lobe cortical gray matter volume	−0.801	(−2.146, 0.544)	0.243	0.365	0.48	(−0.329, 1.289)	0.245	0.602	−2.687	(−4.580, −0.794)	**0.005**	0.081
Left temporal lobe cortical gray matter volume	−1.71	(−2.585, −0.834)	**0.000**	0.001	−0.326	(−0.852, 0.200)	0.224	0.602	−1.055	(−2.286, 0.176)	0.093	0.215
Right temporal lobe cortical gray matter volume	−1.892	(−2.745, −1.038)	**<0.0001**	**<0.001**	−0.442	(−0.954, 0.071)	0.092	0.344	−1.235	(−2.435, −0.034)	**0.044**	0.144

(*continued on next page*)

Table 3 (*continued*)

MRI volumetric variables (all continuous)	Anxiety (Yes vs. No)				APOE ε4 (Yes vs. No)				Anxiety*APOE ε4			
	B	95% CI	*p* value	FDR *p* value	*B*	95% CI	*p* value	FDR *p* value	*B*	95% CI	*p* value	FDR *p* value
Total temporal lobe cortical gray matter volume	−3.605	(−5.232, −1.978)	**<0.0001**	**<0.001**	−0.754	(−1.732, 0.223)	0.131	0.408	−2.308	(−4.596, −0.020)	**0.048**	0.144

* $N = 1512$, adjusted by intracranial volume, sex, age, education, race, and Hispanic ethnicity.

and left amygdala, and lower fractional anisotropy in the right uncinate fasciculus. Their results, like our study and Mohlman et al. [48] analysis, highlight a potential role for the orbitofrontal cortex in anxiety in older adults [49]. Although unlike Mohlman et al. [48] who documented greater frontal gray matter volumes among worriers, data from our larger, well-powered sample suggest that gray matter atrophy in this region may be associated with deficits in emotional regulation. Such results are in line with previous studies that implicate (pre)frontal cortex ROIs in the neural regulation of emotion [67].

Our identification of general gray matter atrophy in the total cerebrum gray matter volume and all temporal regions in anxious participants represents a novel finding [47] and may be linked to age [58], highlighting the necessity of exploring late-life anxiety separately from early and middle age anxiety. The current study also identified lower mean volumes in all hippocampal features. While Mohlman et al. [48] and Andreescu et al. [49] did not measure hippocampal volumes in the context of anxiety disorders, non-geriatric samples have produced an association between hippocampal volume and GAD as well as social anxiety disorder, however not consistently [44–46,68–70]. Hippocampal volume has long been a variable of interest due to its association with late life memory dysfunction and AD disease progression [71], and its potential sensitivity to HPA axis dysfunction [72], which has been observed in individuals with anxiety [73]. Our earlier research revealed that anxiolytics used to treat GAD lowered the hazard for AD in APOE ε4 carriers [29]. Such results suggest that anxiety-related changes to brain structure and/or functioning may impact AD progression.

Despite links between anxiety and AD [47], and gray matter atrophy and cognitive deterioration [74], the moderating influence of anxiety on the association between cognitive status and MRI features was limited to right and total temporal lobe cortical gray matter volumes in participants in the MCI and dementia groups. The left temporal lobe cortical gray matter volume was significant in the interaction with anxiety and MCI; however, this significant association did not survive FDR correction. Wide-scale temporal lobe degeneration has been associated with greater emotional contagion (but not depression) in those with MCI and AD [75], highlighting this region as a site for future research investigating emotional regulation in the context of cognitive decline. Further investigation is needed to understand why this effect was limited to the right and total temporal lobe cortical gray matter volumes, given that medial temporal cortex atrophy has been identified as a biomarker for AD [76] and as a predictor of progression from MCI to AD [77].

The results of this study on the link between anxiety, AD and APOE ε4 carrier status could not support fully accepting the *a priori* hypotheses due to the complex nature of the relationship between ApoE ε4 carrier state, sex, years before or since menopause, obesity, diet, the environment, and other genetic traits. Recent studies have shown that there is a blunting of ApoE effects on AD risk in those of African ancestry, which may be due to other genetic variations [78]. The breadth and effects of these factors are not wholly understood. Some of these factors, particularly, timing to menopause, environmental factors, diet, obesity, and other concomitant, contributory genetic variations were not controlled for in this study [79,80]. Furthermore, in this study, late-onset Alzheimer's disease was studied as a homogeneous entity. Different subtypes of AD may exist. Further research is needed that is powered to capture any differences in the effects of anxiety and APOE carrier state not only by Alzheimer's disease subtype (i.e., typical (tau accumulation and atrophy in both hippocampus and association cortex), limbic-predominant, hippocampal-sparing, primary progressive aphasia, and minimal atrophy [19,81]) but also by severity of disease [82].

