Received: 8 June 2022 | Accepted: 24 November 2022

DOI: 10.1002/gps.5858

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Persistent depressive symptoms are associated with frontal regional atrophy in patients with Alzheimer's disease

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Funding information
National Institute for Health Research, Grant/Award Number: U01 AG024904; Alzheimer's Society, Grant/Award Number: 518; NIA/NIH, Grant/Award Number: U24 AG072122

Abstract

Background: Depression in individuals with Alzheimer's disease (AD) is common, difficult to treat and inadequately understood. Previous studies have identified possible differences in regional brain atrophy in individuals with AD and depression, but the results have been inconsistent and some studies had less robust definitions of depression. We aimed to examine regional brain atrophy in two large dementia focused cohorts.

Methods: We used data from Alzheimer's disease neuroimaging initiative (ADNI) and the National Alzheimer's Co-ordinating Center (NACC), for those with data from at least one MRI scan. Depression ratings were available using the Geriatric Depression Scale (GDS) and Neuropsychiatric Inventory (NPI). Intermittent depressive symptoms were defined as one episode above threshold (≥8 on GDS, ≥6 on NPI depression subscale and ≥2 on the Neuropsychiatric Inventory version Q depression sub-scale) and persistent as ≥2 episodes. Derived regional volumetric data was available from ADNI and the NACC.

Results: Data was available from 698 individuals with AD in NACC and from 666 individuals in ADNI. We found no evidence of between group differences in regional brain volume at baseline, or of differential atrophy in NACC. In ADNI we found evidence of increased brain atrophy in several frontal brain areas.

Limitations: Because this study was limited to those with MRI data, the numbers in some analyses were low. MRI parcellation differed between studies making direct comparison difficult. For some individuals only the NPI was used to rate depression.

Conclusions: We have found mixed evidence of increased regional atrophy in depression in AD, mainly in frontal brain regions. We found no evidence to support a vascular basis for depression in AD.

KEYWORDS
Alzheimer's disease, dementia, depression, depressive disorder

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Key points

- We found, unlike some previous studies, that there was no evidence of differences in regional brain volumes at baseline.
- Likewise we found no evidence to support a link between depression in AD and increased white matter hyperintensities.
- We found in Alzheimer's disease neuroimaging initiative, but not in National Alzheimer's Co-ordinating Center, that persistent depression in those with AD may be associated with greater regional atrophy in several brain areas which were predominantly frontal

1 | INTRODUCTION

Depression and Alzheimer's Disease (AD) are both common disorders. Depression is more common in AD than in older people without dementia, affecting ~16% of individuals with AD.[1] It is distressing for patients and may increase carer burden.[2–4] Depression in dementia is difficult to treat, the symptoms appear to be different (e.g., less guilt/worthlessness) and currently available anti-depressant medications do not work. Separate diagnostic criteria have been proposed for depression in AD, but not yet adopted in routine practice.[5]

The underlying biology of depression in AD is not known. Some, but not all research, has suggested that it may have a vascular component (e.g.[6,7]). A large case series using the HAM-D scale found that depression in AD is not merely a symptom of the dementia.[8] Patients with depression in AD are more likely than non-depressed AD patients to develop psychotic symptoms and have been shown to have increased cortical tangles suggesting more severe disease pathology.[4,9] They also seem to have reduced frontal perfusion and reduced connectivity between the amygdala and the frontal cortex.[10,11]

There have been relatively few neuroimaging studies. Decreased thalamic grey matter volume has been shown in two well powered and performed MRI studies[12,13] with resting state abnormalities found in a small rsMRI study.[14] In the hippocampus increased plaques and tangles have been reported in individuals without dementia but with a lifetime history of depression.[15] In studies of depression in AD some but not all studies have reported larger hippocampal volumes in depression plus AD, suggesting that the AD may be less advanced in these individuals.[16–18] Several studies have reported decreased grey matter volume in other temporal areas (e.g., the left inferior temporal gyrus, superior temporal, middle temporal gyrus, parahippocampus and entorhinal cortex.[19–23] One of these studies used a Geriatric Depression Scale (GDS) threshold of only 5,[21] others were small[19,23] and another defined depression as a positive response to the Neuropsychiatric Inventory version Q (NPI-Q) depression screening question.[22]

The largest studies in this field were by Karvasillis et al. In two well powered MRI studies they found that, in addition to decreased thalamic grey matter volume, depression in AD was associated with decreased grey matter volume in the middle occipital gyrus, lateral occipital gyrus, postcentral gyrus, paracentral area and multiple frontal lobe areas (precentral area (primary motor cortex), superior frontal gyrus, middle frontal gyrus, insula, superior medial frontal gyrus and medial orbitofrontal gyrus)[12,13] Other studies have also reported frontal grey matter volume loss.[20] A study using a GDS threshold of 5 provides support for parietal volume loss (posterior cingulate, precuneus)[21] as did another small MRI study (postcentral gyrus).[19] Overall the pattern from the existing literature suggests that different brain areas may be affected in depression in AD to depression per se.

Despite decades of investigation the reasons why some patients develop depression during AD and others do not remain obscure. The biological underpinnings of depression in AD and whether this differs to depression per se also remain unclear.

1.1 | Aims and objectives

We aimed to examine whether depression in AD is associated with volumetric differences in brain areas known to be related to either AD or depression.

2 | METHODS

We obtained information from two large cohort studies which focused on Alzheimer's Disease.

3 | NACC

The National Alzheimer's Co-ordinating Center (NACC) (https://naccdata.org/) was established in 2005 and collects information from Alzheimer's Disease Research Centres across the USA using uniform data sets. Individuals with normal cognition, mild cognitive impairment (MCI) and Alzheimer's Disease are included. Each centre has its own enrolment protocol which can include clinician referral, self-referral, active recruitment by community organisations and volunteers with normal cognition. As such it is not representative of the general US population. Participants are seen approximately annually. MRIs were performed on a subset of individuals. Imaging and data acquisition protocols differ between contributing centres.

Depressive symptoms were measured using the NPI-Q and the GDS.[24,25] Unlike Alzheimer's disease neuroimaging initiative (ADNI) individuals with depressive symptoms at baseline were included.

Individuals were included in this study if they had at least one MRI scan with calculated volumes available, had at least one visit with information on current/previous depression (e.g., depression rating scale, or self-reported clinical diagnoses of depression) and either had a diagnosis of AD on at least one occasion, a diagnosis of impaired cognition during follow-up or normal cognition at all visits. Data was obtained from the September 2019 data freeze. MRI Volumetric calculations were performed by the IDeA lab (http://idealab.ucdavis.edu/) using ADNI protocols.

4 | ADNI

ADNI (http://www.adni-info.org/) is a longitudinal study established in 2004 to develop biomarkers and other indicators for early detection of AD. It has clinical data on >800 individuals including positron emission tomography and MRI.[26,27] Participants included in the trial had either early AD, MCI or normal cognition at baseline. After screening participants have assessments at 0,3 6 and 12 months and thereafter every 6 months.[26] ADNI was carried out in phases; ADNI1 in 2004; Alzheimer's disease neuroimaging initiative - GO (ADNI-GO) in 2009; ADNI 2 in 2011; and ADNI3 in 2016. Many individuals were seen in more than one phase with existing participants included in the recruitment for each successive phase.

