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Anatomical Correlates of the Neuropsychiatric Symptoms in Alzheimer's Disease

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Abstract: The current study aimed to assess the relationship between the neuropsychiatric symptoms in Alzheimer's disease (AD) and the regional grey matter (GM) volume using voxel based morphometry (VBM). Data of 85 AD patients, 208 subjects with mild cognitive impairment (MCI), and 131 healthy controls were selected from the Alzheimer's Disease Neuroimaging Initiative. Individual VBM models across the entire sample for each items of the Neuropsychiatric Inventory Questionnaire as variables of interest were specified with four nuisance covariates, including age, sex, total intracranial volume (TIV), and Mini-Mental State Examination (MMSE) score. Agitation was related to the GM atrophy in the left inferior frontal/insula and bilateral retrosplenial cortices. Aberrant motor behavior (AMB) was related to the GM reductions in the right basal ganglia. The VBM models were recalculated by specifying three nuisance covariates (age, sex, TIV), and by excluding voxels related to AD severity by applying a MMSE mask. This procedure confirmed the first results, and additionally revealed associations between depression and GM atrophy in the left middle frontal cortex, between agitation and the GM atrophy in the left middle frontal cortex, and between AMB and GM reduction in the right inferior frontal cortex. Hierarchical multiple regression analyses using extracted mean GM value in these additional regions confirmed these associations. Finally, VBM analyses within a subgroup (85 AD patients and 41 MCI converters) largely confirmed the results. Our results suggest that specific patterns of GM atrophy within AD related neurodegeneration predispose to certain neuropsychiatric symptoms, suggesting distinct neurobiological mechanisms.

Keywords: Aberrant motor behavior, agitation, Alzheimer's disease, depression, mild cognitive impairment, neuropsychiatric symptoms, voxel based morphometry.

1. INTRODUCTION

In Alzheimer's Disease (AD) the term neuropsychiatric symptoms refers to behavioral, non-cognitive symptoms, which may occur in AD patients, but which are not required for the diagnosis of AD. Neuropsychiatric symptoms include depression, anxiety, hallucinations, delusions, apathy, agitation, aberrant motor behavior (AMB) and others [1]. The neurobiological basis of these neuropsychiatric symptoms is only poorly understood. This is remarkable as these symptoms are very common in AD patients and in subjects with mild cognitive impairment (MCI), which is a risk syndrome of AD [2-4]. Prevalence estimation of neuropsychiatric symptoms range from 25% to 85% in AD [3] and MCI [2,4]. Neuropsychiatric symptoms increase the rate of conversion from MCI to AD [5]. In AD patients, neuropsychiatric symptoms are associated with more severe cognitive deficits and a more rapid cognitive and functional deterioration [6]. The neuropsychiatric symptoms are often resistant to treatment [7], highly impact on nursing home and outpatient care [8] and increase the overall disease related costs [7]. Therefore, it is critical to advance the understanding of the neurobiology of neuropsychiatric symptoms in AD. A core question is whether specific patterns of grey matter (GM) atrophy are related to the occurrence of specific neuropsychiatric symptoms. If this was the case, it would suggest that the variations in the pattern of neurodegeneration differentially predispose individuals with AD to different neuropsychiatric symptoms.

The current study aimed at investigating the neuroanatomical correlates of neuropsychiatric symptoms in AD spectrum in a large sample using the Alzheimer's Diease Neuroimaging Initiative (ADNI) database. Previous studies have used ADNI database for investigating the neuroanatomical substrates of neuropsychiatric symptom. Reduced baseline inferior temporal cortical thickness was found to be predictive of increasing apathy over time, and reduced baseline supramarginal cortical thickness was said to be predic-

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[#]*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.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*

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tive of increasing hallucinations over time [9]. Depression was associated with reduced cortical thickness in the entorhinal cortex at baseline and accelerated cortical thinning in anterior cingulate cortex [10]. In another study, depression was associated with cortical thinning in temporal and parietal regions [11]. To our best knowledge, no previous studies have been published investigating anatomical correlates of neuropsychiatric symptoms in AD spectrum based on the ADNI database using the voxel based morphometry (VBM) technique.

VBM approach involves a voxel-wise comparison of the local image signal between groups or a voxel-wise regression of the local image signal on a variety of interest [12]. Compared to conventional brain morphological methods, such as manual tracing of a specific structure, which may typically involves the defining brain regions that have unambiguous borders, the VBM approach is hypothesis free and is not biased to a particular structure [12]. Therefore, there is a need to investigate the neuroanatomical correlates of neuropsychiatric symptoms using the VBM technique.

A few magnetic resonance imaging (MRI) studies using the VBM technique have assessed the association of GM atrophy with neuropsychiatric symptoms in AD [13-19]. In these studies, agitation was found to be associated with GM atrophy in the left insular cortex and bilateral anterior cingulate cortices [14]. Apathy has been associated with GM reduction also in the bilateral anterior cingulate [14, 18], the left medial frontal cortex [18], as well as the lateral frontal and basal ganglia regions [14]. Disinhibition has been related to GM volume atrophy in bilateral cingulate and right middle frontal gyri in a mixed group of dementia of Alzheimer's and other types [16]. AMB was found to be associated with GM volume atrophy in right cingulate gyrus and left premotor cortex [15]. An association between delusion and GM atrophy in frontal and hippocampal regions was found in some studies [13,14,16]. And depression has been related to the GM loss in the left inferior temporal cortex [19].

However, the listed VBM studies have used much smaller sample (AD subjects: n<54; MCI subjects: n<58) than the ADNI dataset. And these studies have also employed different image pre-processing procedures, which may account for variations in results [20]. A recent VBM study [21] that compared different pre-processing procedures in an aging population, suggested that image segmentation can be improved by increasing the number of tissue classes, and image registration can be improved by using a diffeomorphic flow based algorithm [22] rather than a "constrained warp" approach. In the current study, we applied the whole brain VBM technique with these improved image preprocessing steps to a large set of structural MRI data obtained from the ADNI database, to investigate the association of neuropsychiatric symptoms and regional GM structures.

