Acta Neurologica Belgica
https://doi.org/10.1007/s13760-020-01349-8

ORIGINAL ARTICLE

Neuroanatomical associations of depression, anxiety and apathy neuropsychiatric symptoms in patients with Alzheimer's disease

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Received: 16 December 2019 / Accepted: 24 March 2020

Abstract

Depression, anxiety and apathy are 'common neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD). We aimed to find regional gray matter (GM) volume difference of these symptoms, in AD patients compared to AD control, and investigate possible associations of GM atrophy with cognitive covariant. Study subjects were retrieved from the Alzheimer's Disease Neuroimaging Initiative database. Thirty-five participants are AD control, 27 AD patients with anxiety, 19 with depression and 24 with apathy, ages ≥ 55.1 years. Recruited subjects had an assessment of their clinical and structural MRI data. GM differences and clinical data were analyzed using voxel-based morphometry and ANOVA with Scheffe post hoc test, respectively. We found significant GM volumes differences in the left insula, left parahippocampal, posterior cingulate and the bilateral putamen in the anxiety group. The results also revealed that the right parahippocampal, Brodmann area 38 and the middle frontal gyrus were significant in patients with depression. Significant results were with a $p < 0.05$, corrected with AlphaSim program for multiple comparisons. The left insula had a strong negative association with Clinical Dementia Rate Sum of Boxes and Alzheimer's Disease Assessment Scale-cognitive subscale-13 items in anxiety and apathy groups. The difference in GM density in the left insula and hippocampus plays a crucial role in depression, anxiety and apathy NPS and outline precise approaches to test these symptoms.

Keywords Alzheimer's disease · Anxiety · Apathy · Depression · Neuropsychiatric symptoms · Left insula

Introduction

Many neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) are universal, existing and highly profound [1]. It is necessarily be considered as early clinical markers, and gets a priority in diagnosis as well as cognitive impairment [2, 3].

The diagnosis of NPS in AD is a convoluted process. However, some overlaps between NPS were found [4]. In some cases, the diagnosis of NPS may be confused. Hence, it is difficult to obtain a precise diagnosis for each symptom, regardless of some different characteristics. Recent imaging techniques play a significant role in confirming the diagnosis of NPS and assist in their classification. The study of the neuroanatomical association of each symptom with brain region atrophy may help to clarify their possible pathogenic mechanism.

Apathy, anxiety and depression are NPS that display distinctive clinical patterns of expression through the course in AD and carry significant predictive and functional

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://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 the 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.

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Published online: 21 April 2020

disturbance consequences [5, 6]. At the early stage of AD, patients may encounter one or several NPS [1, 7]. Fortunately, with the existence of recent advances in MRI technology, the conduction and combining of clinical and imaging assessment may integrate and distinguish these NPS. Currently, applying of neuroimaging and neurochemistry tests has focused on a clear understanding of the association between the causal of AD brain disease and the clinical appearances of NPS [8].

Different adverse outcomes, reduced daily activity, loss of interest or hedonism are important issues for patients with apathy and depression [9]. Moreover, distress and burden to AD patients, their caregivers and relatives are considered more vulnerable in AD patients with NPS than those without [7]. Also, several consequences, including more rapid cognitive worsening and institutionalization, were thought as results of NPS [2, 10]. The presence and prevalence of each symptom are varying among AD patients. These variations were attributed to the differences in the assessment methods, characteristics of the studied sample, and AD severity [7, 11].

Clinical evaluation of NPS in AD has been addressed in the research field [5]. However, the neuroanatomical localization and functional mechanisms involved in the development of these NPS remain poorly understood.

Structural magnetic resonance imaging (sMRI) was used to support the clinical and cognitive measurements in the diagnosis of AD. Cross-sectional studies on MRI had reported a decrease in the volume of medial temporal structures of the brain, in the hippocampus and the entorhinal cortex of AD patients compared to healthy controls [12]. Also, it was used to evaluate several NPS in AD patients [13–15], mild cognitive impairment (MCI) patients with depression found to be converted to AD at a considerably higher rate. In contrast, those patients with minor behavioral impairment might develop dementia, although they had normal cognition [1].

Cerebral circuits and regions are overlapping, underpinning both cognitive decline and emotional disorders [16, 17]. Thus, identifying each symptom with a unique brain regional GM volume atrophy may assist in highlighting their possible pathogenic mechanism, increase their diagnostic probabilities and aid in producing an effective treatment that may alleviate these symptoms. Depression and apathy are the most common symptoms and are clinically associated with dementia [18]. In subjects with MCI, apathy, anxiety and depression may be precursors for AD [19]. Currently, it was reported that anxiety was associated with the accumulation of total tau (t-tau) and Aβ42 in the cerebrospinal fluid in vivo biomarkers in patients with mild cognitive impairment [19]. The critical challenge in this study is defining a region or regions of brain atrophy within the complexities of the brain regions involved in each NPS. Nevertheless, sharing brain region atrophy will be present between some NPS.

We selected our study groups to include one behaviour or symptom in one group, and excluding those subjects with other symptoms, to the best of our knowledge, previous works had less clarified such selection in their studies. Moreover, the inclusion of anxiety group in this study was to further clarify the neuroanatomical association of this symptom in AD participants. The neuroanatomical association of anxiety behaviour had been less thoroughly investigated, even though it has a high prevalence in the clinical studies [20, 21].