There are differences in the data collected in each phase. The full Neuropsychiatric Inventory (NPI) was used in ADNI 2 and 3 whereas the shorter NPI-Q was used in ADNI 1 and ADNI-GO. Depression either at entry to the study or in the 2 years preceding study entry was an exclusion, meaning that very few participants had significant depressive symptoms at baseline.

Depressive symptoms were measured using the NPI or NPI-Q and the GDS.[24,25,28] The final dataset was downloaded in May 2021. Regional brain atrophy data used in this study was derived by Ledig et al.[29] White matter hyperintensity data was generated by Schwarz et al. using a Markov random field framework.[30]

4.1 | Definition of depressive symptoms

A cut-off of ≥8 was used for the GDS as it has the best balance of sensitivity and specificity.[31,32] For the NPI sub-scale scores were calculated for depression by multiplying the frequency and severity items for each symptom.[28] A cut-off was used of ≥2 for the NPI-Q and ≥6 for the NPI depression sub-scale. The NPI cut-off of 6 was chosen as individuals would have to have depressive symptoms often/frequently/very frequently and at least of moderate severity. Whilst the NPI is predominantly a screening tool it has previously been used to diagnose depression and define clinically significant behavioural and psychological symptoms of dementia.[33–35]

Individuals scoring above the threshold on either the NPI, NPI-Q or GDS met criteria for depression caseness. Intermittent depression was defined as one episode above threshold and persistent as at least two episodes above threshold on any scale.

The GDS-15 is a self-rated 15 item scale and thus can only be completed by individuals with better cognition. There were high levels of missing data for individuals who were more cognitively impaired. The NPI in contrast is informant rated and uses screening questions for each of 12 neuropsychiatric symptoms, with follow-up questions to assess both the frequency and severity. Whilst imperfect as a diagnostic tool for depression the NPI allowed us to capture individuals with significant depressive symptoms who were too cognitively impaired to be able to complete the GDS.[36]

In those with normal cognition the NPI was not used to define depression caseness as the GDS has a better evidence base in this population.

4.2 | Dataset exclusions

Because we aimed to study persistent depressive symptoms those with only one study visit were dropped from the analysis. Participants who had failed the screening visit were also excluded from the analysis. Individuals with treated depression (i.e., they were on antidepressants at baseline but did not score above the threshold on the GDS at any point during follow-up) were excluded. Eighteen NACC individuals were on antidepressants at baseline only but were not depressed and 105 were taking antidepressants at at least 2 timepoints but never met caseness criteria. In ADNI very few individuals were taking antidepressants at baseline due to ADNI exclusion criteria. In ADNI those with maximum GDS scores between 5 and 7 (i.e., sub threshold depression) who never met NPI criteria for depression caseness were excluded.

In the NACC dataset, in which some participants were seen several times before they developed MCI or dementia, for each participant any visits and scans prior to the time at which they developed MCI were dropped for the AD group. For the atrophy analysis individuals with other conditions with the potential to cause significant cognitive decline for example, Parkinson's Disease, epilepsy and cerebral neoplasms were excluded. The ADNI dataset did not have such precise information on such disorders.

4.3 | Statistical analysis

In both studies a comparison between those without depressive symptoms and those with persistent depression was made. Individuals with intermittent depression were included only in the post hoc depressive symptom clusters analysis. Chi squared tests were used to assess differences in baseline categorical variables. Parametric analyses were used wherever possible to examine between group differences in continuous baseline characteristics. Data was examined for normal distribution using histograms and P normal and

Q normal plots. Where necessary the Shapiro Wilk test was used. Where data was not normally distributed and could not be transformed to a normal distribution the Kruskal Wallis test was used. Imputation was not possible for either dataset due to data missing not at random.

The primary outcome was regional brain atrophy and volumetric differences at baseline in brain areas known to be affected by depression, AD or both. Following the a priori analysis secondary analyses were performed including the analysis of NPI sub scales and principal component analysis to identify symptom clusters. These were not included in the power calculation prior to study commencement. An a prior power calculation assuming an SD of 330 mm^3 and an alpha of 0.05, a sample size of 50 in each group would give 80% power to detect a between-group difference of 200 mm^3.[37] Brain areas under investigation were chosen as being known to be involved in/affected by depression, mood regulation, Alzheimer's Disease or all 3. In ADNI all regressions included age, gender, ethnicity, apolipoprotein E status, GDS score, antidepressant use at baseline and years of education as covariates. In NACC all regressions were adjusted for age, gender, history of depression and history of psychiatric illness.

As previously described (paper in submission) we used polychoric principal component analysis including NPI and GDS scores see Table S6 to allow for the semi categorical nature of the NPI. Three factors emerged: factor 1 (the majority of the NPI sub scales), factor 2 (NPI depression, anxiety and some loading for apathy) and factor 3 (GDS depression). It was not technically possible to perform principal component analysis in the ADNI dataset due to missing data (particularly because the NPI and NPIQ were not administered to all participants) but sufficient data were available to look at depression alone versus depression plus the additional symptoms identified in the NACC data.

4.4 | Ethical approvals

The NACC database itself is exempt from institutional review board (IRB) review and approval because it does not involve human subjects, as defined by federal and state regulations. However, all contributing ADCs are required to obtain informed consent from their participants and maintain their own separate IRB review and approval from their institution prior to submitting data to NACC.

As this study's use of ADNI data fell into the category of secondary analysis of anonymised data, under UK law, no separate ethical approval was required for these analyses.

5 | RESULTS

5.1 | NACC

As shown in Table 1 and Table S1, 698 individuals with AD were included in this study, with 16.1% of individuals meeting criteria for persistent depressive symptoms and 26.9% meeting criteria for intermittent depressive symptoms. Individuals with depressive symptoms were more likely to be female, to report suffering with depression in the last 2 years and to be taking antidepressants. They also had slightly higher baseline NPI apathy (mean diff 0.31 in persistent depression group) and anxiety scores (mean diff 0.30 in persistent depression group).

There were 711 individuals with normal cognition in the NACC cohort, but numbers with either persistent depression (n = 23) or intermittent depression (n = 23) were low see Table S2. This is in keeping with the lower incidence of depression in cognitively unimpaired older adults.

5.2 | ADNI

Six hundred and sixty six individuals with AD were included in the cohort for this study see Table 1 and Table S15. Few individuals had depression at baseline and depression in this cohort developed during study follow-up. Unlike the NACC cohort there was no evidence of a gender difference in those with depression. Individuals with depression had a higher mini-mental state examination (MMSE) score at baseline, a lower CDR sum of boxes and a lower (better) RAVLT forgetting score. Unlike the NACC cohort there was no evidence that individuals with those with depressive symptoms had higher NPI apathy and anxiety scores at baseline. Only 9.9% of those with AD met criteria for persistent depressive symptoms and 23.0% met criteria for intermittent depressive symptoms.

There were 669 cognitively unimpaired individuals see Table S9, but cases of depression were again low (n = 44 intermittent and n = 10 persistent).

In both cohorts although the groups represent depressive symptoms they are referred to in the tables and figures as intermittent depression and persistent depression for the sake of brevity.

5.3 | Baseline volume differences by presence/absence of depressive symptoms

As shown in Table 2 and Table S7 there was no evidence of a between group difference in baseline regional brain volume in NACC. A post hoc power calculation demonstrated >95% power to find a difference of 1 cm^3 and 78% power to find a difference of 0.7 mm^3

In ADNI, which was also adequately powered according to our a priori power calculation, there was again no difference in regional brain volumes in individuals with persistent depressive symptoms (see Table 3).