2. MATERIAL AND METHODS

2.1. Alzheimer's Disease Neuroimaging Initiative (ADNI)

The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California - San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. For up-to-date information, see www.adni-info.org.

2.2. Selection of MRI Data

Data used in the preparation of this study were obtained from the ADNI-1 phase. All T1 weighted images from the ADNI database were acquired using 1.5T MRI scanners at baseline. As described in Jack *et al.* [23], typical acquisition parameters of these T1 weighted scans were: repetition time=2400 ms, minimum full echo time, inversion time=1000 ms, flip angle=8°, field of view=240×240 mm^2, 192×192×166 acquisition matrix in the x, y and z dimensions, yielding a voxel size of 1.25×1.25×1.2 mm^3.

Images were selected according to the following criterions: 1) having received maximum correction including gradient non-linearity distortion correction, intensity non-uniformity correction, and scaling for gradient drifts using the phantom data by the ADNI imaging procedures; 2) considered best in the ADNI MRI quality ratings; and 3) availability of behavioral and cognitive data of the respective subjects, including the scores of Neuropsychiatric Inventory Questionnaire (NPI-Q) and Mini-Mental State Examination (MMSE).

According to our selection criterion, all together 395 subjects were excluded, and 424 subjects were remained in the VBM analysis (85 AD patients, 208 cases with MCI and 131 healthy subjects). The mean age of the included subjects was 75.1 ± 6.7 years (range = 55-90) and the mean education was 15.7 ± 3.0 years (range = 6-20). Two sample t-tests showed that, there was no significant differences between the included and excluded subjects in nine of the twelve NPI-Q subscales: delusion ($t(817) = 1.15$, $p > 0.05$), hallucination ($t(817) = 0.63$, $p > 0.05$), agitation ($t(817) = 0.44$, $p > 0.05$), depression ($t(817) = 1.02$, $p > 0.05$), euphoria ($t(817) = 0.93$, $p>0.05$), apathy ($t(817) = 1.77$, $p>0.05$), disinhibition ($t(817) = 1.68$, $p > 0.05$), AMB ($t(817) = 1.07$, $p > 0.05$), and appetite ($t(817) = 1.95$, $p > 0.05$). Both groups were also not different from each other in the demographical data such as age ($t(817) = 0.92$, $p > 0.05$), and education years ($t(817) = -1.86$, $p > 0.05$). Chi-square test also revealed no significant differences in sex between the included and excluded groups ($X^2(1,813)=0.001$, $p>0.05$). Compared with subjects who were included in the analysis, subjects who were excluded from the analysis had higher scores on three of the NPI-Q subscales, including anxiety ($t(817) = 2.53$, $p < 0.05$), irritability

($t(817) = 2.67$, $p < 0.05$), and sleep disturbance ($t(817)=1.99$, $p < 0.05$). The included subjects had marginal higher MMSE scores (26.9 ± 2.6) than those who were excluded (26.5 ± 2.8) ($t(817) = -2.15$, $p = 0.031$).

2.3. Image Pre-Processing

The pre-processing of all T1 weighted images was performed with SPM8 (Wellcome Trust Centre for Neuroimaging, London). The origin of each individual T1 image was manually positioned at the anterior commissure. All the T1 images were segmented using the "new segmentation" tool, an extension of the default unified segmentation [24], which uses an improved image registration model and an extended set of tissue probability maps. Grey and white matter maps in native space and the rigidly aligned forms were generated through segmentation. The following steps were applied with diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) tools of SPM8 [22]: a custom template was generated based on all 424 pairs of rigidly aligned grey and white matter segments, and the DARTEL flow field for each subject was calculated. All segmented GM maps in native space were modulated by the Jacobian determinants and by the DARTEL flow field, and normalized to Montreal Neurological Institute (MNI) space with a resampled voxel size of 1.5×1.5×1.5 mm. Finally, all modulated and normalized GM maps were spatially smoothed using an 8-mm full-width at half maximum isotropic Gaussian kernel.

2.4. Neuropsychiatric Symptom Scores

The NPI-Q scores were obtained from the ADNI database. NPI-Q is a short version of the Neuropsychiatric Inventory (NPI), which is a standard instrument for the assessment of neuropsychiatric symptoms in AD [25,26]. The NPI-Q differs from the NPI by rating only severity, but not frequency of each symptom domain. Also it is reformatted to be a self-administered questionnaire for the caregiver instead of a caregiver interview. The NPI-Q rates the presence (1=yes, 0=no) and severity (1=mild, 2=moderate, 3=severe) of each symptom domain over the period of one month. The symptom domains measured by NPI-Q include delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, AMB, sleep disturbance and eating disorders. In addition to the NPI-Q scores, the MMSE scores of the respective individuals were obtained from the ADNI database.

2.5. VBM Group-Level Analyses

All VBM analyses were carried out using general linear models (GLM) with voxel-wise GM volume as a dependent variable, and each NPI-Q domain with sufficient frequency in the entire sample (prevalence > 5%) as independent variables in each separated model. The severity ratings of each NPI-Q symptom domain were used as the NPI domain score (scoring: 1 to 3). The absence of the symptom was denoted as 0. In the standard procedure of VBM, an absolute threshold mask is used to exclude the voxels outside brain. However, applying the standard procedure to studies with MRI of atrophied brains is associated with the risk of excluding those voxels with greatest atrophy [27]. Therefore, we applied an explicit masking procedure. The explicit mask was created based on the entire sample by SPM masking toolbox using the standard approach [27]. The regression models were calculated across the entire sample. This approach was chosen as the symptomatic manifestation of AD is conceptualized as a continuous process rather than a categorical event. Also this approach provided the greatest statistical power by including all subjects in the regression model.

As a first step of the group level analyses, age, sex, total intracranial volume (TIV), and the MMSE score were included as nuisance covariates. A family-wise error (FWE) corrected statistical threshold of $p<0.05$ at the cluster level was adopted (height threshold: $T = 3.11$, $p = 0.001$; extent threshold: $k = 1630$) for these analyses.