Our analysis of NACC data sought to address a gap in the literature examining regional volume differences in the brains of adults with late-life anxiety, including the influence of APOE genotype and cognitive status on results. The inclusion of four cognitive status groups allowed for precision regarding interactions between reports of anxiety and cognitive functioning, and as nearly half of our sample were ε4 carriers, should provide confidence in results documenting a role for APOE ε4 status in late-life anxiety. While this study has many strengths, certain limitations exist. As a secondary data analysis, the selection of additional or alternate measures was not possible. The NPI is a validated measure, and the anxiety item used for this study asks about the presence of multiple behaviors, but it cannot provide information about cognitive aspects of anxiety ("worry") as assessed in other studies [48,83,84] and therefore cannot distinguish between regional changes associated with somatic and cognitive complaints. This study was also cross-sectional, so it cannot account for change across time or provide clarity about whether anxiety is a prodromal symptom of AD or an independent risk factor [47].

Conclusion

Our current analysis detected a 33% higher rate of anxious symptoms in ε4 carriers compared to non-carriers, which is interesting in light of rodent studies that have found that apolipoprotein "plays a role in the regulation of anxiety which might involve histamine receptor-mediated signaling and steroidogenesis in the adrenal gland [85]." APOE ε4 carriers in the current study had different mean volumes for global measures (total white matter, total brain gray matter, total brain WMH, total cerebrum gray matter) as well as temporal and parietal MRI features. We could not identify other studies that examined the influence of APOE ε4 status on regional brain volumes in the context of anxiety, thus, the current study represents novel, but not surprising findings given the association between APOE ε4 and poorer cognitive performance in older adulthood [86] and in those with higher trait anxiety [87], as well as lower gray matter volumes [60,61], greater WMH [59], and poorer white matter structural integrity [88]. Our identification of greater ventricular volumes, while not examined elsewhere in GAD or late-life anxiety literature, has been observed in response to atrophy associated with bipolar disorder [89], schizophrenia [90], and neurodegenerative diseases [31], indicating that reductions in gray matter volume may contribute to ventricular expansion [91]. Future studies must incorporate methodologies that allow investigators to account for change across time and provide clarity about whether anxiety is a prodromal symptom of AD or an independent risk factor. Such knowledge is crucial to the development of tools that seek to predict AD and can assist researchers with the development and evaluation of interventions that improve quality of life in late adulthood and stave off the devastating effects of AD.

CRediT authorship contribution statement

Shanna L. Burke: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration,

Table 3a
Moderation effect of APOE E4 for participants reporting anxiety.