We aimed to identify regional GM volume atrophies in depression, anxiety and apathy in AD and find a possible correlation with cognitive measurements.

Methods

Data used in the preparation of this study were obtained from the ADNI database (https://adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild MCI and early Alzheimer's disease (AD).

Subjects

ADNI-1 has 200 early AD included in the study [22]. The inclusion criteria in this study were based on the score of the Neuropsychiatric Inventory Questionnaire (NPI-Q) [23]. A total of 105 AD patients were enrolled, age range 55.1–87.7 years; (mean ± SD age; 76.9 ± 6.5). AD patients were further grouped as follows; 19 AD subjects having a score of ≥ 1 on the depression sub-domain and without apathy and/or anxiety symptoms (scores of zero in these two domains), 27 AD patients with anxiety, having score of ≥ 1 on the anxiety sub-domain and without depression and/or apathy and 24 AD with apathy score ≥ 1 on apathy sub-domain and without depression and/or anxiety. The AD control group was 35 subjects that had scores of zero in all NPI-Q domains.

Neuropsychiatric and cognitive assessments

The AD control subjects had a Mini-Mental State Examination (MMSE) scores between 20 and 28 [24] and Clinical Dementia Rating (CDR) of 0–2.0 [25]. All AD patients were diagnosed based on the criteria established by the

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) [26]. The CDR range (0.5–2) and MMSE range (20–26) scores for AD patients at the baseline visit, there are no subjects with CDR of 0 in the AD patients and the CDR was in the range of 0.5–2.0. NPS was measured using the NPI-Q [23], a caregiver-based instrument that measures the presence (1 = yes, 0 = no) and only rates the severity of the symptoms (1 = mild, 2 = moderate, 3 = severe) over the prior month of 12 symptom domains: delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behavior, nighttime disturbances, and eating disturbances.

VBM: image processing

We downloaded baseline MRI scans from the ADNI public database (https://www.loni.ucla.edu/ADNI/Data/). Study subjects were scanned with a standardized MRI protocol developed for ADNI [27]. Structural brain MRI scans were acquired at all participating sites using 1.5 T MRI scanners with different scanner types and software platforms (Pewaukee, Wisconsin; Philips Medical Systems, General Electric Healthcare, Andover, Siemens Medical Solutions, Malvern and Pennsylvania). A sagittal three-dimensional magnetization, prepared rapid acquisition gradient echo (3D MP-RAGE) scanning protocol which was used with the following acquisition parameters: repetition time of 2400 ms, minimum full echo time, inversion time of 1000 ms, 8° flip angle, 24 cm field of view, and $192 \times 192 \times 166$ acquisition matrix in the x, y, z dimensions, yielding a voxel size of $1.25 \times 1.25 \times 1.2$ mm^3.

Data were processed using Statistical Parametric Mapping software (SPM8) (Welcome Department of Imaging Neuroscience, London), running in MATLAB R2012b. The images were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the unified segmentation procedure [28]. The diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) algorithm [29] was then used to normalize the segmented images spatially, DARTE-customized template was used to normalize all subjects to standard MNI space, then all images were resliced to $1.5 \times 1.5 \times 1.5$ mm voxels and smoothed using 4 mm full width at half maximum. Smoothed modulated GM tissues were used in the statistical comparison.

Statistical analysis

We performed statistical analyses using IBM SPSS software for Windows, version 25 (SPSS Inc., Chicago, IL, USA). For group comparisons of cognitive and behavioral performance, a one-way analysis of variance (ANOVA) was performed, followed by Scheffe tests for post hoc analysis of significant group differences. Results were presented as mean values ± SD for continuous variables, and a p value of 0.05 was considered statistically significant. In this study, we have unequal group size. The assumptions of a normal distribution of the variables were tested using the Kolmogorov–Smirnov test. We used the non-parametric test to evaluate the categorical variable.

Statistical analyses for MRI data were performed on a voxel-by-voxel basis using a general linear model (GLM) approach implemented in Rest-fMRI software [30]. A one-way ANOVA was performed to compare the smoothed, modulated normalized GM maps between the groups. Two-sample t tests to compare the GM differences between the apathy, anxiety and depression subgroups and AD control were carried out. The covariances applied were age, gender, years of education and intracranial volume (ICV), and minimum cluster size (k) of 23 voxels was required for significance. An explicit GM mask was used to restrict analyses to GM regions. The statistical threshold significance level was set at $p < 0.05$. The results were corrected for multiple comparisons which were determined by Monte Carlo simulation, AlphaSim method written by D. Ward, https://afni.nimh.nih.gov/afni/doc.pdf/AlphaSim.pdf (parameters: single voxel $p = 0.01$, 1000 simulation, full width at a half maximum estimated = 8.75 mm, cluster connection radius = 5 mm, with a re-sliced GM mask, which resulted in a corrected threshold of $p < 0.05$). Furthermore, a correlation between GM densities and cognitive domains was conducted. The mean GM density in the regions showing significant GM atrophy in the statistical comparison was extracted. Using ROI signal extraction features in (REST), ROI signal intensities were used in correlation analysis with CDR-SB and ADAS-cog-13 item scores.

Results

Demographic finding characteristics

The characteristics of the study sample are shown in Table 1. Female subjects (68.4%) were dominant in the depression group. Significant differences were noted in most of the cognitive domain measurements CDR ($p < 0.001$), CDR-SB ($p < 0.001$), ADAS-cog-13item ($p < 0.011$) and MMSE ($p < 0.001$). There was no significant difference found in education and total ICV between groups on both comparisons, $p > 0.05$.