The choice of the nuisance covariates may influence the VBM results [20, 21, 28]. Some combinations of covariates may exhibit collinearity, which results in the over-fitting of the analysis model and reduces the robustness of the statistics [28, 29]. In the current study, the MMSE score correlated with the NPI-Q domain scores ($r = -0.10 \sim -0.25$). Thus, the inclusion of the MMSE as a covariate in the VBM regression model may limit the size of the multiple regression coefficients and confound the determination of the effect of the predictor variables of interest (in this study, the NPI-Q scores) [28]. A common way of dealing with the collinearity in the regression model is model re-specification by dropping one (or more) independent variables that are inter-correlated from the regression equation [30]. Since the NPI-Q scores are our variables of interest, we choose to drop the MMSE as nuisance covariate. However, the MMSE is an important indicator of the cognitive deterioration in AD, and may be therefore significantly contribute to most (but NOT all) of the cortical atrophies in AD related sample. The puzzle of determination of the optimal combination of nuisance covariates in the VBM study can be resolved by testing different combinations of nuisance covariates, such that identifying regions that are differently significant across various VBM models, and by retesting the extracted regional volume data using more sophisticated statistical techniques in SPSS [20].

As a second step of the analyses, additional VBM models were calculated by including age, sex, and TIV as covariates, and excluding the voxels related to AD pathology by a MMSE mask. (1) We estimated a regression model using the MMSE score as variable of interest, and age, sex and TIV as nuisance covariates (height threshold: $T=4.35$, $p_{FWE} < 0.05$, voxel level corrected). The resulting regression map (positive correlation between the regional GMV and the MMSE score) was converted to a binary mask (MMSE mask). (2) We re-estimated the regression models for the NPI-Q scores using age, sex and TIV as nuisance covariates (height threshold: $T = 3.11$, $p = 0.001$; extent threshold: $k = 1630$). (3) We excluded the voxels within the MMSE mask from the re-estimated models for the NPI-Q scores (height threshold: $T = 3.11$, $p = 0.001$; extent threshold: $k = 1630$).

For the analyses of step 1 and 2, we also calculated the models with an additional covariate, the years of education, as well as another additional covariate derived from the ADNI database, the sum of error score of the American National Adult Reading Test, which is an indicator of premorbid IQ. Models with these additional covariates revealed the same

results as without these covariates; therefore the results of these additional models are not shown later.

The results of VBM models with and without MMSE as nuisance covariate, from step 1 and step 2 respectively, were compared, and regions that were significant in step 2 but not in step 1 were identified. The mean regional GM volume of each of these regions was extracted using the Marsbar toolbox [31] and was defined as a dependent variable for the hierarchical multiple regression analyses in SPSS. For the first model of the hierarchical multiple regression analyses, age, sex and TIV were entered as independent variables. The MMSE score was then entered into the second model. For the last model, all NPI-Q symptoms, which were found to be related to GM atrophy, were entered in a stepwise manner (criteria of inclusion, $p < 0.05$; criteria of exclusion, $p > 0.10$; for the significant change of the F statistics). NPI-Q symptoms, which meet the statistic threshold of the $p < 0.001$ for the regression coefficient in the last model, were considered as significantly related to the reduction in the extracted mean regional GM volumes.

As a last step of the analyses, we repeated the VBM analyses in a subsample of AD patients and subjects with MCI, who converted to AD within one year (n=126, mean age = 74.6, 67 males). For this last step, we only restricted the analyses within the result maps from the second step and applied a lower height threshold of $p < 0.005$ (uncorrected).

3. RESULTS

The prevalence of each symptom is shown in Table **1**. As three of the twelve symptom domains (i.e. delusion, hallucination and euphoria) had prevalence below 5% in the total sample, we excluded these in further analyses. Chi-square test revealed no significant differences in sex between the patient groups ($X^2(2,424) = 2.87$, $p = 0.24$). One way ANOVA revealed no significant differences in age ($F(2,421) = 0.54$, $p = 0.56$), but significant differences in years of education ($F(2,421) = 8.61$, $p < 0.001$) between the AD, MCI and healthy subject groups. Bonferroni post-hoc test showed that the AD patients had fewer education years than the MCI patients ($p < 0.01$) and the healthy subjects ($p < 0.001$).

The first step of the VBM analyses with four nuisance covariates (age, sex, TIV, and MMSE) revealed a negative correlation between agitation and GM volume in left inferior frontal gyrus (pars orbitalis and pars opercularis) extended to insula, bilateral retrosplenial cortex (left precuneus, bilateral posterior cingulate cortices) (Table **2**; Fig. **1A**). Trend of significant associations were found between AMB and GM

Table 1. Percentage of presence of each neuropsychiatric symptom (measured by NPI-Q) in the total sample and subgroups.

	Total Sample (n=424)	Healthy Subjects (n=131)	MCI			AD (n=85)	AD and MCI Converters (n=126)
			Total (n=208)	Converters (n=41)	Non-converters (n=167)		
Gender (males)	248	73	130	22	108	45	67
Age (mean ± std.)	75.1±6.7	75.6±5.0	75.0±7.2	74.4±7.1	75.1±7.2	74.6 ± 7.7	74.6 ± 7.5
Education years	15.7±3.0	16.3±2.7	15.9±3.0	15.3±3.0	16.0±3.0	14.6 ± 3.0	14.9 ± 3.0
MMSE score	27.0±2.6	29.2±1.0	27.0±1.8	26.4±1.8	27.1±1.7	23.4 ± 2.1	24.4 ± 2.4
NPIQ symptom domains							
Delusion (%)	2.1	0.0	0.5	0.0	0.6	9.4	6.3
Hallucination (%)	1.2	0.8	1.0	2.4	0.6	2.4	2.4
Agitation (%)	15.3	3.1	18.3	36.6	13.8	27.1	30.2
Depression (%)	17.5	5.3	18.3	24.4	16.8	34.4	31.0
Anxiety (%)	14.6	2.3	15.9	26.8	13.2	30.6	29.4
Euphoria (%)	2.1	0.0	2.9	4.9	2.4	3.6	4.0
Apathy (%)	13.2	0.8	13.5	17.1	12.6	31.8	27.0
Disinhibition (%)	6.4	0.0	6.7	4.9	7.2	16.3	11.9
Irritability (%)	20.3	4.6	24.5	17.1	26.3	34.1	28.6
Aberrant motor behavior (%)	5.4	0.8	3.8	4.9	3.6	16.5	12.7
Sleep disturbance (%)	12.5	7.6	11.5	9.8	12.0	22.4	18.3
Eating disorders (%)	7.8	0.0	10.6	17.1	9.0	12.9	14.3
NPI-Q total score > 0 (%)	50.5	20.6	55.8	68.3	52.7	83.5	78.6