5.4 | White matter hyperintensities

In the NACC cohort there was an increase in white matter hyperintensity volume in the persistent depression group at baseline (Table 2, mean difference 3.5 cm^3, p = 0.022).

TABLE 1 Baseline characteristics of the cohorts in this study

	NACC				ADNI			
	AD no dep $N = 393$	AD intermittent dep $N = 185$	AD persistent dep $N = 111$	Statistical evidence	AD, no dep $n = 447$	AD, intermittent dep $n = 153$	AD, persistent dep $n = 66$	Statistical evidence
Age at baseline (mean (SD))	78.2 (8.5)	76.1 (9.4)	74.4 (10.3)	$p = 0.935$	74.5 (7.6)	73.8 (7.1)	74.6 (7.1)	$p = 0.579$
Sex				$p = 0.035$				$p = 0.213$
Male	56.2%	48.1%	44.1%		58.17%	54.90%	46.97%	
Female	43.8%	51.9%	55.9%		41.83%	45.10%	53.03%	
Marital status				$p = 0.30$				$p = 0.778$
Married	65.1%	67.0%	70.3%		83.7%	81.7%	83.3%	
Widowed	20.4%	16.2%	15.3%		10.1%	10.5%	10.6%	
Divorced	8.7%	12.4%	7.2%		3.8%	5.9%	6.1%	
Separated	0.5%	0.0%	1.8%					
other	5.4%	4.3%	5.2%		2.5%	2.0%	0.0%	
Ethnicity				$p = 0.61$				$p = 0.974$
White	84.2%	89.2%	82.0%		94.2%	93.5%	92.4%	
Black or african american	11.2%	7.0%	14.4%		3.1%	3.3%	4.6%	
Native american/asian	4.4%	3.7%	3.6%		2.8%	3.3%	3.0%	
Prescribed an antidepressant at baseline	0.0%	31.9%	34.2%	$p < 0.001$	0.0%	2.6%	3.0%	$p = 0.001$
GDS score at baseline	1.5 (1.5)	2.7 (2.4)	4.4 (3.5)	Kwallis $p < 0.001$	1.3 (1.1)	2.0 (1.6)	2.4 (1.8)	Kwallis $p < 0.001$
NPI depression score at baseline	0.1 (0.3)	0.8 (0.9)	1.1 (1.0)	Kwallis $p < 0.001$	1.8 (1.0)	2.6 (2.1)	2.4 (1.8)	Kwallis $p = 0.015$
MMSE score	25.1 (3.9)	24.8 (6.9)	25.4 (8.2)	KWallis $p = 0.067$	24.7 (2.8)	25.5 (2.5)	26.1 (2.5)	Kwallis $p < 0.001$

Note: Note that restricted only to those who were ever diagnosed with AD and baseline visit was first visit where cognition was noted to be impaired. Individuals prescribed an antidepressant at baseline who were not depressed were excluded from the no depression group. ANOVAs included age and sex as co-variates.

Abbreviations: ADNI, Alzheimer's disease neuroimaging initiative; MMSE, mini-mental state examination; NACC, National Alzheimer's Co-ordinating Center; NPI, Neuropsychiatric Inventory.

In ADNI, although the data for white matter hyperintensity had to be analysed separately for ADNI 1 and ADNI2/3/GO which may have reduced statistical power, there was no evidence that individuals with depression in AD had increased white matter hyperintensities (see Table S9.

5.5 | Longitudinal regional atrophy in depression

Parcellation of the MRI into different brain areas was performed differently in NACC and ADNI making direct comparison difficult. Fewer people completed follow-up scans and therefore baseline volumetric analyses have higher statistical power.

In NACC no differences were seen in the bilateral grey matter atrophy rate per year for any brain area (see Table S5 but numbers of individuals with persistent depression with follow-up scans were low ($n = 19$).

In ADNI there was data on regional atrophy at 12 and 24 months. At 24 months (see Table S12) numbers were much lower ($n = 20$ in persistent depression group) but there was evidence of increased atrophy in the frontal operculum (mean difference 1.854 mm^3, $p = 0.033$), medial orbital gyrus ($\beta = -2.071$ (-4.030 to -0.112) $p = 0.038$), and posterior insula ($\beta = -2.071$ (-3.915 to -0.226) $p = 0.028$) (see Table S10). At 12 months there were 27 individuals with persistent depression (see Table S11). Again there was evidence of increased atrophy in the frontal operculum in individuals

TABLE 2 Baseline regional brain volumes in NACC in AD without depression and those with persistent depression

Volume in cm^3 at first MRI	AD no depression (*n* = 377) Mean	SD	AD with persistent depression (*n* = 107) Mean	SD	Statistical evidence adjusted for age, ethnicity, Hx of depression, psych Hx at baseline and gender
Caudal anterior cingulate	5.32	1.12	5.39	0.98	$\beta = -0.080$ (−0.396 to 0.235) $p = 0.616$
Entorhinal	7.32	1.39	7.43	1.59	$\beta = -0.024$ (−3.767 to 0.328) $p = 0.892$
Frontal lobe	160.24	20.73	160.04	22.79	$\beta = 0.037$ (−4.822–4.896) $p = 0.988$
Hippocampus	5.7	0.99	5.66	1.04	$\beta = -0.061$ (−0.314 to 0.192) $p = 0.634$
Insula	11.88	1.63	11.72	1.92	$\beta = -0.123$ (−0.405 to 0.381) $p = 0.951$
Isthmus cingulate	5.15	0.99	5.2	0.9	$\beta = 0.109$ (−0.148–0.367) $p = 0.404$
Lateral orbitofrontal	15.81	2.1	15.48	2.58	$\beta = -0.002$ (−0.499 to 0.496) $p = 0.995$
Lingual	79.07	10.73	79.18	11.89	$\beta = 0.021$ (−2.483–2.525) $p = 0.987$
Insula	13.61	2.27	13.34	2.35	$\beta = 0.056$ (−0.529–0.641) $p = 0.850$
Medial orbitofrontal	8.5	1.35	8.36	1.38	$\beta = -0.066$ (−0.404 to 0.271) $p = 0.700$
Paracentral	7.08	1.61	7.07	1.67	$\beta = -0.149$ (−0.570 to 0.273) $p = 0.489$
Pars orbitalis	3.7	0.72	3.66	0.79	$\beta = 0.004$ (−0.182–0.189) $p = 0.969$
Pars operculum	8.38	1.44	8.51	1.6	$\beta = -0.244$ (−0.608 to 0.120) $p = 0.189$
Pars triangularis	7.62	1.31	7.76	1.36	$\beta = -0.018$ (−0.360 to 0.324) $p = 0.917$
Postcentral	16.16	2.97	16.26	2.6	$\beta = 0.076$ (−0.609–0.761) $p = 0.828$
Posterior cingulate	7.69	1.35	7.79	1.38	$\beta = 0.120$ (−0.228–0.468) $p = 0.497$
Precentral	20.77	3.7	20.95	3.81	$\beta = -0.134$ (−0.821–1.090) $p = 0.782$
Precuneus	17.71	2.84	17.96	3.11	$\beta = -0.238$ (−0.948 to 0.472) $p = 0.510$
Rostral anterior cingulate	6.24	1.24	6	1.19	$\beta = -0.210$ (−0.523 to 0.104) $p = 0.190$
Rostral middle frontal	20.29	3.18	20.25	3.62	$\beta = 0.222$ (−0.605–1.050) $p = 0.598$
Superior frontal	42.52	6.34	43.04	7.31	$\beta = -0.426$ (−1.251–2.104) $p = 0.618$
White matter hyperintensity volume	10.086	13.203	13.543	14.846	$p = 0.022$