Multiple comparisons by Scheffe's post hoc test revealed that the anxiety group versus apathy was statistically significant in the domain of CDR-SB (mean − 1.3, $p = 0.03$), and the depression vs apathy pair was statistically

Table 1 Demographics and clinical characteristics (mean ± SD) for AD control, AD with anxiety, depression and apathy groups

Variables	Total ($n=105$)	AD control ($n=35$)	Anxiety ($n=27$)	Depression ($n=19$)	Apathy ($n=24$)	p value (4 groups comparison)
Age	75.7 ± 7.6	76.9 ± 6.5	74.2 ± 8.8	73.3 ± 8.2	77.5 ± 6.8	0.15
Gender % men	52.7	57.1	52.0	31.6	66.7	
Education	15.1 ± 3.1	15.3 ± 3.2	14.8 ± 3.3	14.8 ± 3.5	15.3 ± 2.3	0.91
CDR[b]	0.8 ± 0.4	0.7 ± 0.3	0.9 ± 0.4	0.8 ± 0.3	1.1 ± 0.5	< 0.001
CDR-SB[a,b]	4.3 ± 1.8	3.6 ± 1.7	4.3 ± 1.7	4.1 ± 1.3	5.5 ± 1.9	< 0.001
ADAS-cog-13[b]	28.5 ± 7.7	26.0 ± 7.4	28.9 ± 7.5	26.5 ± 5.4	33.5 ± 7.8	0.011
MMSE	23.2 ± 2.0	23.6 ± 2.2	23.3 ± 1.7	23.5 ± 1.8	22.2 ± 2.1	0.06
Depression	0.2 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	1.1 ± 0.3	0.0 ± 0.0	< 0.001
Anxiety	0.3 ± 0.6	0.0 ± 0.0	1.2 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	< 0.001
Apathy	0.3 ± 0.6	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	1.4 ± 0.50	< 0.001
The NPI-Q total scores	2.8 ± 3.4	0.0 ± 0.0	4.3 ± 3.9	2.8 ± 1.9	5.2 ± 3.10	< 0.001
ICV	1,551,612.90 ± 193,712.5	1,539,285.71 ± 179,173.6	1,532,000.00 ± 201,494.4	1,542,105.26 ± 150,243.5	1,600,000.00 ± 238,746.7	0.178

All values represent mean ± SD in the ANOVA test unless indicated otherwise

AD Alzheimer disease, *CDR* clinical dementia rate, *CDR-SB* clinical dementia rate sum of boxes, *ADAS-cog-13* Alzheimer's disease sssessment scale-cognitive subscale-13 items, *MMSE* Mini-mental state examination, *NPI-Q* neuropsychiatric inventory-questionnaire, *ICV* intracranial volume. p value < 0.05

[a]Significant difference between apathy vs anxiety in the Scheffe test

[b]Significant difference between apathy vs depression in Scheffe test

significant in several cognitive domain (CDR, mean − 0.35, $p=0.011$, CDR-SB, mean − 1.5, $p=0.015$, ADAS-cog-13, mean − 7.16, $p=0.008$, the other domains did not differ significantly for all pairwise.

VBM comparison of gray matter volume between patients with anxiety, apathy and depression and AD controls

There were statistically significant differences in cognitive function among AD subtypes. Subsequent MRI analysis included CDR-SB and ADAS-Cog-13 as nuisance covariates. The general mean values of GM volumes revealed significant differences in the left insula, left middle temporal gyrus, anterior cingulate gyrus and the thalamus regions between all groups. Those AD patients with anxiety compared to AD control showed significant GM volume differences in the left parahippocampal, the posterior cingulate gyrus, the left insula and the bilateral putamen (see Table 2, Fig. 1a). The left insula, the right middle temporal, the superior temporal, the parahippocampal gyrus, putamen and the Brodmann area 38 (BA 38) showed GM volume differences in the AD patients with apathy compared to AD control, Table 2 and Fig. 1b. We also found significant differences in the right parahippocampal, the BA 38, the right insula, the middle temporal and the frontal gyrus and the hippocampus in depression groups. As depicted in Table 2 and Fig. 1, the anatomical structures with a significant difference in GM volume associated with these groups. All p values < 0.01, corrected AlphaSim. Cognitive status, measured by the CDR-SB and ADAS-cog-13 items was selected as a covariate in analyses of GM volumes associated with these NPS, considering the significant differences in their post hoc results.

The correlation between cognitive scores and regions of significant GM atrophy

The voxel-based multiple regression analysis showed significant partial correlations between GM density values in some cortical and subcortical structures and the cognitive measures of CDR-SB and ADAS-Cog-13 (Fig. 2). Bivariate correlations for anxiety group revealed that there were significant negative associations between left insula regions GM atrophy and CDR-SOB $r=0.588$, $p < 0.001$ and ADAS-Cog-13 $r=0.504$, $p < 0.001$, and a significant negative associations for depression group were found between the GM atrophy of the hippocampus gyrus and the CDR-SOB $r=-0.494$, $p < 0.001$ and ADAS-Cog-13 $r=-0.474$, $p < 0.001$ cognitive measures (see Figs. 3, 4). Bivariate correlations of the general mean values of left insula GM atrophy revealed significant negative associations with the above-mentioned cognitive domains (see Fig. 5).