Note. AD: Alzheimer's Disease; MCI: mild cognitive impairment; NPI-Q: Neuropsychiatric Inventory Questionnaire; MMSE: Mini-Mental State Examination

Table 2. Loci of regional grey matter volume negatively correlated with neuropsychiatric symptoms (agitation, aberrant motor behavior) across the entire sample (p_{FWE}<0.05, cluster level corrected) by using the VBM models with four nuisance covariates (age, sex, total intracranial volume, and MMSE).

Location	R/L	MNI Coordinates			T	Z	Cluster Size
		X	Y	Z			
Agitation							
Precuneus	L	-9	-55	22	4.25	4.20	2501
Posterior cingulate cortex	L	-2	-34	46	3.72	3.69	
Posterior cingulate cortex	R	3	-58	30	3.92	3.88	
Inferior frontal gyrus (pars opercularis)	L	-45	14	22	3.80	3.77	1643
Inferior frontal gyrus (pars orbitalis)	L	-38	21	-8	4.01	3.97	
Insula	L	-33	21	-6	4.10	4.05	
Aberrant Motor Behavior							
Rectal gyrus	R	14	20	-12	3.90	3.86	1231[b]
Pallidum	R	14	8	-3	3.44	3.41	

Note. R: right hemisphere; L: left hemisphere; MMSE: Mini-Mental State Examination; MNI: Montreal Neurological Institute; [b]: this cluster has a trend of significance (p_{FWE}=0.09).

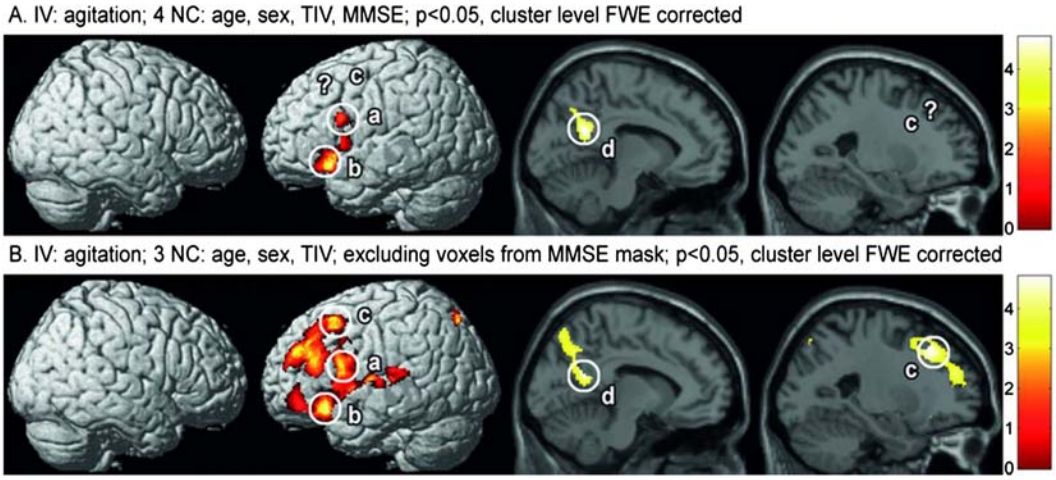

Fig. (1). Negative correlations between agitation and regional grey matter volume across the entire sample. Panel **A**: by using the voxel based morphometry (VBM) model with four nuisance covariates (NC). Panel **B**: by using the VBM model with three NC and by excluding the voxels from the MMSE mask (Fig. **3G**). The significant clusters are indicated by the following circles: a) left inferior frontal gyrus (pars opercularis); b) left inferior frontal gyrus (pars orbitalis); c) left middle frontal gyrus; d) left precuneus. The cluster c) was significant in the 3 NC model but not in the 4 NC model (indicated by question marks). IV: independent variable. TIV: total intracranial volume. MMSE: Mini-Mental State Examination. FWE: family-wise error.

reduction in the right rectal gyrus, and the right pallidum (Table **2**; Fig. **2A**).

In the second step of the analyses, the VBM models with three nuisance covariates (age, sex, and TIV) revealed significant negative correlations within various regions in six symptom domains (Fig. **3A-F**), including agitation, depression, anxiety, apathy, irritability, and AMB. A regression map was generated to identify cortical atrophy that is related to AD severity (positive correlation with the MMSE score). The map included the bilateral temporal lobe, the insular cortex, fusiform areas, inferior and medial parietal regions, basal ganglia, and the frontal regions (Fig. **3G**). The application of the MMSE mask revealed following significant relationships: (1) agitation was related to GM volume atrophy in lateral parts of bilateral precuneus, the inferior frontal cortex (pars orbitalis and pars opercularis) extended to the left middle frontal cortex (Table **3**; Fig. **1B**); (2) AMB was related to GM tissue loss in the right rectal gyrus, and the right inferior frontal gyrus (pars opercularis) (Table **3**; Fig. **2B**); (3) in two clusters in the left middle frontal cortex, GM was found to be negatively related to depression (Table **3**; Fig. **4B**).