Note: All regressions were adjusted for age, gender, Hx of depression and Hx of psychiatric illness.
Abbreviation: NACC, National Alzheimer's Co-ordinating Center.

with persistent depression ($\beta = -2.153$ (−3.704 to −0.602) $p = 0.007$), the medial orbital gyrus ($\beta = -1.595$ (−3.113 to −0.077 $p = 0.040$). In addition persistent depression seemed to be associated with increased atrophy of the superior frontal gyrus medial segment ($\beta = -1.948$ (−3.307 to −0.590) $p = 0.005$) and the lingual gyrus ($\beta = 0.685$ (0.026–1.345) $p = 0.042$). A sensitivity analysis looking at laterality at 12 and 24 months (see Table S12, Figures 1 and 2) found that there was the best evidence of increased atrophy in individuals with persistent depression was for the superior frontal gyrus medial segment, the frontal operculum and the medial orbital gyrus.

5.6 | Baseline and atrophy differences by NPI symptom profiles

We used a secondary, post-hoc, principal component analysis to identify symptom clusters (see Tables S3-4), as individuals with AD are more likely to have multiple NPI symptoms than one alone. Individuals were divided into AD without depression, AD + depression but no clinically significant NPI symptoms, AD + depression with other clinically significant NPI symptoms and AD + depression + either clinically significant anxiety/apathy. Using these groupings there was again no difference in the regional atrophy rates for any brain area (see Table S6). Looking at baseline volumes, which had higher numbers (see Figure 3, Table S7), individuals with depression plus apathy/anxiety had great white matter hyperintensity volumes (mean difference 107.1 cm^3, $p = 0.004$) and smaller pars orbitalis (mean difference −0.17, $p = 0.014$).

To see if the result from NACC on baseline volumes in depression + apathy/anxiety was replicable we repeated this analysis using ADNI baseline volumetric data (see Table S12). The depression + apathy/anxiety group ($n = 93$) had reduced frontal opercular size (mean difference 15.6 mm,^{3} $p = 0.0031$).

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TABLE 3 Baseline regional volumes in the ADNI cohort in relation to depression

All volumes are in cm^3	AD no depression *n* = 221		AD, persistent depression *N* = 45		Statistical evidence
	Mean	SD	Mean	SD	
Anterior cingulate	7.04	1.4	6.89	1.12	$\beta = -0.106$ (−0.551 to 0.339) $p = 0.639$
Anterior insula	6.78	1.21	6.83	1	$\beta = 0.187$ (−0.173–0.546) $p = 0.308$
Entorhinal	3.64	0.79	3.68	0.73	$\beta = 0.115$ (−0.115–0.347) $p = 0.327$
Frontal operculum	2.51	0.52	2.54	0.36	$\beta = 0.065$ (−0.094–0.223) $p = 0.422$
Hippocampus	6.25	1.04	6.30	0.92	$\beta = 0.123$ (−0.181–0.426) $p = 0.428$
Lingual gyrus	15.89	2.31	15.38	2.38	$\beta = -0.240$ (−0.922 to 0.442) $p = 0.489$
Medial orbital gyrus	8.53	1.23	8.48	0.87	$\beta = -0.061$ (−0.426 to 0.305) $p = 0.743$
Middle frontal gyrus	30.27	4.6	29.14	4.58	$\beta = -0.965$ (−2.419–0.490) $p = 0.193$
Medial superior frontal gyrus	10.27	1.77	10.03	1.65	$\beta = -0.164$ (−0.690 to 0.362) $p = 0.539$
Pars orbitalis	2.59	0.62	2.44	0.58	$\beta = -0.171$ (−0.372 to 0.028) $p = 0.091$
Pars triangularis	5.42	0.92	5.40	0.84	$\beta = 0.029$ (- 0.271–0.328) $p = 0.851$
Posterior central gyrus	17.90	2.43	17.48	2.21	$\beta = -0.377$ (−1.142–0.387) $p = 0.332$
Posterior cingulate	7.11	1.05	7.17	1.07	$\beta = 0.117$ (−0.210–0.445) $p = 0.481$
Posterior insula	3.34	0.61	3.34	0.61	$\beta = 0.037$ (−0.145–0.219) $p = 0.688$
Precentral gyrus	12.70	1.73	12.22	1.91	$\beta = -0.390$ (−0.937 to 0.157) $p = 0.162$
Precuneus	18.94	3.35	18.57	3.23	$\beta = -0.160$ (−1.205–0.884) $p = 0.762$
Superior frontal gyrus	23.05	3.16	22.52	2.91	$\beta = -0.126$ (−1.103–0.851) $p = 0.800$
Thalamus	13.66	1.37	13.52	1.4	$\beta = -0.023$ (−0.411 to 0.365) $p = 0.906$

Note: All regressions included age, gender, ethnicity, APOE status, GDS score, antidepressant use at baseline and years of education as co-variates.
Abbreviations: ADNI, Alzheimer's disease neuroimaging initiative; APOE, apolipoprotein E.

6 | DISCUSSION

In summary we have examined 2 large dementia focused cohorts to identify differences in brain regional volumes in individuals with depressive symptoms in AD. We found no evidence of differences in brain volume at baseline in individuals with persistent depressive symptoms. There was a suggestion of increased white matter hyperintensities at baseline in persistent depressive symptoms in the NACC cohort, but this was not replicated in ADNI. Unlike previous studies we have focused on persistent depressive symptoms which may explain our discrepant findings of no baseline differences.[12,13] We also used a higher GDS cut off than some other previous studies.[21]

We found no evidence of increased regional atrophy in NACC. In ADNI, which had lower numbers, there was evidence of increased regional atrophy in those with persistent depression. Despite the low numbers, which would increase the risk of type 1 errors, the findings were relatively consistent between 12 and 24 months. The most consistent pattern observed was that of changes in frontal brain areas (medial orbital gyrus, superior frontal gyrus, frontal operculum). This is consistent with the largest previous studies,[12,13] although changes in the pars operculum have not previously been reported. These brain areas are different to those which are known to be most affected by AD itself.

We found evidence that depression in AD may be linked to apathy and anxiety more than other NPI sub scales and we examined whether this is associated with a change in regional atrophy. Whilst there was no change in regional atrophy there was evidence of baseline differences in those with depression plus anxiety and apathy in both NACC and ADNI. This was a post hoc analysis so these findings require replication and should be treated with caution until replicated.