MRI volumetric variables (all continuous)	Anxiety (Yes vs. No)				APOE e4 (Yes vs. No)				Anxiety*APOE e4			
	B	95% CI	*p* value	FDR *p* value	*B*	95% CI	*p* value	FDR *p* value	*B*	95% CI	*p* value	FDR *p* value
Total white matter volume	−2.102	(−8.550, 4.345)	0.523	0.695	−0.347	(−4.217, 3.524)	0.861	0.904	10.907	(1.959, 19.855)	0.017	0.150
Total brain volume	−0.499	(−7.408, 6.411)	0.887	0.985	3.167	(−0.981, 7.314)	0.134	0.431	0.143	(−9.446, 9.731)	0.977	0.977
Total brain CSF volume	2.133	(−4.542, 8.808)	0.531	0.695	−2.504	(−6.511, 1.503)	0.220	0.431	−3.089	(−12.352, 6.174)	0.513	0.641
Total brain gray matter volume	−0.031	(−4.778, 4.717)	0.990	0.990	2.851	(0.001, 5.700)	0.050	0.293	−7.818	(−14.406, −1.230)	**0.020**	0.150
Total brain white matter volume	−0.468	(−7.001, 6.065)	0.888	0.985	0.316	(−3.606, 4.238)	0.874	0.904	7.961	(−1.106, 17.027)	0.085	0.245
Total brain white matter hyperintensity volume	−1.634	(−3.682, 0.413)	0.118	0.479	−0.663	(−1.892, 0.566)	0.290	0.470	2.947	(0.105, 5.788)	**0.042**	0.245
Total cerebrum cranial volume	−1.203	(−4.311, 1.905)	0.448	0.695	−1.228	(−3.093, 0.638)	0.197	0.431	2.115	(−2.199, 6.428)	0.336	0.486
Total cerebrum brain volume	−3.078	(−9.239, 3.083)	0.327	0.654	1.072	(−2.627, 4.770)	0.570	0.686	4.161	(−4.389, 12.711)	0.340	0.486
Total cerebrum CSF volume	1.875	(−4.024, 7.775)	0.533	0.695	−2.299	(−5.841, 1.242)	0.203	0.431	−2.046	(−10.234, 6.141)	0.624	0.693
Total cerebrum gray matter volume	−1.238	(−5.929, 3.454)	0.605	0.756	1.615	(−1.201, 4.432)	0.261	0.460	−6.447	(−12.958, 0.064)	0.052	0.245
Total cerebrum white matter volume	−0.255	(−6.527, 6.018)	0.937	0.985	0.106	(−3.660, 3.871)	0.956	0.956	7.683	(−1.022, 16.388)	0.084	0.245
Left hippocampus volume	−0.039	(−0.109, 0.031)	0.275	0.635	−0.040	(−0.082, 0.003)	0.066	0.293	−0.012	(−0.109, 0.085)	0.810	0.863
Right hippocampus volume	−0.078	(−0.148, −0.009)	0.027	0.423	−0.044	(−0.086, −0.002)	0.040	0.293	−0.036	(−0.133, 0.060)	0.460	0.628
Hippocampal volume	−0.117	(−0.249, 0.014)	0.080	0.423	−0.083	(−0.162, −0.005)	0.038	0.293	−0.048	(−0.230, 0.134)	0.604	0.693
Left lateral ventricle volume	−1.206	(−2.972, 0.560)	0.181	0.524	−0.665	(−1.725, 0.396)	0.219	0.431	1.382	(−1.069, 3.833)	0.269	0.448
Right lateral ventricle volume	−0.661	(−2.363, 1.042)	0.447	0.695	−0.694	(−1.717, 0.328)	0.183	0.431	1.250	(−1.113, 3.613)	0.300	0.473
Total lateral ventricle volume	−1.871	(−5.213, 1.472)	0.272	0.635	−1.362	(−3.368, 0.644)	0.183	0.431	2.635	(−2.003, 7.274)	0.265	0.448
Total third ventricle volume	−0.036	(−0.119, 0.047)	0.400	0.695	−0.041	(−0.091, 0.009)	0.107	0.401	0.110	(−0.006, 0.225)	0.063	0.245
Left frontal lobe cortical gray matter volume	−0.203	(−1.379, 0.972)	0.734	0.881	0.068	(−0.637, 0.774)	0.850	0.904	−0.585	(−2.216, 1.046)	0.482	0.629
Right frontal lobe cortical gray matter volume	−0.957	(−2.019, 0.104)	0.077	0.423	−0.198	(−0.835, 0.439)	0.542	0.686	−0.158	(−1.630, 1.315)	0.834	0.863
Total frontal lobe cortical gray matter volume	−1.152	(−3.317, 1.013)	0.297	0.636	−0.107	(−1.406, 1.193)	0.872	0.904	−0.812	(−3.817, 2.192)	0.596	0.693
Left occipital lobe cortical gray matter volume	0.632	(−0.010, 1.273)	0.054	0.423	0.135	(−0.250, 0.521)	0.490	0.681	−0.734	(−1.625, 0.156)	0.106	0.245
Right occipital lobe cortical gray matter volume	0.259	(−0.384, 0.902)	0.430	0.695	0.111	(−0.274, 0.497)	0.571	0.686	−0.567	(−1.459, 0.325)	0.212	0.398
Total occipital lobe cortical gray matter volume	0.912	(−0.262, 2.085)	0.128	0.479	0.250	(−0.454, 0.954)	0.486	0.681	−1.300	(−2.929, 0.328)	0.117	0.252
Left parietal lobe cortical gray matter volume	0.466	(−0.230, 1.162)	0.189	0.524	0.728	(0.310, 1.145)	0.001	0.019	−1.408	(−2.374, −0.443)	**0.004**	0.128
Right parietal lobe cortical gray matter volume	−0.022	(−0.746, 0.702)	0.953	0.985	0.404	(−0.031, 0.839)	0.068	0.293	−0.928	(−1.933, 0.077)	0.070	0.245
Total parietal lobe cortical gray matter volume	0.447	(−0.864, 1.758)	0.504	0.695	1.131	(0.344, 1.918)	0.005	0.073	−2.340	(−4.159, −0.520)	**0.012**	0.150
Left temporal lobe cortical gray matter volume	−0.541	(−1.354, 0.272)	0.192	0.524	0.299	(−0.189, 0.787)	0.230	0.431	−0.747	(−1.875, 0.382)	0.194	0.389
Right temporal lobe cortical gray matter volume	−0.768	(−1.563, 0.026)	0.058	0.423	0.164	(−0.313, 0.641)	0.499	0.681	−0.941	(−2.044, 0.161)	0.094	0.245
Total temporal lobe cortical gray matter volume	−1.314	(−2.809, 0.180)	0.085	0.423	0.476	(−0.421, 1.373)	0.298	0.470	−1.709	(−3.783, 0.365)	0.106	0.245