The correlation analysis showed that a significant negative correlation existed in the apathy group, in the left insula and CDR-SB and Alzheimer's disease assessment scale-cognitive-13 item Fig. 4

Table 2 Anatomical structures showing significant differences in GM volumes between the three groups and control groups ($p < 0.01$, AlphaSim corrected)

Anatomical regions	*X*	*Y*	*Z*	Cluster size	*F* values
ANOVA					
Insula_L	−21	−10.5	−6	126	6.31
Temporal_Mid_R	−43.5	−12	−18	99	5.59
Anterior cingulate	9	10.5	16.5	362	7.40
Thalamus_L	16.5	−3	6	258	4.96
Anxiety vs AD control					*T* values
Parahippocampal_L	−39	−1.5	−27	38	2.95
Putamen_L	22.5	19	10.5	156	5.34
Putamen_R	33	−4.5	−12	56	3.13
Insula_L	−33	−4.5	−10.5	138	3.57
Posterior cingulate	28.5	−63	18	23	4.09
Apathy vs AD control					
Brodmann area 38	−46.5	22.5	−27	88	3.13
Temporal_Mid_R	72	−33	−4.5	179	2.61
Superior temporal gyrus	−64.5	−6	−4.5	142	3.03
Putamen_L	−21	−9	−4.5	51	4.24
Putamen_R	22.5	−7.5	−4.5	704	3.69
Parahippocampal gyrus	21	−58.5	−6	33	3.44
Insula_L	−30	6	12	116	3.22
Depression vs AD control					
Brodmann area 38	−9	16.5	13.5	164	4.66
Parahippocampal_R	22.5	−10.5	−7.5	209	3.04
Middle temporal gyrus	45	−52.5	6	188	3.80
Insula_R	63	5.5	−2.8	44	3.07
Hippocampus	21	−61.5	−4.5	42	3.31
Middle frontal gyrus	28.5	3	42	42	2.94

L left, *R* right, *Mid* middle, *X, Y, Z* coordinates of primary peak locations in the MNI space T values; peak intensities of significant GM atrophy between the three groups compared to AD control

Discussion

We aimed to identify regional GM differences of the most prevalent NPS in AD participants (depression, anxiety and apathy). These symptoms were reported with various percentages in a correlation of cerebrospinal fluid markers in subjects with MCI [20], pointing out, their existence in this earliest clinical appearance of AD pathophysiology must be flagged. The principal results in our study were a GM volume difference found in the left insula and the right putamen in both anxiety and apathy groups. Further similar findings were in the middle temporal gyrus and BA 38 regions in the apathy and depression groups. As well as several disparate regions of the brain, the right insula region, the left parahippocampal and the hippocampus regions in the studied groups (Table 2, Fig. 1). GM densities revealed significant differences in the left insula, left middle temporal gyrus, anterior cingulate gyrus and the thalamus regions between all groups. These results go beyond previous reports, showing that atrophy in the anterior cingulate cortex was substantially relevant. While others reported on apathetic group compared to control normal or apathy and depression, an associated GM density loss in the anterior cingulate [13, 31].

Association between neuropsychiatric symptoms in the study and insula cortex

In this study, the insula cortex showed GM differences in all AD groups compared to AD control. In contrast, while the right insula in the depression group had a substantial GM difference compared to AD control, the left insula was depicted in the anxiety and apathy groups and had a strong negative correlation with cognitive measures of CDR-SB and ADAS-Cog-13 items scores. Previous study found predominant behavioral symptoms, have a tendency to affect areas concerned in the salience network, including the anterior insula, the anterior cingulate cortex (ACC), medial orbital prefrontal cortex, thalamus, striatum, and amygdala regions implicated in social and emotional processing, researchers found associations between rapid degeneration in the ACC and reduced cortical thickness in the entorhinal and depression in MCI