Apathy is one of the most common neuropsychiatric symptoms in dementia.[38,39] There has been a long debate in the literature about whether it is a distinct symptom or linked to depression. It can be difficult to distinguish the two clinically, particularly as individuals with AD become more cognitively impaired and less able to express themselves. One previous large cross-sectional study used factor analysis to show that apathy and appetite were distinct from depression and anxiety.[38] Our study is smaller, but has longitudinal data which may allow more precise phenotyping. A smaller study by the same group had failed to distinguish between mood and apathy, suggesting that size in this instance does matter.[40] A cross-sectional study in Korea ($n = 778$) found that anxiety and depression were separable from apathy (plus sleep and appetite) using factor analysis of the NPI.[41]

Several studies have reported that depressive symptoms vary during follow-up.[42,43] Aalten et al found in a 2 years follow-up study

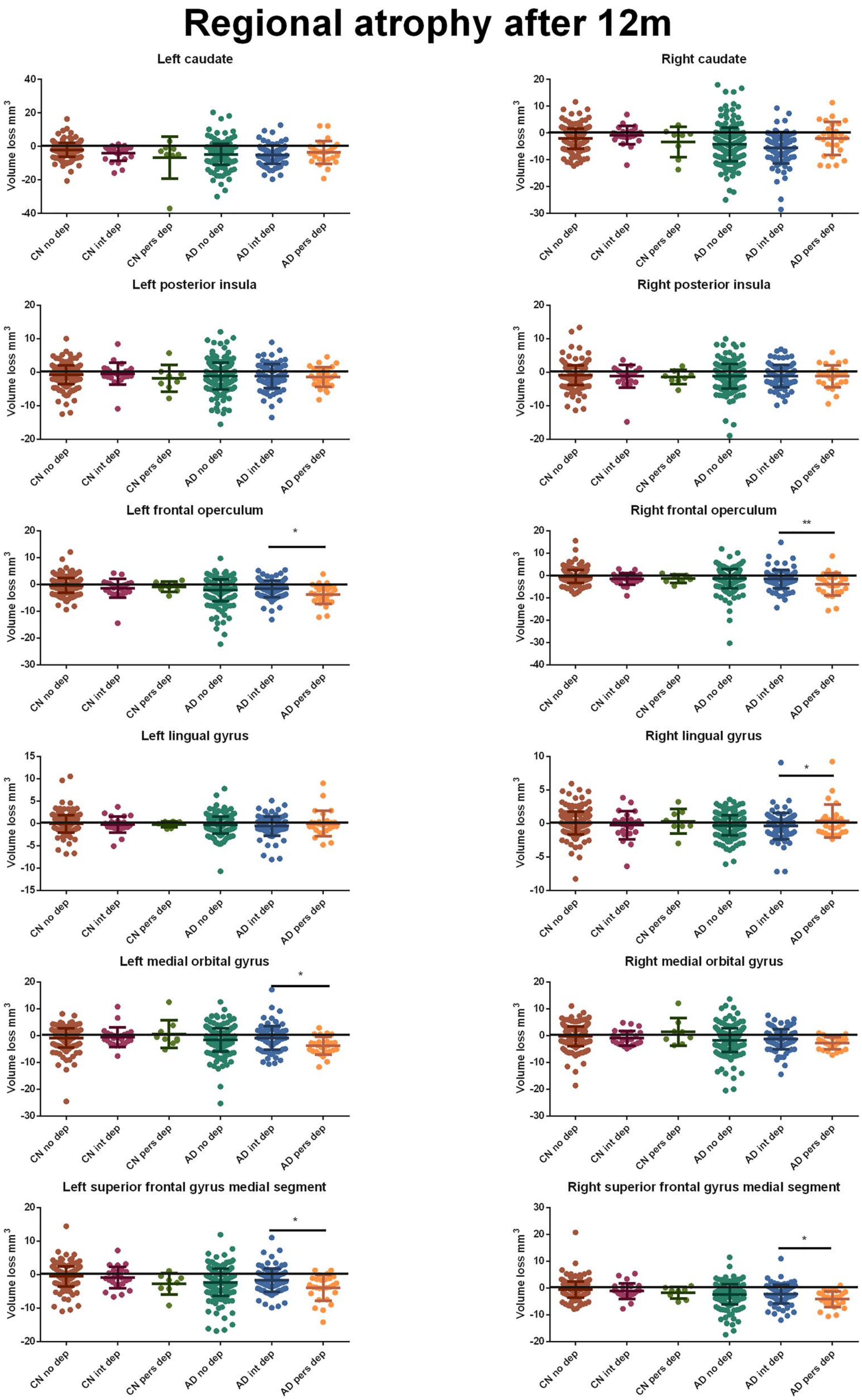

FIGURE 1 Regional atrophy in ADNI at 12 months in selected brain areas. ADNI, Alzheimer's disease neuroimaging initiative

(n = 199) that depression and apathy loaded onto the same factor, with anxiety as a separate symptom.[44] In an Italian study (n = 157) depression again loaded onto the same factor as apathy. A small UK study (n = 84) suggested that factor analysis may yield different combinations at baseline to during a 2 year follow-up,[45] which was also shown in a large US study (n = 447) which found that depression was particularly ill defined in term of which factor it loaded onto over time.[46] The authors suggested that future research should consider

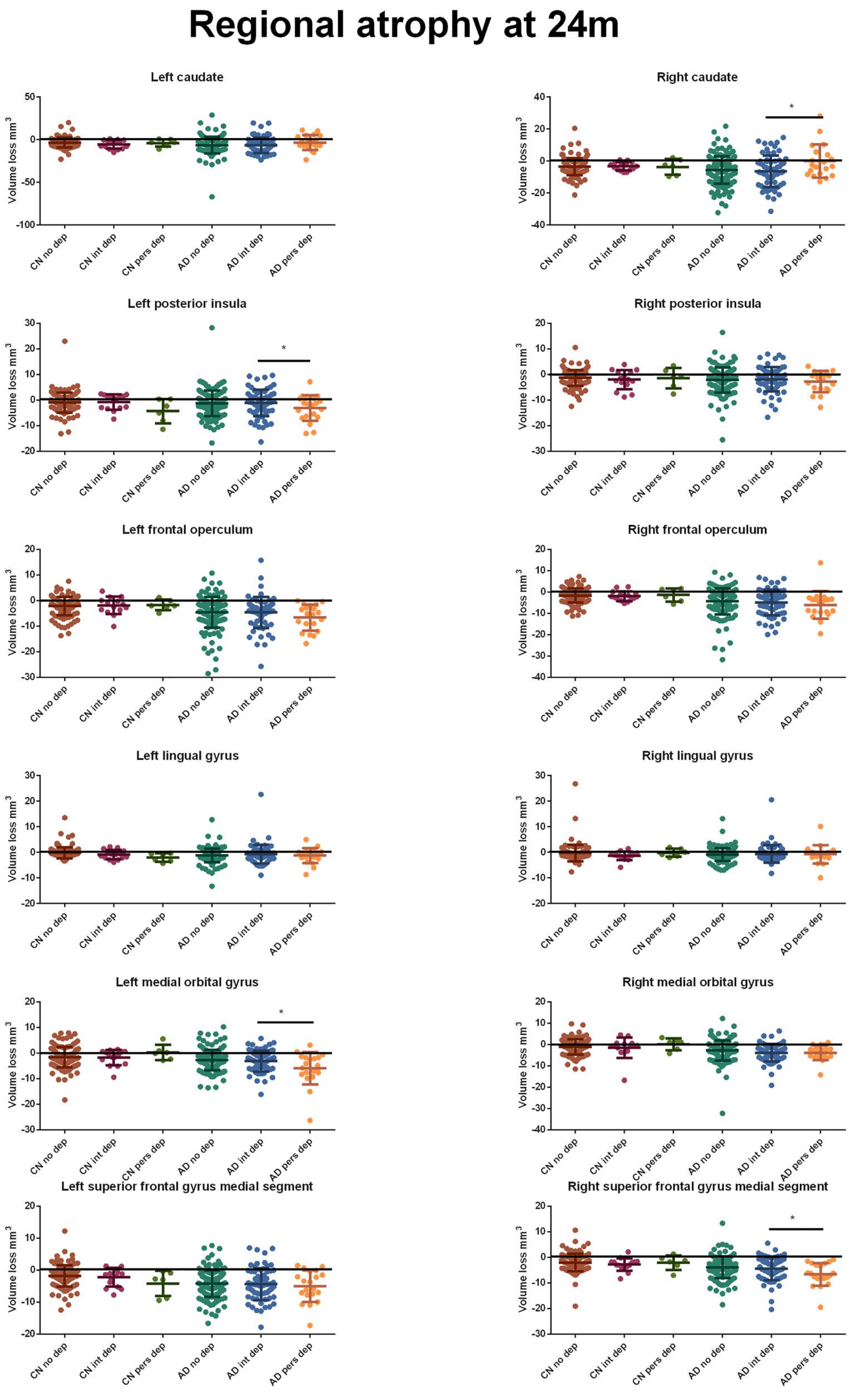

FIGURE 2 Regional atrophy in ADNI at 24 months in selected brain areas. ADNI, Alzheimer's disease neuroimaging initiative

pairs or small groups of symptoms to identify causal underpinnings, as performed in this study.