The analysis of step 2 using the three nuisance covariates and the MMSE mask has confirmed the results of step 1. Comparing the results to step 1, following regions were additionally identified in step 2 (marked with question marks in the figures indicating the results of step 1): the left middle frontal cortex is associated with agitation (Fig. **1A**, **c**); the right inferior frontal gyrus with AMB (Fig. **2A**, **a**), and two

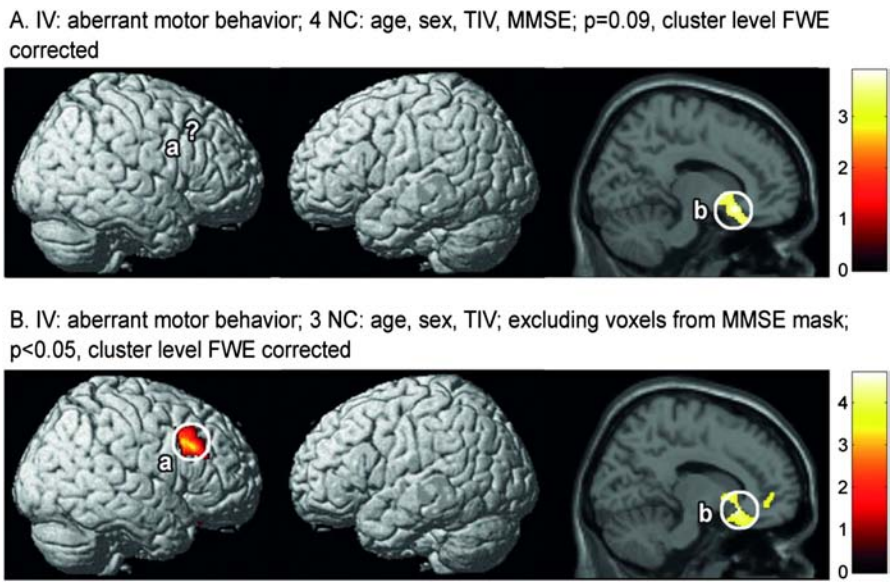

Fig. (2). Negative correlations between aberrant motor behavior and regional grey matter volume across the entire sample. Panel **A**: by using the voxel based morphometry (VBM) model with four nuisance covariates (NC). Panel **B**: by using the VBM model with three NC and by excluding the voxels from the MMSE mask (Fig. **3G**). The significant clusters are indicated by the following circles: a) right inferior frontal gyrus (pars opercularis); b) the right rectal gyrus. The cluster a) was significant in the 3 NC model but not in the 4 NC model (indicated by the question mark). IV: independent variable. TIV: total intracranial volume. MMSE: Mini-Mental State Examination. FWE: family-wise error.

clusters in the left middle frontal cortex with depression (Fig. **4A**). The mean GM volumes of these regions were extracted based on the results of the step 2 analyses except for the correlational result between agitation and the left middle frontal cortex, since the cluster has extended to several other regions (Table **3**; Fig. **1B**). Therefore the mean GMV was extracted by manually defining 10 mm sphere centered at the local maximum of the cluster within the left middle frontal cortex [-24 27 42]. The hierarchical multiple regressions controlling for age, sex, TIV, MMSE revealed following results: Agitation was associated with the mean GM volume reduction in the left posterior middle frontal cortex (supplementary Table **1**); AMB was related to the mean GM volume reduction in the right inferior frontal cortex (supplementary Table **2**); and the anterior (not the posterior) cluster of the left middle frontal cortex was negatively associated with depression (supplementary Tables **3** and **4**).

In the subsample of AD patients and those subjects with MCI who developed AD after one year (MCI converters), the regression analysis confirmed the majority of negative correlations revealed by analyses using the entire sample (step 1 and 2) at a lower statistic threshold ($p<0.005$, uncorrected; Table **4**; Fig. **5**). Agitation was associated with GM atrophy in left middle and inferior frontal cortices, but not in the retrosplenial cortex. AMB was negatively correlated with GM volume in right inferior and middle frontal gyri, right olfactory gyrus extended to pallidum and rectal gyrus, and right medial orbitofrontal gyrus. Depression was related to GM volume reduction in left middle frontal cortex extended to superior frontal cortex.

4. DISCUSSION

We investigated the neuroanatomical correlates of neuropsychiatric symptoms in a large cohort of elderly individuals ranging from cognitively normal subjects to AD patients. The prevalence of the neuropsychiatric symptoms were similar to those reported in previous large cohort study investigating patients recruited from the memory clinics [1]. Using a VBM model with four nuisance covariates (age, sex, TIV, and MMSE), we found strong association between agitation and GM atrophy in the left inferior frontal/insula cortex, and the bilateral retrosplenial cortices. We found also a trend of significant association between AMB and the GM volume in the right basal ganglia region. Using a VBM model with three nuisance covariates (age, sex, and TIV) and excluding the voxels from the MMSE mask, the regions found in the VBM model with four nuisance covariates were confirmed. Additionally, we also found the negative association between agitation and the GM volume in the posterior part of the left middle frontal cortex; between AMB and the GM volume in the right inferior frontal gyrus; and between depression and the GM volume in the anterior part of the left middle frontal cortex. These associations were confirmed by the hierarchical multiple regression analyses using extracted mean GM volume of these additional regions. In the subgroup of patients with AD and MCI converters, the results from the whole group analyses were largely observed by applying a lower significant threshold. Our results suggest that specific patterns of GM atrophy are associated with specific neuropsychiatric symptoms in AD.

Our results of the negative correlation between agitation and the GM volume in the left inferior frontal/insula and the left middle frontal cortex are largely in agreement with previous findings. An earlier VBM study [14] showed associations between GM loss in the left insula and bilateral anterior cingulate cortices in AD. Another MRI study [32] using the region of interest approach showed significant associations between the severity of agitation/aggression and the greater

