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

Running title: Brain volumes in depression and AD

Sinclair, Lindsey Isla MBBS PhD <sup>1,2</sup>

Ballard, Clive G MBBS PhD <sup>3</sup>

for the Alzheimer's Disease Neuroimaging Initiative\*

1. Dementia Research Group, Bristol Medical School, University of Bristol, Bristol UK
2. Population health sciences, Bristol Medical School, University of Bristol, Bristol UK
3. Medical School, University of Exeter, Exeter UK

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Corresponding author: Dr Lindsey Sinclair, Dementia Research Group, Level 1 Learning & Research Building, Southmead Hospital, Bristol BS10 5NB, [lindsey.sinclair@bristol.ac.uk](mailto:lindsey.sinclair@bristol.ac.uk)

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LS 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.

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## **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 ADNI and the NACC, for those with data from at least one MRI scan. Depression ratings were available using the GDS and NPI. Intermittent depressive symptoms were defined as one episode above threshold ( $\geq 8$  on GDS,  $\geq 6$  on NPI depression subscale and  $\geq 2$  on the NPI-Q depression sub-scale) and persistent as  $\geq 2$  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

Depressive disorder, depression, Alzheimer's Disease, dementia



## 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.<sup>1</sup> It is distressing for patients and may increase carer burden.<sup>2-4</sup> 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.<sup>5</sup>

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.<sup>6,7</sup>). A large case series using the HAM-D scale found that depression in AD is not merely a symptom of the dementia.<sup>8</sup> 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.<sup>4,9</sup> They also seem to have reduced frontal perfusion and reduced connectivity between the amygdala and the frontal cortex.<sup>10,11</sup>

There have been relatively few neuroimaging studies. Decreased thalamic grey matter volume has been shown in two well powered and performed MRI studies<sup>12,13</sup> with resting state abnormalities found in a small rsMRI study.<sup>14</sup> In the hippocampus increased plaques and tangles have been reported in individuals without dementia but with a lifetime history of depression<sup>15</sup>. 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.<sup>16-18</sup> 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).<sup>19-23</sup> One of these studies used a GDS threshold of only 5<sup>21</sup>, others were small<sup>19,23</sup> and another defined depression as a positive response to the NPI-Q depression screening question.<sup>22</sup>

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)<sup>12,13</sup> Other studies have also reported frontal grey matter volume loss.<sup>20</sup> A study using a GDS threshold of 5 provides support for parietal volume loss (posterior cingulate, precuneus)<sup>21</sup> as did another small MRI study (postcentral gyrus).<sup>19</sup> 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.

## **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.

## Methods

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

### NACC

The 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, 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.<sup>24,25</sup> Unlike 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.

## **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 PET and MRI.<sup>26,27</sup> 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.<sup>26</sup> ADNI was carried out in phases; ADNI1 in 2004; 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 & 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 Geriatric Depression Scale (GDS).<sup>24,25,28</sup> The final dataset was downloaded in May 2021. Regional brain atrophy data used in this study was derived by Ledig et al.<sup>29</sup> White matter hyperintensity data was generated by Schwarz et al. using a Markov random field framework.<sup>30</sup>

## **Definition of Depressive symptoms**

A cut-off of  $\geq 8$  was used for the GDS as it has the best balance of sensitivity and specificity.<sup>31,32</sup>

For the NPI sub-scale scores were calculated for depression by multiplying the frequency and severity items for each symptom.<sup>28</sup> A cut-off was used of  $\geq 2$  for the NPI-Q and  $\geq 6$  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.<sup>33-35</sup>

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 2 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.<sup>36</sup>

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.

### **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 the NACC dataset, in which some participants were seen several times before they developed mild cognitive impairment (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 e.g. Parkinson's Disease, epilepsy and cerebral neoplasms were excluded. The ADNI dataset did not have such precise information on such disorders.

## 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 priori power calculation assuming an SD of  $330 \text{ mm}^3$  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  $200 \text{ mm}^3$ .<sup>37</sup> 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, APOE status, GDS score, antidepressant use at baseline and years of education as co-variates. 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 s8) 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 PCA 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.

### **Ethical Approvals**

The NACC database itself is exempt from 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.

## Results

### NACC

As shown in table 1, 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 two 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.

### ADNI

Six hundred and sixty six individuals with AD were included in the cohort for this study (see table 1). 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 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 s11), 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.

### Baseline volume differences by presence/absence of depressive symptoms

As shown in table 2 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 1cm<sup>3</sup> and 78% power to find a difference of 0.7mm<sup>3</sup>.

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).

### 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 3.5cm<sup>3</sup>, p=0.022).

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 s12).

### 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 s7) 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 s15) 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<sup>3</sup>, 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 s13). At 12 months there were 27 individuals with persistent depression (see table s14). Again there was evidence of increased atrophy in the frontal operculum in individuals 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 to 1.345) p=0.042). A sensitivity analysis looking at laterality at 12 and 24 months (see table s15, figures 1 & 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.

### Baseline and atrophy differences by NPI symptom profiles

We used a secondary, post-hoc, principal component analysis to identify symptom clusters, 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 s8). Looking at baseline volumes, which had higher numbers (see figure 3, table s10), individuals with depression plus apathy/anxiety had great white matter hyperintensity volumes (mean difference 107.1cm<sup>3</sup>, 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 s16). The depression +apathy/anxiety group (n=93) had reduced frontal opercular size (mean difference 15.6mm<sup>3</sup>, p=0.0031).