Strengths of this study include the multiple cohorts, higher thresholds than some previous studies to define depression so that only clinically significant depression was included, studying persistent depression which may be a more specific phenotype, the relatively large numbers and the length of follow-up data available, which was much longer than most previous studies. This allowed a more

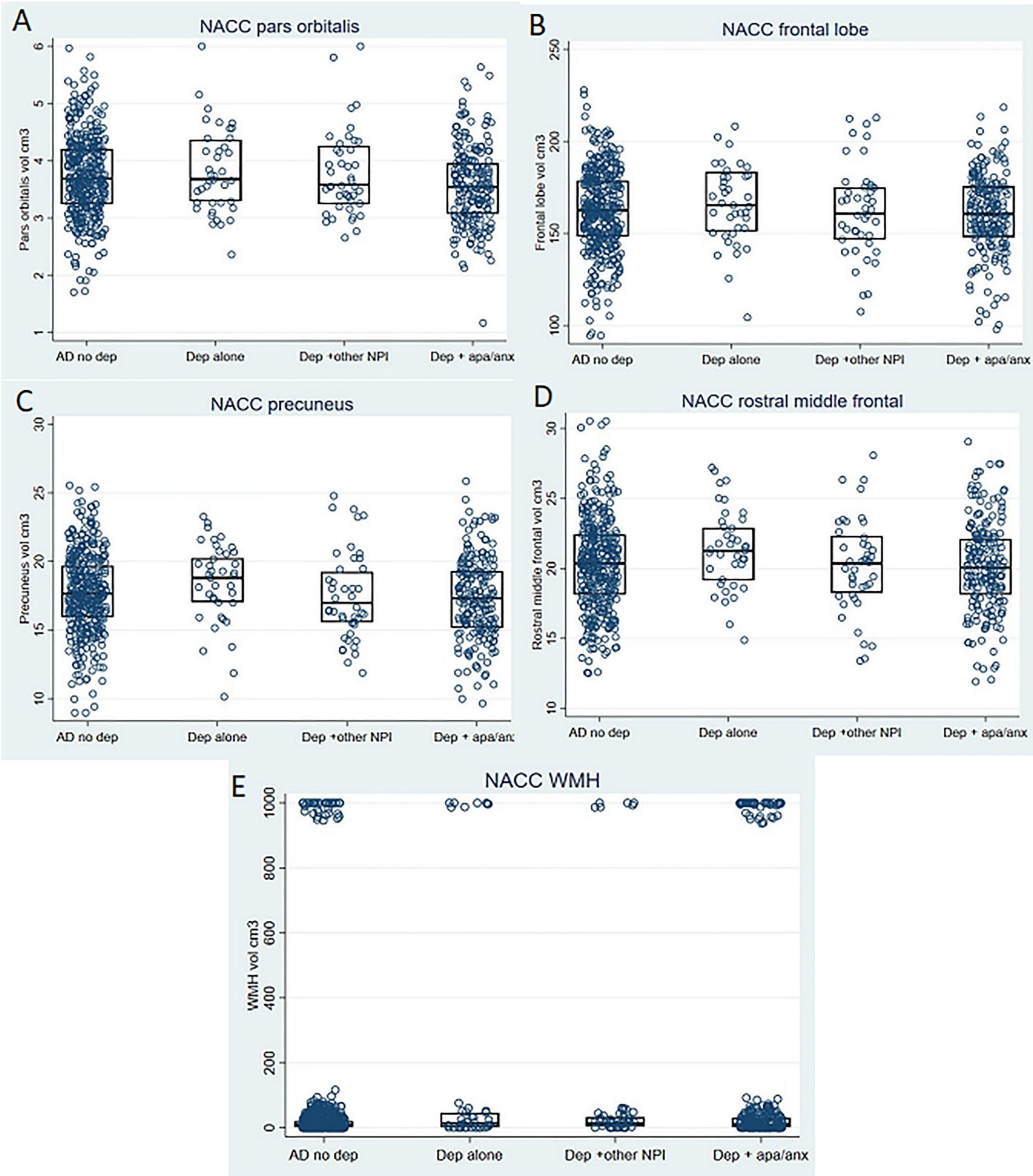

FIGURE 3 Baseline volumetric differences in relation to NPI symptom clusters in NACC. Individuals with depression + anxiety/apathy had decreased volume of the frontal lobe in general (B) and more specifically of the pars orbitalis (A) and rostral middle frontal cortex (D), slightly smaller precuneus (C) and increased white matter hyperintensities (E). NACC, National Alzheimer's Co-ordinating Center; NPI, Neuropsychiatric Inventory.

longitudinal view of depression in AD. Limitations include the relatively low numbers of individuals with follow-up MRI scans in NACC and the low numbers of individuals with persistent depression in ADNI. In ADNI individuals with depression had higher MMSE scores so may have had less underlying AD pathology than individuals without depression, although several previous studies have suggested that those with depression have similar or increased levels of pathology.[9,47,48] The GDS is a self-rated scale and the NPI is informant rated, so they may have identified different severities of depression. Whilst we have carried out some secondary, post hoc analyses we have clearly identified which analyses these were and have advised that the results be treated with caution until replicated.

Future work should include a more detailed examination of regional atrophy in larger cohorts and examination of the genetic underpinnings of depression in AD.

To conclude we have used data from 2 large cohorts to study depression in AD. We found mixed, possibly underpowered evidence of increased regional atrophy in depression in AD, mainly in frontal brain regions

ACKNOWLEDGEMENTS

We are immensely grateful to the participants, volunteers and staff of NACC and ADNI without whom this research would not have been possible. Lindsey Isla Sinclair is funded by a junior fellowship from the Alzheimer's Society (grant no. 518). Clive G. Ballard is funded by the NIHR. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defence award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Ageing, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research and Development, LLC.; Johnson and Johnson Pharmaceutical Research and Development LLC.; Lumosity; Lundbeck; Merck and Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADCs: P50 AG005131 (PI James Brewer, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG005138 (PI Mary Sano, PhD), P50 AG005142 (PI Helena Chui, MD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005681 (PI John Morris, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG008051 (PI Thomas Wisniewski, MD), P50 AG008702 (PI Scott Small, MD), P30 AG010124 (PI John Trojanowski, MD, PhD), P30 AG010129 (PI Charles DeCarli, MD), P30 AG010133 (PI Andrew Saykin, PsyD), P30 AG010161 (PI David Bennett, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG013846 (PI Neil Kowall, MD), P30 AG013854 (PI Robert Vassar, PhD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P30 AG019610 (PI Eric Reiman, MD), P50 AG023501 (PI Bruce Miller, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P30 AG028383 (PI Linda Van Eldik, PhD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P30 AG035982 (PI Russell Swerdlow, MD), P50 AG047266 (PI Todd Golde, MD, PhD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG049638 (PI Suzanne Craft, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Marwan Sabbagh, MD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), P30 AG072959 (PI James Leverenz, MD).