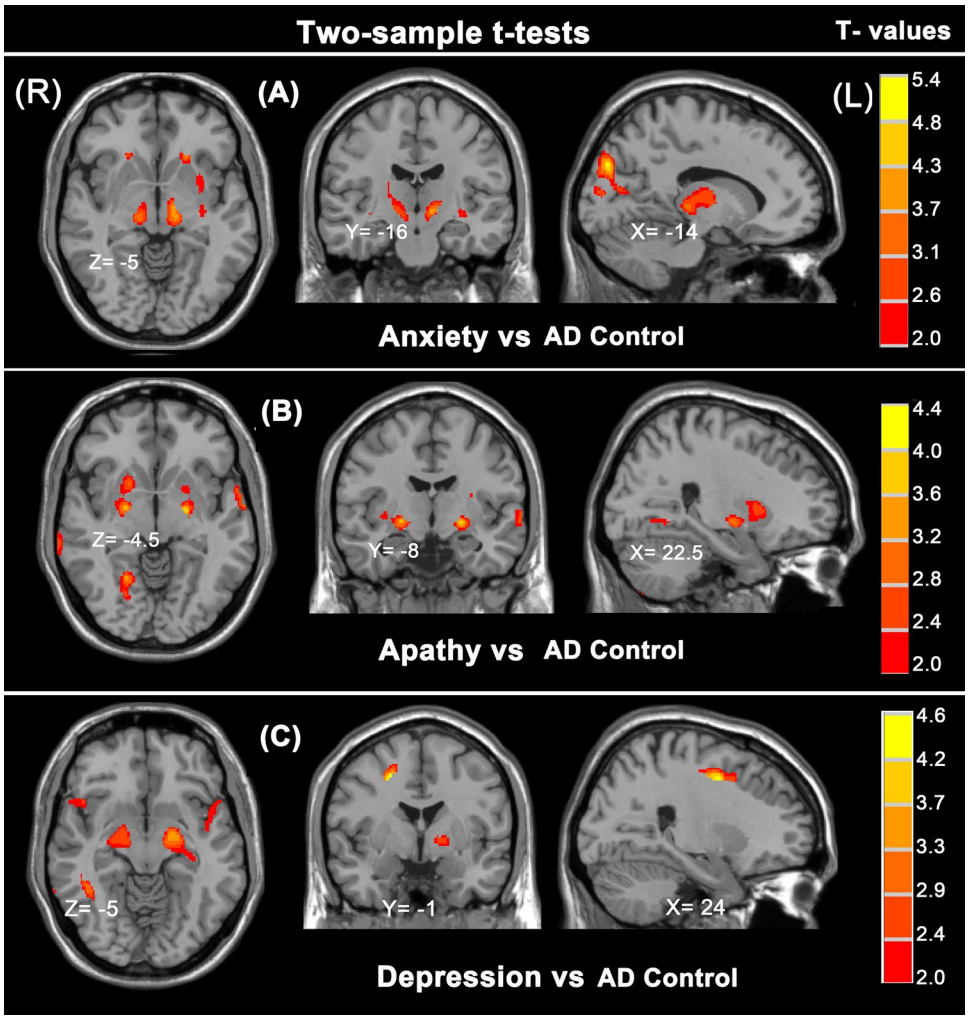

Fig. 1 Demonstrates the statistical maps of the whole-brain voxel-wise two-sample t tests anatomical structures with a significant difference in gray matter volume associated with top: **a** anxiety, middle: **b** apathy and bottom: **c** depression in AD patients compared to AD control, threshold for significance determined by cluster-level inference ($p < 0.05$, AlphaSim corrected, voxel level at $p < 0.01$). The colour bars to the left of the image show the significant thresholds (t scores). *L* left, *R* right

participants [8]. Symptoms of depression and anxiety were associated with atrophy of insular, right frontal, and temporal cortices [32]. Additionally, hyperactivity disorder was reported with increased connectivity in the salience network (SN) in the right insula and anterior cingulate cortex [32]. While insular roles remain completely not understood, there is evidence that the anterior part of the insula, processes emotional experiences. Based on the role of the insula encoding interoceptive signals from the body's internal milieu that reflect autonomic activity, an argument was raised by Damasio that the insula is the part of the brain that generates subjective feelings of emotion [33]. The gray matter density of the left insula in AD with anxiety or apathy and of the right hippocampus in AD with depression were negatively correlated with cognitive measures. Therefore, these brain regions might be more associated with cognitive impairment than NSP, although cognitive measures were used as covariates in the VBM analysis.

Structural associations of anxiety and depression disorders

In the present study, the anxiety group was taken together with those commonly investigated symptoms, apathy and depression. Literature reported few studies on structural or metabolic associations of anxiety in AD. The emphasis on the diagnosis of generalized anxiety has to be focused on neuroimaging and genetic research [34]. Our image data analysis demonstrated several regions of similar GM atrophy (Table 2, Fig. 1) and some slight regional GM differences between the three groups. These results are supported by published literature reported on the associations of NPS using clinical and neuropsychiatric measurements combined with imaging methods [9, 13, 35].

Our findings were further strengthened by consistent relevant from the literature, a study on stable MCI and healthy control participants reported the spreading of differences in the comparison of GM maps. MCI-stable participants