## 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.<sup>12,13</sup> We also used a higher GDS cut off than some other previous studies.<sup>21</sup>

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<sup>12,13</sup>, 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 & 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.<sup>38,39</sup> 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 that apathy & appetite were distinct from depression & anxiety.<sup>38</sup> 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.<sup>40</sup> A cross-sectional study in Korea (n=778) found that anxiety and depression were separable from apathy (plus sleep & appetite) using factor analysis of the NPI.<sup>41</sup>

Several studies have reported that depressive symptoms vary during follow-up.<sup>42,43</sup> Aalten et al found in a 2 year follow-up study (n=199) that depression and apathy loaded onto the same factor, with anxiety as a separate symptom.<sup>44</sup> 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 two year follow-up,<sup>45</sup> 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.<sup>46</sup> The authors suggested that future research should consider 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 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.<sup>9,47,48</sup> 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.

## Data Availability Statement

The data used in this study was obtained from ADNI ([www.loni.ucla.edu/ADNI](http://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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	NACC				ADNI			Statistical Evidence
	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	
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
<i>male</i>	56.2%	48.1%	44.1%		58.17%	54.90%	46.97%	
<i>female</i>	43.8%	51.9%	55.9%		41.83%	45.10%	53.03%	
Marital status				p=0.30				p=0.778
<i>married</i>	65.1%	67.0%	70.3%		83.7%	81.7%	83.3%	
<i>widowed</i>	20.4%	16.2%	15.3%		10.1%	10.5%	10.6%	
<i>divorced</i>	8.7%	12.4%	7.2%		3.8%	5.9%	6.1%	
<i>separated</i>	0.5%	0.0%	1.8%					
<i>other</i>	5.4%	4.3%	5.2%		2.5%	2.0%	0.0%	
Ethnicity				p=0.61				p=0.974
<i>white</i>	84.2%	89.2%	82.0%		94.2%	93.5%	92.4%	
<i>black or african american</i>	11.2%	7.0%	14.4%		3.1%	3.3%	4.6%	
<i>native american/asian</i>	4.4%	3.7%	3.6%		2.8%	3.3%	3.0%	
<i>Prescribed an antidepressant at baseline</i>	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

Table 1: Baseline characteristics of the cohorts in this study. 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.

Volume in cm <sup>3</sup> at first MRI	AD no depression (n=377)		AD with persistent depression (n=107)		Statistical Evidence adjusted for age, ethnicity, Hx of depression, psych Hx at baseline and gender
	Mean	SD	Mean	SD	
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 to 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 to 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 to 2.525) $p=0.987$
Insula	13.61	2.27	13.34	2.35	$\beta = 0.056$ (-0.529 to 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 to 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 to 0.761) $p=0.828$
Posterior cingulate	7.69	1.35	7.79	1.38	$\beta = 0.120$ (-0.228 to 0.468) $p=0.497$
Precentral	20.77	3.7	20.95	3.81	$\beta = -0.134$ (-0.821 to 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 to 1.050) $p=0.598$
Superior frontal	42.52	6.34	43.04	7.31	$\beta = -0.426$ (-1.251 to 2.104) $p=0.618$
White matter hyperintensity volume	10.086	13.203	13.543	14.846	$p = 0.022$

Table 2: Baseline regional brain volumes in NACC in AD without depression and those with persistent depression. All regressions were adjusted for age, gender, Hx of depression and Hx of psychiatric illness.

All volumes are in cm <sup>3</sup>	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 to 0.546) $p=0.308$
Entorhinal	3.64	0.79	3.68	0.73	$\beta = 0.115$ (-0.115 to 0.347) $p=0.327$
Frontal operculum	2.51	0.52	2.54	0.36	$\beta = 0.065$ (-0.094 to 0.223) $p=0.422$
Hippocampus	6.25	1.04	6.30	0.92	$\beta = 0.123$ (-0.181 to 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 to 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 to 0.328) $p=0.851$
Posterior central gyrus	17.90	2.43	17.48	2.21	$\beta = -0.377$ (-1.142 to 0.387) $p=0.332$
Posterior cingulate	7.11	1.05	7.17	1.07	$\beta = 0.117$ (-0.210 to 0.445) $p=0.481$
Posterior insula	3.34	0.61	3.34	0.61	$\beta = 0.037$ (-0.145 to 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 to 0.884) $p=0.762$
Superior frontal gyrus	23.05	3.16	22.52	2.91	$\beta = -0.126$ (-1.103 to 0.851) $p=0.800$
Thalamus	13.66	1.37	13.52	1.4	$\beta = -0.023$ (-0.411 to 0.365) $p=0.906$

*Table 3: Baseline regional volumes in the ADNI cohort in relation to depression. All regressions included age, gender, ethnicity, APOE status, GDS score, antidepressant use at baseline and years of education as co-variates.*

## Figure Legends

*Figure 1: Regional atrophy in ADNI at 12 months in selected brain areas*

*Figure 2: Regional atrophy in ADNI at 24 months in selected brain areas*

*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).*