CONFLICT OF INTEREST

Lindsey Isla Sinclair has no relevant conflicts of interest to disclose. She has previously received a travel award from the RCPsych/Gatsby Foundation and is the finance office for the Academic Faculty of the Royal College of Psychiatrists. She has received research funding in the past from the Mason Medical Research Foundation, the David Telling Charitable Trust, BRACE Alzheimer's Research and the British Neuropathological Society. ML has no relevant conflicts of interest to disclose. He has received research funding from the MS Society, Parkinson's UK and the NIHR HTA. During the last 3 years, Clive G. Ballard has received consulting fees from Acadia pharmaceutical company, AARP, Addex pharmaceutical company, Eli Lily, Enterin pharmaceutical company, GWPharm, H. Lundbeck pharmaceutical company, Novartis pharmaceutical company, Janssen Pharmaceuticals, Johnson and Johnson pharmaceuticals, Novo Nordisk pharmaceutical company, Orion Corp pharmaceutical company, Otsuka America Pharm Inc, Sunovion Pharm. Inc, Suven pharmaceutical company, Roche pharmaceutical company, Biogen pharmaceutical company, Synexus clinical research organization and tauX pharmaceutical company and research funding from synexus clinical research organization, Roche pharmaceutical company, Novo Nordisk pharmaceutical company, Novartis pharmaceutical company, Medical research council (UK), Wellcome trust (UK), National Institute for Health Research (UK), National Institute for Health (US), IMI (Eu), Michael J Fox foundation (US), Alzheimer's Disease Drug Discovery foundation (US), Alzheimer's Society (UK), Parkinson's Society (UK), Alzheimer's Research UK, the Gilling's foundation and BRACE (UK).

DATA AVAILABILITY STATEMENT

The data used in this study was obtained from ADNI (www.loni.ucla.edu/ADNI) and the NACC (https://naccdata.org/) Data is available free of charge to bona fide researchers who submit a research proposal.

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REFERENCES

1. Asmer MS, Kirkham J, Newton H, et al. Meta-analysis of the prevalence of major depressive disorder among older adults with dementia. *J Clin Psychiatr*. 2018;79(5). https://doi.org/10.4088/jcp.17r11772
2. Sousa MFB, Santos RL, Turró-Garriga O, Dias R, Dourado MCN, Conde-Sala JL. Factors associated with caregiver burden: comparative study between Brazilian and Spanish caregivers of patients with Alzheimer's disease (AD). *Int Psychogeriatrics*. 2016;28(8):1363-1374. https://doi.org/10.1017/s1041610216000508
3. Dudas R, Malouf R, McCleery J, Dening T. Antidepressants for treating depression in dementia. *Cochrane Database Syst Rev*. 2018;8(8):Cd003944.
4. Zubenko GS, Zubenko WN, McPherson S, et al. A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. *Am J Psychiatr*. 2003;160(5):857-866. https://doi.org/10.1176/appi.ajp.160.5.857
5. Olin JT, Schneider LS, Katz IR, et al. Provisional diagnostic criteria for depression of Alzheimer disease. *Am J Geriatric Psychiatry*. 2002;10(2):125-128. https://doi.org/10.1097/00019442-200203000-00003
6. Lee JJ, Lee EY, Lee SB, et al. Impact of white matter lesions on depression in the patients with Alzheimer's disease. *Psychiatry Investig*. 2015;12(4):516-522. https://doi.org/10.4306/pi.2015.12.4.516
7. Anor CJ, O'Connor S, Saund A, Tang-Wai DF, Keren R, Tartaglia MC. Neuropsychiatric symptoms in Alzheimer disease, vascular dementia, and mixed dementia. *Neurodegener Dis*. 2017;17(4-5):127-134. https://doi.org/10.1159/000455127
8. Chemerinski E, Petracca G, Sabe L, Kremer J, Starkstein SE. The specificity of depressive symptoms in patients with Alzheimer's disease. *Am J Psychiatr*. 2001;158(1):68-72. https://doi.org/10.1176/appi.ajp.158.1.68
9. Rapp MA, Schnaider-Beeri M, Purohit DP, Perl DP, Haroutunian V, Sano M. Increased neurofibrillary tangles in patients with Alzheimer disease with comorbid depression. *Am J Geriatr Psychiatr*. 2008;16(2):168-174. https://doi.org/10.1097/jgp.0b013e31816029ec
10. Levy-Cooperman N, Burhan AM, Rafi-Tari S, et al. Frontal lobe hypoperfusion and depressive symptoms in Alzheimer disease. *J Psychiatry Neurosci*. 2008;33(3):218-226.
11. Guo Z, Zhang J, Liu X, et al. Neurometabolic characteristics in the anterior cingulate gyrus of Alzheimer's disease patients with depression: a (1)H magnetic resonance spectroscopy study. *BMC Psychiatr*. 2015;15(1):306. https://doi.org/10.1186/s12888-015-0691-7
12. Karavasilis E, Parthimos TP, Papatriantafyllou JD, et al. The power of sample size through a multi-scanner approach in MR neuroimaging regression analysis: evidence from Alzheimer's disease with and without depression. *Australas Phys Eng Sci Med*. 2019;42(2):563-571. https://doi.org/10.1007/s13246-019-00758-1
13. Karavasilis E, Parthimos TP, Papatriantafyllou JD, et al. A specific pattern of gray matter atrophy in Alzheimer's disease with depression. *J Neurology*. 2017;264(10):2101-2109. https://doi.org/10.1007/s00415-017-8603-z
14. Liu X, Guo Z, Ding Y, et al. Abnormal baseline brain activity in Alzheimer's disease patients with depression: a resting-state functional magnetic resonance imaging study. *Neuroradiology*. 2017;59(7):709-714. https://doi.org/10.1007/s00234-017-1854-7
15. Rapp MA, Schnaider-Beeri M, Grossman HT, et al. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. *Arch Gen Psychiatr*. 2006;63(2):161-167. https://doi.org/10.1001/archpsyc.63.2.161
16. Auning E, Selnes P, Grambaite R, et al. Neurobiological correlates of depressive symptoms in people with subjective and mild cognitive impairment. *Acta Psychiatr Scand*. 2015;131(2):139-147. https://doi.org/10.1111/acps.12352
17. Enache D, Cavallin L, Lindberg O, et al. Medial temporal lobe atrophy and depressive symptoms in elderly patients with and without Alzheimer disease. *J Geriatr Psychiatr Neurol*. 2015;28(1):40-48. https://doi.org/10.1177/0891988714541873
18. Dhikav V, Sethi M, Anand KS. Medial temporal lobe atrophy in Alzheimer's disease/mild cognitive impairment with depression. *Br J Radiol*. 2014;87(1042):20140150. https://doi.org/10.1259/bjr.20140150
19. Son JH, Han DH, Min KJ, Kee BS. Correlation between gray matter volume in the temporal lobe and depressive symptoms in patients with Alzheimer's disease. *Neurosci Lett*. 2013;548:15-20. https://doi.org/10.1016/j.neulet.2013.05.021
20. Hayata TT, Bergo FP, Rezende TJ, et al. Cortical correlates of affective syndrome in dementia due to Alzheimer's disease. *Arq Neuropsiquiatr*. 2015;73(7):553-560. https://doi.org/10.1590/0004-282x20150068
21. Lebedeva A, Westman E, Lebedev AV, et al. Structural brain changes associated with depressive symptoms in the elderly with Alzheimer's disease. *J Neurol Neurosurg Psychiatr*. 2014;85(8):930-935. https://doi.org/10.1136/jnnp-2013-307110
22. Zahodne LB, Gongvatana A, Cohen RA, Ott BR, Tremont G, Alzheimer's Disease Neuroimaging I. Are apathy and depression independently associated with longitudinal trajectories of cortical atrophy in mild cognitive impairment? *Am J Geriatric Psychiatry official J Am Assoc Geriatric Psychiatry*. 2013;21(11):1098-1106. https://doi.org/10.1016/j.jagp.2013.01.043
23. Lebedev AV, Beyer MK, Fritze F, Westman E, Ballard C, Aarsland D. Cortical changes associated with depression and antidepressant use in Alzheimer and Lewy body dementia: an MRI surface-based morphometric study. *Am J Geriatr Psychiatr*. 2014;22(1):4-13. e11. https://doi.org/10.1016/j.jagp.2013.02.004
24. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12(2):233-239. https://doi.org/10.1176/jnp.12.2.233
25. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982;17(1):37-49. https://doi.org/10.1016/0022-3956(82)90033-4
26. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's disease neuroimaging initiative (ADNI). *Clinical characterization*. 2010;74(3):201-209. https://doi.org/10.1212/wnl.0b013e3181cb3e25
27. Misra C, Fan Y, Davatzikos C. Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI. *Neuroimage*. 2009;44(4):1415-1422. https://doi.org/10.1016/j.neuroimage.2008.10.031
28. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-2314. https://doi.org/10.1212/wnl.44.12.2308
29. Ledig C, Schuh A, Guerrero R, Heckemann RA, Rueckert D. Structural brain imaging in Alzheimer's disease and mild cognitive impairment: biomarker analysis and shared morphometry database. *Sci Rep*. 2018;8(1):11258. https://doi.org/10.1038/s41598-018-29295-9
30. Schwarz C, Fletcher E, DeCarli C, Carmichael O. Fully-automated white matter hyperintensity detection with anatomical prior