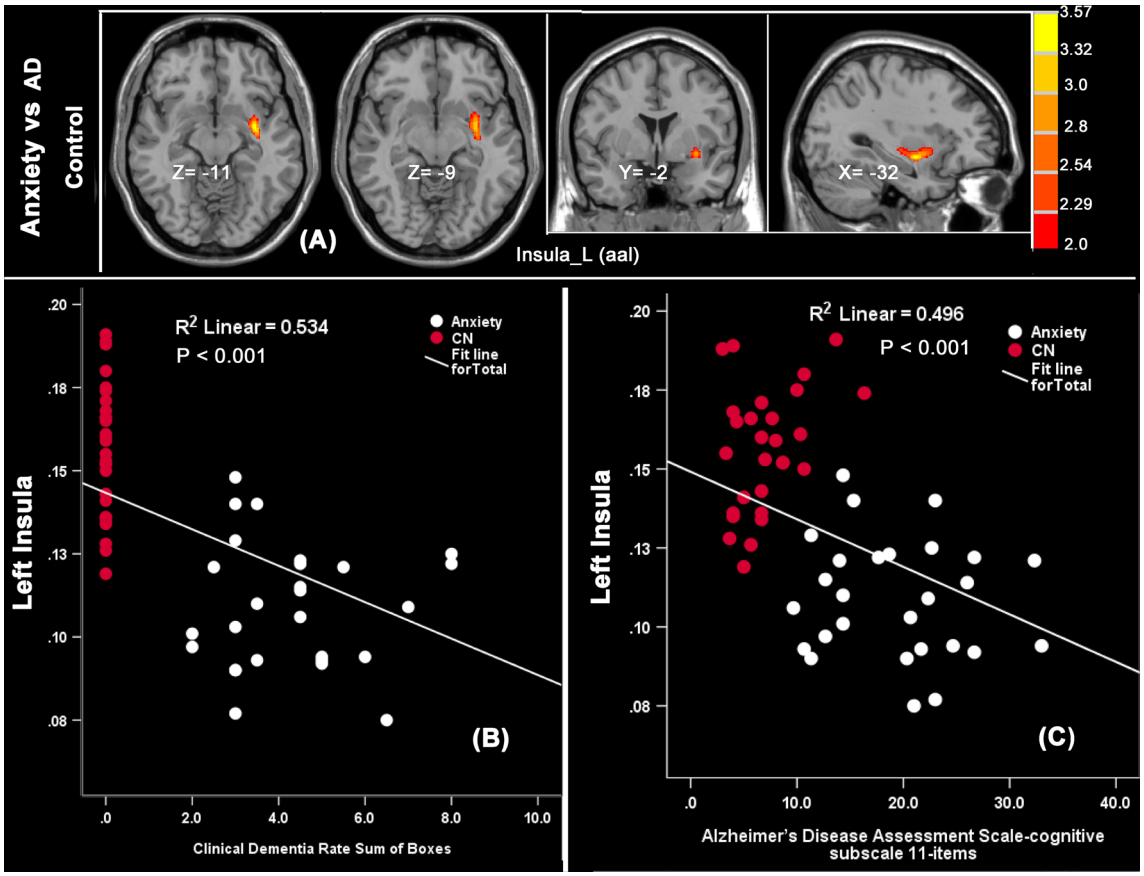

Fig. 2 Top: **a** areas of statistically significant correlation with the GM atrophy and anxiety group in the left insula (axial, sagittal and coronal views) and bottom scatter plots showing a significant negative correlation between left insula cortex and **b** CDR-SB, **c** Alzheimer's disease assessment scale-cognitive-13 item scores

showed reduced GM density with a global maximum in the right parahippocampal gyrus. Additionally, local maxima in the bilateral putamen and hippocampus regions [36]. Compared to a healthy control group, the MCI group showed decreased gray matter volume in the right parahippocampal gyrus, dementia with depression showed significant GM differences than dementia only compared to AD control. Furthermore, dementia with depression was reported with GM differences than MCI with depression [37]. Moreover, the right parahippocampal region thinning in a study on cortical changes was associated with antidepressant use in Alzheimer's and Lewy body dementia. Furthermore, volume loss in the hippocampal region has been reported in depression [38, 39].

Structural associations of apathy disorder

Apathy in AD patients, in a positron emission tomography deoxyglucose (FDG-PET) studies, has demonstrated that it is associated with reduced metabolism in the medial thalamus, orbitofrontal cortex and anterior cingulate cortex, and some temporal structures [40, 41]. Interestingly, our study revealed that there is a substantial decreased GM volume in right thalamus region in the anxiety group, this is in accord with the findings reported by Irena et al. [42], they conducted vertex analysis and found that there were volumes decreased of the thalami and hippocampi in AD patients. In another study, a meta-analysis conducted in 2013, including MRI in late-life depression, reported substantially decreased volumes in the thalamus, orbitofrontal cortex and putamen [43].

Compared to AD control, GM volume atrophy was found in the hippocampal and parahippocampal regions, and a significant negative correlation with CDR-SB and ADAS-cog-13 scores was also found in the hippocampal region. Middle frontal gyrus showed atrophy in the depression group. Our data also addressed GM volume reductions in the temporal cortices, insula, and BA 38, which is in line with previous studies [13–15, 41]. GM atrophy in the amygdala-hippocampal area, thalamus and insula-characterized patients with amnestic MCI from cognitively healthy normal. The parietal and cingulate regional volume loss were