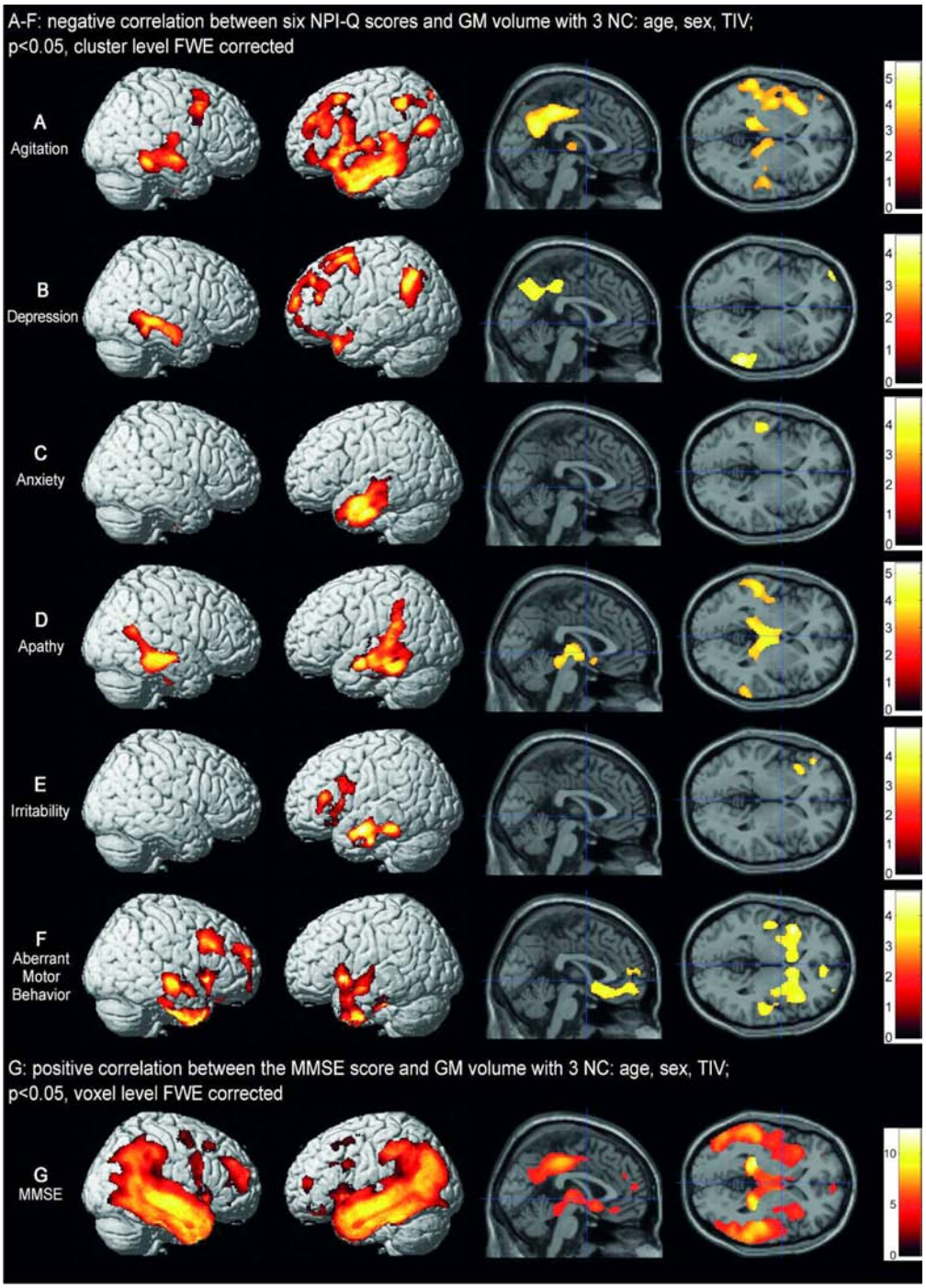

Fig. (3). Panels **A-F**: negative correlations between six neuropsychiatric symptoms (agitation, depression, anxiety, apathy, irritability, and aberrant motor behavior) and regional grey matter volume across the entire sample by using the voxel based morphometry (VBM) model with three nuisance covariates (NC). Panel **G**: generated MMSE mask (positive correlation between the MMSE score and the regional grey matter volume across the entire sample with 3 NC). NPI-Q: Neuropsychiatric Inventory Questionnaire. GM: grey matter. TIV: total intracranial volume. MMSE: Mini-Mental State Examination. FWE: family-wise error.

atrophy in the frontal, insular, amygdala, cingulate and hippocampal regions. Decreased metabolism and decreased perfusion in lateral prefrontal and temporal regions were reported to be related to agitation in AD patients and with other dementias [33, 34]. Increased neurofibrillary tangles burden in left orbitofrontal cortex was found to be associated with agitation in AD patients [35]. Furthermore, a recent resting-state functional MRI study [36] showed significant correlation between the hyperactivity syndrome (a composition score of agitation and other symptoms) and the functional connectivity within the anterior salient network (insula and anterior cingulate cortex). Overall, our results support previous observation that the frontal lobe pathology contribute to the agitation in AD [8, 32, 34].

Table 3. Loci of regional grey matter volume negatively correlated with neuropsychiatric symptoms (agitation, aberrant motor behavior, and depression) across the entire sample (p_{FWE}<0.05, cluster level corrected) by using the VBM models with three nuisance covariates (age, sex, and total intracranial volume), excluding voxels from the MMSE mask.

Location	R/L	MNI Coordinates			T	Z	Cluster Size
		X	Y	Z			
Agitation							
Precuneus	L	-9	-55	19	4.80	4.73	2295
Precuneus	L	-5	-75	55	4.00	3.96	
Precuneus	R	3	-60	33	4.57	4.51	
Inferior frontal cortex (pars orbitalis)	L	-30	24	-9	4.70	4.64	9283
Inferior frontal cortex (pars orbitalis)	L	-39	21	-8	4.70	4.63	
Inferior frontal cortex (pars opercularis)	L	-44	14	21	4.54	4.48	
Inferior frontal cortex (pars triangularis)	L	-47	32	16	4.25	4.20	
Insula	L	-39	-15	0	3.81	3.78	
Middle frontal cortex	L	-24	27	42	4.69	4.63	
Middle frontal cortex	L	-32	44	25	4.06	4.02	
Middle orbitofrontal cortex	L	-47	47	-11	3.61	3.58	
Superior temporal cortex	L	-53	-30	9	3.71	3.68	
Aberrant Motor Behavior							
Rectal gyrus	R	12	21	-12	4.70	4.63	2424
Pallidum	R	14	8	-3	4.20	4.15	
Orbital medial frontal cortex	R	6	45	-11	4.24	4.19	
Caudate	L	-11	11	-2	3.85	3.81	
Inferior frontal cortex (pars opercularis)	R	45	18	33	4.65	4.59	923
Depression							
Middle frontal cortex	L	-29	11	63	4.02	3.98	2706
Middle frontal cortex	L	-30	24	49	3.65	3.62	
Middle frontal cortex	L	-42	38	36	3.85	3.81	2769
Middle frontal cortex	L	-35	35	19	3.84	3.80	