* $N = 1512$, adjusted by intracranial volume, sex, age, education, race, Hispanic ethnicity, and cognitive status.

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Table 4
Moderation effect of anxiety on cognitive status.

MRI volumetric variables (all continuous)	Anxiety*impaired not MCI				Anxiety *MCI				Anxiety *dementia				Anxiety*cognitive status	
	B	95% CI	*p*	FDR *p* value	***B***	95% CI	*p*	FDR *p* value	*B*	95% CI	*p*	FDR*	Type III *p* value	FDR p value
Total white matter volume	−14.018	(−40.578, 12.543)	0.301	0.757	−0.841	(−11.810, 10.128)	0.880	0.911	−10.776	(−22.678, 1.127)	0.076	0.300	0.230	0.634
Total brain volume	−1.852	(−30.300, 26.597)	0.898	0.968	−1.840	(−13.589, 9.909)	0.759	0.813	−8.858	(−21.607, 3.890)	0.173	0.370	0.580	0.669
Total brain CSF volume	5.442	(−22.034, 32.919)	0.698	0.910	4.824	(−6.524, 16.172)	0.405	0.636	10.992	(−1.321, 23.305)	0.080	0.300	0.380	0.634
Total brain gray matter volume	8.575	(−10.994, 28.145)	0.390	0.757	−3.983	(−12.065, 4.100)	0.334	0.636	−0.216	(−8.986, 8.554)	0.961	0.961	0.537	0.664
Total brain white matter volume	−10.427	(−37.323, 16.469)	0.447	0.757	2.142	(−8.965, 13.250)	0.705	0.803	−8.642	(−20.695, 3.411)	0.160	0.370	0.304	0.634
Total brain white matter hyperintensity volume	−3.590	(−12.020, 4.840)	0.404	0.757	−2.984	(−6.465, 0.498)	0.093	0.349	−2.134	(−5.911, 1.644)	0.268	0.447	0.359	0.634
Total cerebrum cranial volume	−7.682	(−20.475, 5.112)	0.239	0.757	1.624	(−3.660, 6.908)	0.547	0.713	−0.293	(−6.026, 5.440)	0.920	0.952	0.535	0.664
Total cerebrum brain volume	−9.675	(−35.033, 15.682)	0.454	0.757	−4.131	(−14.603, 6.342)	0.439	0.636	−8.531	(−19.894, 2.833)	0.141	0.370	0.491	0.664
Total cerebrum CSF volume	1.993	(−22.295, 26.282)	0.872	0.968	5.756	(−4.275, 15.787)	0.261	0.558	8.238	(−2.647, 19.122)	0.138	0.370	0.472	0.664
Total cerebrum gray matter volume	8.009	(−11.318, 27.336)	0.416	0.757	−3.067	(−11.049, 4.914)	0.451	0.636	1.018	(−7.643, 9.679)	0.818	0.918	0.615	0.683
Total cerebrum white matter volume	−14.083	(−39.905, 11.738)	0.285	0.757	1.932	(−8.732, 12.596)	0.722	0.803	−7.514	(−19.085, 4.057)	0.203	0.381	0.303	0.634
Left hippocampus volume	−0.009	(−0.297, 0.280)	0.954	0.987	−0.076	(−0.195, 0.043)	0.213	0.514	0.024	(−0.105, 0.153)	0.720	0.864	0.464	0.664
Right hippocampus volume	0.070	(−0.215, 0.356)	0.630	0.900	−0.118	(−0.235, 0.001)	0.051	0.333	−0.046	(−0.174, 0.082)	0.481	0.759	0.205	0.634
Hippocampal volume	0.062	(−0.479, 0.602)	0.823	0.968	−0.193	(−0.416, 0.030)	0.090	0.349	−0.022	(−0.264, 0.220)	0.857	0.918	0.318	0.634
Left lateral ventricle volume	−3.354	(−10.625, 3.918)	0.366	0.757	−1.183	(−4.186, 1.820)	0.440	0.636	−0.352	(−3.610, 2.907)	0.832	0.918	0.745	0.793