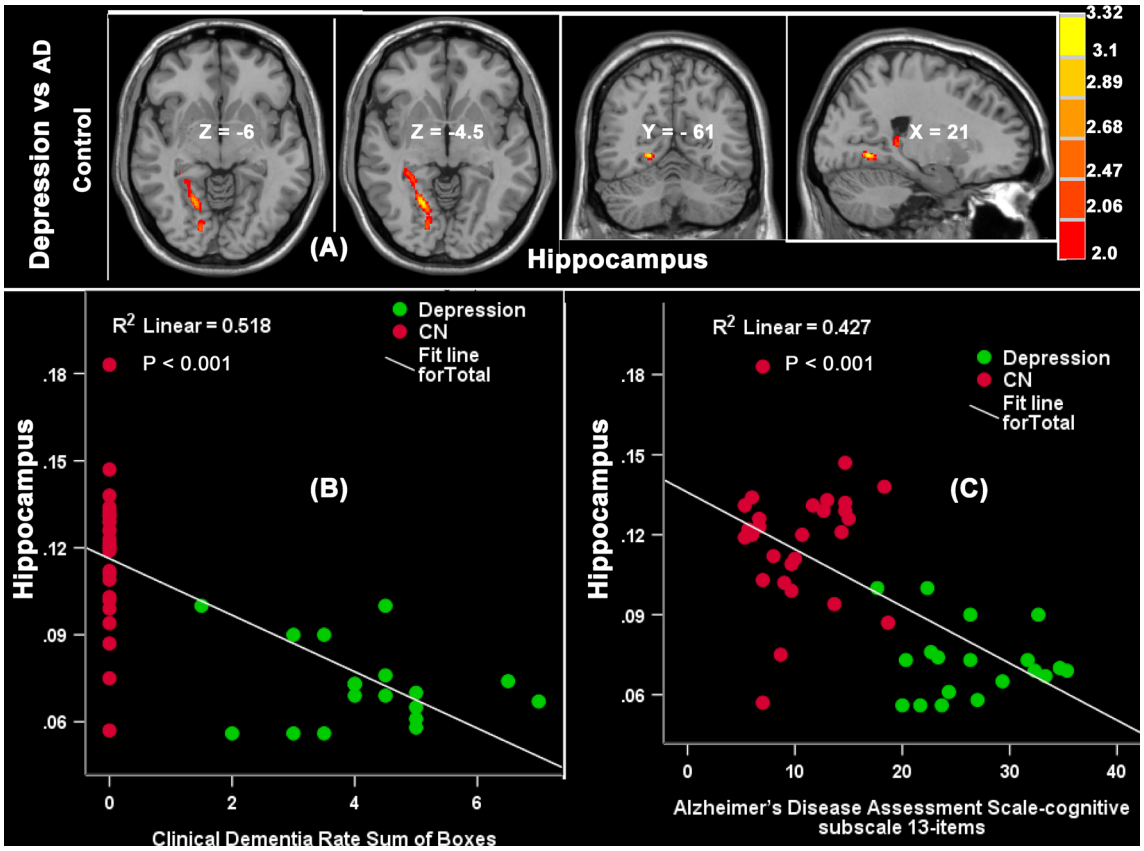

Fig. 3 Top **a** areas of statistically significant correlation with the GM atrophy and depression group in the hippocampus (axial, sagittal and coronal views) and bottom scatter plots showing a significant negative correlation between the hippocampus and **b** CDR-SB, **c** Alzheimer's disease assessment scale-cognitive-13 item scores

also considered. BA 38 is the anterior end of the temporal lobe, connected to the amygdala and orbital prefrontal cortex and it is involved in social and emotional processing, which are core features disrupted in apathy [44].

It is essential to highlight, however, in this work, we found differences in the region of Broadman area 38 associated with depression and apathy groups compared to AD control. A popular explanation is that Broadman area 38 is located in the temporal cortex of the human brain, functioning as connectors in several networks specifically that for the memory process, this brain region had been detected in previous works on MRI based on automated detection of brain atrophy patterns to predict AD [45].

Limitations

First, although the NPI-Q has been verified to provide acceptable test–retest reliability and convergent validity for evaluating a broad range of NPS [23], using specified behavior assessment tools with each symptom (e.g., the apathy evaluation, geriatric depression scales) may strengthen these findings. Second, the small sample size could limit the dimensions to detect smaller group differences and Third, regarding the effects of medication used, we did not have the likelihood to check the effects of (cholinesterase inhibitors and memantine) or other medications that some of the patients were receiving, mainly the selective serotonin reuptake inhibitor (SSRI) for those with apathy.

Conclusion

We conducted a VBM study identifying regional GM volume atrophies associated with depression, anxiety and apathy in AD subjects. The results of the study revealed that the left insula and the hippocampus are both associated with NPS and cognitive impairment. Also, it showed that other brain regions as the putamen, and posterior cingulate had significant gray matter atrophy and was not significantly correlated with the cognitive measures. In the depression group, decreased regional GM volumes in the hippocampus were strongly negatively correlated with the CDR-SB and ADADS-Cog-13. Considering the role of these brain regions in depression, anxiety and apathy may