Note. R: right hemisphere; L: left hemisphere; MMSE: Mini-Mental State Examination; MNI: Montreal Neurological Institute

Additional to the frontal lobe abnormity, we also found the relationship between agitation and the bilateral retrosplenial region, which is outside the areas related to AD severity, in the analysis with the entire group. However, this association was not confirmed in the subgroup analysis with AD and MCI converters. Interestingly, a recent MR spectroscopy study [37] on AD revealed negative association between the agitation and the metabolism (NAA/Cr ratio) in the left retrosplenial cortex. Note that the NAA activity has been related to the neural density [37]. Therefore, the mentioned MR spectroscopy study can be served as an indirect proof of the association between agitation and the GM atrophy in the retrosplenial cortex.

The depressive symptom in AD has received more attention in the previous research, since depression and depressive symptoms has been considered a risk factor, a prodromal phase, or a symptom of AD [38]. Our study revealed the association between depression and regional GM atrophy in the left dorsolateral prefrontal cortex (DLPFC) in the whole group analysis as well as the subgroup analysis. This result is in accordance with the previous studies on the neural substrates of the depression in AD. One structural imaging study [39] showed cortical thinning in the left DLPFC in dementia patients with Alzheimer's type and with lewy body etiology. Depression has been related to decreased glucose metabolism rates in the bilateral prefrontal [40] and the left

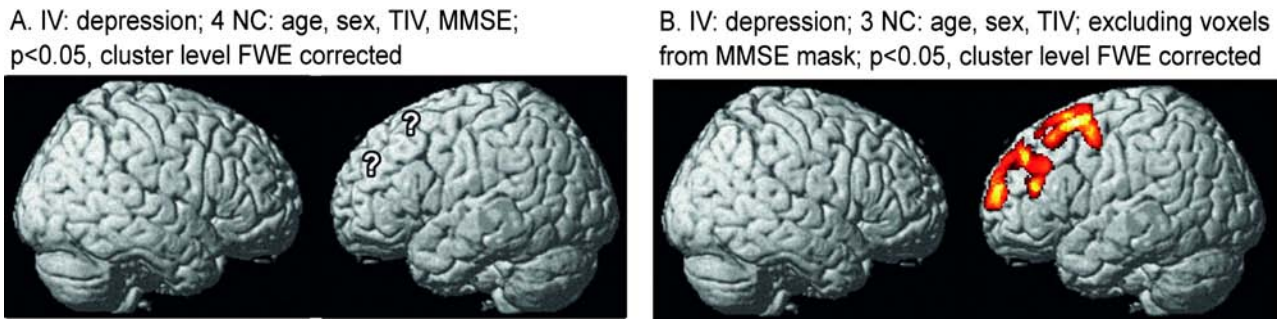

Fig. (4). Negative correlations between depression and regional grey matter volume across the entire sample. Panel **A**: no significant results were revealed by using the voxel based morphometry (VBM) model with four nuisance covariates (NC). Panel **B**: two clusters in left middle frontal cortex were revealed by using the VBM model with three NC and by excluding the voxels from the MMSE mask (Fig. **3G**). The significant clusters in the 3 NC model but not in the 4 NC model (indicated by the question marks): left anterior and posterior middle frontal gyrus. IV: independent variable. TIV: total intracranial volume. MMSE: Mini-Mental State Examination. FWE: family-wise error.

Table 4. Loci of regional grey matter volume negatively correlated with three symptoms (agitation, depression, and aberrant motor behavior) using three nuisance covariates (age, sex, and total intracranial volume) in the subgroup of AD and MCI converters (p<0.005, uncorrected; restricted to the voxels revealed in the step 2 analyses).

Location	R/L	MNI Coordinates			T	Z	Cluster Size
		X	Y	Z			
Agitation							
Inferior frontal cortex (pars orbitalis)	L	-33	24	-9	2.95	2.85	120
Middle frontal cortex	L	-26	30	42	3.00	2.94	243
Middle frontal cortex	L	-30	44	33	2.85	2.77	125
Aberrant Motor Behavior							
Inferior frontal cortex	R	45	27	28	3.77	3.66	1017
Middle frontal cortex	R	46	23	45	3.24	3.17	
Olfactory cortex	R	6	20	-6	3.58	3.48	934
Pallidum	R	24	2	-3	3.34	3.26	
Rectal gyrus	R	11	20	-14	2.99	2.93	
Medial orbitofrontal cortex	R	6	51	6	3.44	3.35	319
Depression							
Middle frontal cortex	L	-33	45	37	3.81	3.70	191
Middle frontal cortex	L	-24	15	64	3.22	3.14	385
Superior frontal cortex	L	-27	62	18	3.11	3.05	187
Middle frontal cortex	L	-36	27	52	2.71	2.66	70

Note. AD: Alzheimer's disease; MCI converters: subjects of mild cognitive impairment who converted into AD within 1 year; MNI: Montreal Neurological Institute.

prefrontal cortex [41] in AD. Depression has been repeatedly related to the hypoperfusion in the bilateral DLPFC [42], the left lateral prefrontal cortex [43,44], and the right lateral prefrontal cortex [45] in AD. And a MR spectroscopy study [37] has demonstrated more Cho/Cr metabolic ratio in left DLPFC in AD. In MCI subjects, altered functional connectivity between DLPFC and amygdala was related to depression [46]. These previous findings, together with our result, indicated that lateral prefrontal regions played an important role in the depressive symptoms in AD.