Right lateral ventricle volume	−3.211	(−10.223, 3.800)	0.369	0.757	0.002	(−2.894, 2.897)	0.999	0.999	−0.932	(−4.074, 2.210)	0.561	0.842	0.766	0.793
Total lateral ventricle volume	−6.570	(−20.334, 7.194)	0.349	0.757	−1.183	(−6.867, 4.501)	0.683	0.803	−1.293	(−7.460, 4.875)	0.681	0.864	0.812	0.812
Total third ventricle volume	−0.170	(−0.512, 0.172)	0.330	0.757	−0.053	(−0.194, 0.088)	0.466	0.636	0.039	(−0.114, 0.192)	0.619	0.856	0.523	0.664
Left frontal lobe cortical gray matter volume	3.430	(−1.397, 8.257)	0.164	0.757	1.498	(−0.495, 3.491)	0.141	0.434	2.750	(0.586, 4.913)	**0.013**	0.258	0.065	0.634
Right frontal lobe cortical gray matter volume	1.571	(−2.795, 5.937)	0.481	0.759	0.761	(−1.042, 2.564)	0.408	0.636	1.349	(−0.607, 3.305)	0.176	0.370	0.554	0.664
Total frontal lobe cortical gray matter volume	5.159	(−3.740, 14.057)	0.256	0.757	2.286	(−1.389, 5.961)	0.223	0.514	4.120	(0.131, 8.107)	**0.043**	0.258	0.188	0.634
Left occipital lobe cortical gray matter volume	−1.124	(−3.763, 1.514)	0.403	0.757	−0.811	(−1.900, 0.279)	0.145	0.434	−1.412	(−2.595, −0.229)	**0.019**	0.258	0.119	0.634
Right occipital lobe cortical gray matter volume	0.163	(−2.480, 2.806)	0.904	0.968	−1.044	(−2.135, 0.047)	0.061	0.333	−0.912	(−2.096, 0.273)	0.131	0.370	0.216	0.634
Total occipital lobe cortical gray matter volume	−0.983	(−5.808, 3.842)	0.689	0.910	−1.865	(−3.858, 0.127)	0.067	0.333	−2.328	(−4.490, −0.165)	**0.035**	0.258	0.138	0.634
Left parietal lobe cortical gray matter volume	1.376	(−1.497, 4.249)	0.348	0.757	−0.802	(−1.988, 0.384)	0.185	0.505	−0.870	(−2.157,0.417)	0.185	0.370	0.241	0.634
Right parietal lobe cortical gray matter volume	2.370	(−0.612, 5.353)	0.119	0.757	−0.226	(−1.457, 1.006)	0.720	0.803	0.266	(−1.071, 1.602)	0.697	0.864	0.380	0.634
Total parietal lobe cortical gray matter volume	3.757	(−1.651, 9.166)	0.173	0.757	−1.024	(−3.257, 1.209)	0.369	0.636	−0.600	(−3.023, 1.824)	0.628	0.856	0.340	0.634
Left temporal lobe cortical gray matter volume	−1.072	(−4.416, 2.272)	0.530	0.795	−1.564	(−2.945, −0.182)	**0.027**	0.265	−0.861	(−2.359, 0.637)	0.260	0.447	0.173	0.634
Right temporal lobe cortical gray matter volume	−0.012	(−3.275, 3.250)	0.994	0.994	−2.048	(−3.395, −0.700)	**0.003**	0.072	−1.608	(−3.070, −0.145)	**0.031**	0.258	**0.017**	0.495
Total temporal lobe cortical gray matter volume	−0.986	(−7.125, 5.153)	0.753	0.941	−3.649	(−6.185, −1.113)	**0.005**	0.072	−2.508	(−5.259, 0.243)	0.074	0.300	**0.038**	0.567

* $N = 1512$, adjusted by intracranial volume, sex, age, education, race, and Hispanic ethnicity; the reference group was normal cognitive status.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2024.100201.

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