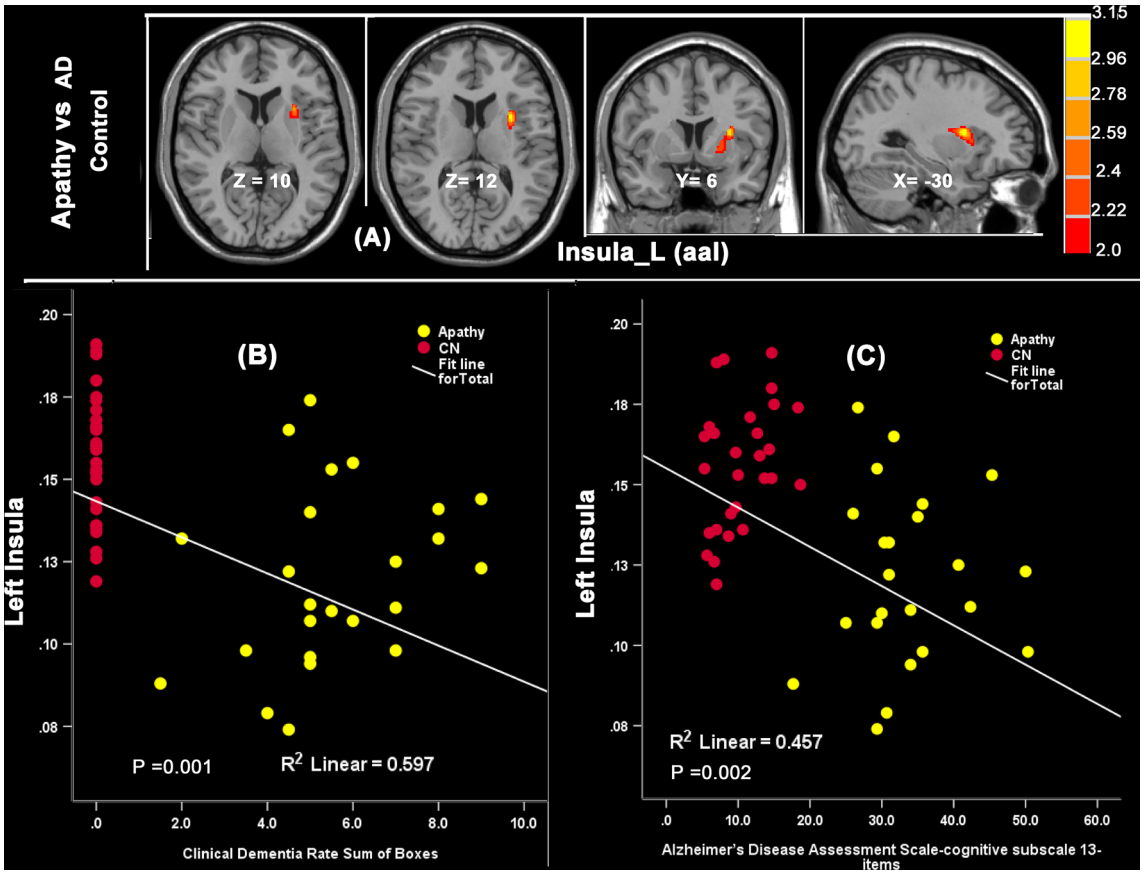

Fig. 4 Top **a** Areas of statistically significant correlation with the GM atrophy and apathy group in the left insula (axial, sagittal and coronal views) and bottom scatter plots showing a significant negative correlation between the left insula and **b** CDR-SB, **c** Alzheimer's disease assessment scale-cognitive-13 item scores

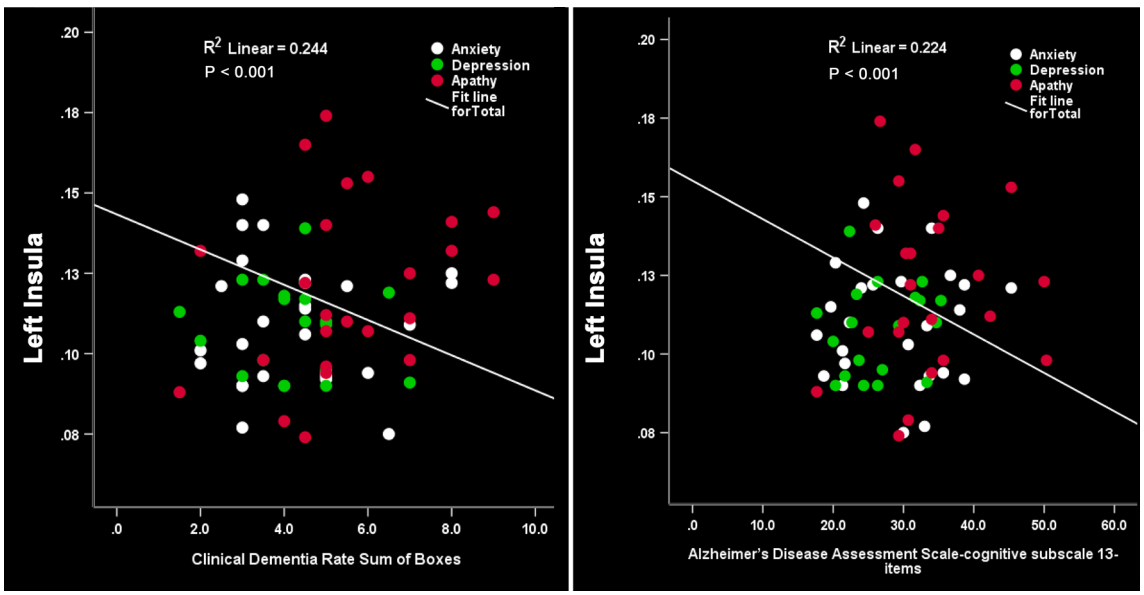

Fig. 5 Scatter plots showing a significant negative correlation between the left insula cortex and **a** CDR-SB, **b** Alzheimer's disease assessment scale-cognitive-13 scores for all groups

lead to the development of a focused treatment that would reduce disease burden caused by these NPS. The present structural-based findings not only revealed overlaps in GM atrophy between the three NPS, but also indicated relevant changes specific to those conditions. Therefore, an early focus on those specificities might be crucial for future diagnosis, differentiation and management.

Further studies are required and should examine whatever these brain regions are reflecting on their functional association with different functional imaging techniques.

Acknowledgements Data collection and sharing for this project were funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, 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 & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & 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 (https://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.

Funding This work was supported by the Major State Basic Research Development Program of China (973 Program; 2013CB733800, 2013CB733803); the National Natural Science Foundation of China (81230034, 81271739, 81501453, 81520108015, and 61601155); the Jiangsu Provincial Special Program of Medical Science (BL2013029); the Jiangsu Provincial Natural Science Foundation (BE2016782 and BK20141342); and the Jiangsu Provincial Medical Youth Talent (QNRC2016810).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest to report.

Informed consent All the research subjects and study cohorts in the Alzheimer's Disease Neuroimaging Initiative (ADNI) participants signed written informed consent for neuropsychological testing and neuroimaging. The relevant institutional review boards approved the study procedures at all the participating sites.

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