knowledge and without FLAIR. *Inf Process Med Imaging*. 2009;21:239-251.
31. Pocklington C, Gilbody S, Manea L, McMillan D. The diagnostic accuracy of brief versions of the Geriatric Depression Scale: a systematic review and meta-analysis. *Int J Geriatr Psychiatr*. 2016;31(8):837-857. https://doi.org/10.1002/gps.4407
32. Goodarzi ZS, Mele BS, Roberts DJ, Holroyd-Leduc J. Depression case finding in individuals with dementia: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2017;65(5):937-948. https://doi.org/10.1111/jgs.14713
33. Caputo M, Monastero R, Mariani E, et al. Neuropsychiatric symptoms in 921 elderly subjects with dementia: a comparison between vascular and neurodegenerative types. *Acta Psychiatr Scand*. 2008;117(6):455-464. https://doi.org/10.1111/j.1600-0447.2008.01175.x
34. Vik-Mo AO, Giil LM, Borda MG, Ballard C, Aarsland D. The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study. *Br J Psychiatry*. 2020;216(1):43-48. https://doi.org/10.1192/bjp.2019.195
35. Vik-Mo AO, Giil LM, Ballard C, Aarsland D. Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study. *Int J Geriatr Psychiatr*. 2018;33(10):1361-1369. https://doi.org/10.1002/gps.4933
36. Gallo JL, Schmidt KS, Libon DJ. An itemized approach to assessing behavioral and psychological symptoms in dementia. *Am J Alzheimer's Dis Other Dementias*. 2009;24(2):163-168. https://doi.org/10.1177/1533317508329480
37. Teipel SJ, Cavedo E, Hampel H, Grothe MJ, AsDNI APMI. Basal forebrain volume, but not hippocampal volume, is a predictor of global cognitive decline in patients with Alzheimer's disease treated with cholinesterase inhibitors. *Front Neurol*. 2018;9(642). https://doi.org/10.3389/fneur.2018.00642
38. Aalten P, Verhey FRJ, Boziki M, et al. Neuropsychiatric syndromes in dementia. *Dementia Geriatric Cognitive Disord*. 2007;24(6):457-463. https://doi.org/10.1159/000110738
39. Savva GM, Zaccai J, Matthews FE, Davidson JE, McKeith I, Brayne C. Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *Br J Psychiatry*. 2009;194(3):212-219. https://doi.org/10.1192/bjp.bp.108.049619
40. Aalten P, de Vugt ME, Lousberg R, et al. Behavioral problems in dementia: a factor analysis of the neuropsychiatric inventory. *Dement Geriatr Cognit Disord*. 2003;15(2):99-105. https://doi.org/10.1159/000067972
41. Kang HS, Ahn IS, Kim JH, Kim DK. Neuropsychiatric symptoms in Korean patients with Alzheimer's disease: exploratory factor analysis and confirmatory factor analysis of the neuropsychiatric inventory. *Dement Geriatr Cognit Disord*. 2010;29(1):82-87. https://doi.org/10.1159/000264629
42. Eustace A, Coen R, Walsh C, et al. A longitudinal evaluation of behavioural and psychological symptoms of probable Alzheimer's disease. *Int J Geriatr Psychiatr*. 2002;17(10):968-973. https://doi.org/10.1002/gps.736
43. Haupt M, Kurz A, Jänner M. A 2-year follow-up of behavioural and psychological symptoms in Alzheimer's disease. *Dement Geriatr Cognit Disord*. 2000;11(3):147-152. https://doi.org/10.1159/000017228
44. Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR. The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatr*. 2005;20(6):523-530. https://doi.org/10.1002/gps.1316
45. Bettney L, Butt S, Morris J, et al. Investigating the stability of neuropsychiatric sub-syndromes with progression of dementia: a 2-year prospective study. *Int J Geriatr Psychiatr*. 2012;27(11):1118-1123. https://doi.org/10.1002/gps.2829
46. Connors MH, Seeher KM, Crawford J, Ames D, Woodward M, Brodaty H. The stability of neuropsychiatric subsyndromes in Alzheimer's disease. *Alzheimers Dement*. 2018;14(7):880-888. https://doi.org/10.1016/j.jalz.2018.02.006
47. McCutcheon ST, Han D, Troncoso J, et al. Clinicopathological correlates of depression in early Alzheimer's disease in the NACC. *Int J Geriatr Psychiatr*. 2016;31(12):1301-1311. https://doi.org/10.1002/gps.4435
48. Gibson LL, Grinberg LT, ffytche D, et al. Neuropathological correlates of neuropsychiatric symptoms in dementia. *Alzheimer's Dementia*. 2022. In press. https://doi.org/10.1002/alz.12765

SUPPORTING INFORMATION

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How to cite this article: Sinclair LI, Ballard CG. Persistent depressive symptoms are associated with frontal regional atrophy in patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 2023;e5858. https://doi.org/10.1002/gps.5858