Previous research has also pointed to the abnormity in other regions to be important for the depressive symptom in AD, such as the medial prefrontal/cingulate cortices [39, 40, 42, 47], basal ganglia [48], temporal regions [19, 39, 49], parietal [39,49], and hippocampal regions [50,51]. As we can see, these regions in previous literature are largely overlapped with the regions related to the AD severity (the MMSE mask; Fig. **3G**). As we mentioned before, the collinearity between the neuropsychiatric symptoms and the AD severity would significantly confound the results. Both

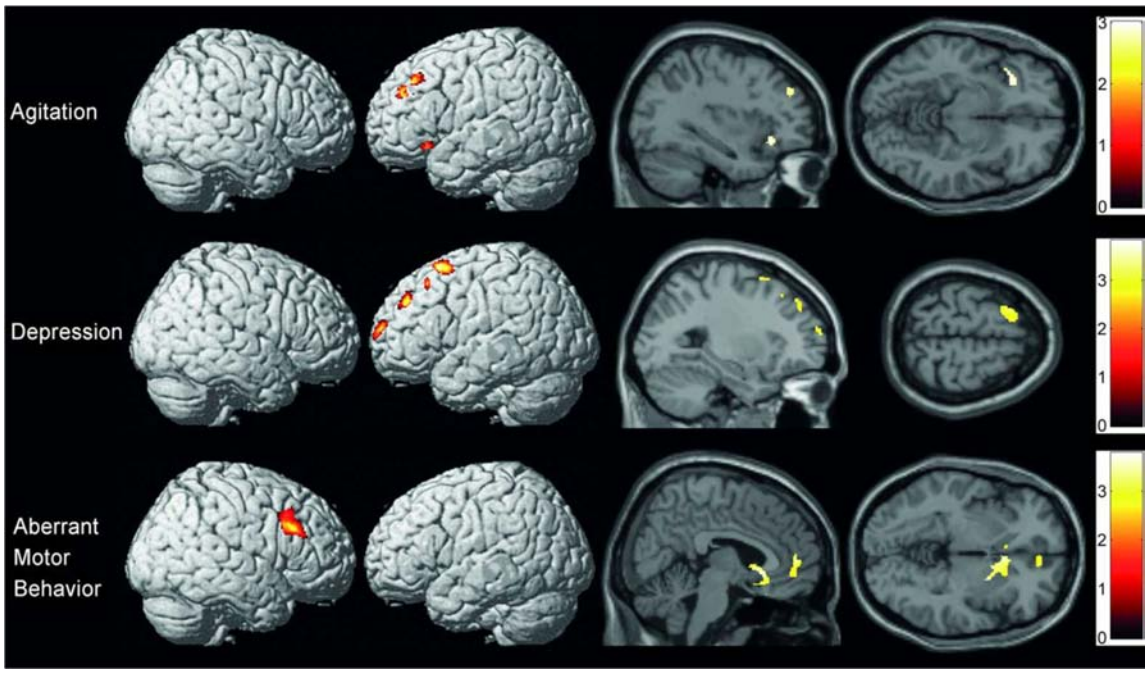

Fig. (5). Negative correlations between regional grey matter volume and the scores on three neuropsychiatric symptoms (agitation, depression, and aberrant motor behavior) in the subgroup of AD and MCI converters only at a lower significant threshold ($p<0.005$, uncorrected), including the voxels which were significant from the step 2 analyses (Fig. **1**, **2** and **4**, Panel **B**).

approaches used in the current study, adding the MMSE score as a covariate (step 1 analysis), and excluding the voxels from the MMSE mask (step 2 analysis), are not efficient for detecting the possible regional atrophy related to the neuropsychiatric symptom within the "classical" Alzheimer's atrophy regions. Therefore, we do not rule out the possibility of contribution of these regions to the depressive symptom. Meanwhile, our results suggest that, the atrophy in the lateral prefrontal cortex predispose to the development of depressive symptom in AD.

We identified an association between AMB and the GM volume reduction in the basal ganglia region extending to the orbitofrontal cortex through the VBM analyses of the entire sample and the subgroup of AD and MCI converters. This is in agreement with previous studies showing associations between AMB and hyperperfusion in orbital frontal cortex in AD [53], as well as with post mortem neurofibrillary tangles density in orbitofrontal cortex in AD [35]. The finding of orbitofrontal cortex pathology in association with AMB in AD is intriguing as this symptom shares both behavioral correlates and neurobiological correlates with other disorders of motor control. AMB in AD describes repetitive and restless motors acts such as pacing and tapping, which is similar to the symptom spectrum in obsessive compulsive disorders [52]. Furthermore, previous studies in obsessive compulsive disorder [53] and Tourette syndrome [54] have suggested that the structural and functional alterations in orbitofrontal cortex led to abnormal, stereotyped, and repetitive motor behavior. Thus, these findings suggest that similar neural mechanisms underlying AMB can be found in AD patients, obsessive compulsive disorders and Tourette syndrome.

In addition, we found for the first time an association between AMB and GM volume reduction in the right inferior frontal gyrus (pars opercularis). This result relates to the role of the right inferior frontal gyrus in regulating motor inhibitory control by interacting with other brain regions, such as basal ganglia and motor cortex [55, 56]. Especially, the subregion of the right inferior frontal gyrus that we found, the pars opercularis, has been suggested to be the key region for inhibition [57]. Dysregulation of the interaction of right inferior frontal gyrus with other brain regions is associated with motor inhibition deficits in other psychiatric disorders, such as disorders of impulsivity and motor control, and obsessive compulsive disorder [58, 59]. Our results showed that, the decreased GM volume in right inferior frontal gyrus, together with the GM reduction in the basal ganglia region, contribute to AMB symptom in AD.

Our study has limitations. First, NPI-Q is a brief questionnaire designed for assessing core symptoms of the behavioral and psychological domains. Although it shows adequate test-retest reliability and convergent validity with the original NPI [26], it does not represent a refined assessment of the psychological state of an individual. Second, it is not possible to disentangle the relationship of specific brain regions (e.g. hippocampus) that are associated with the progression of AD *per se*, and with individual NPI-Q symptoms by our approach. The strengths of the study as compared to previous studies are the large sample, and the improved image pre-processing methods that we employed.

CONCLUSION

To summarize, we identified regional GM areas that are specifically associated with the presence of neuropsychiatric symptoms such as agitation, depression and AMB in AD. The association between these symptoms and specific brain regions cannot be explained by AD severity. Therefore, these

data suggest that neurodegenerative involvement of particular neural circuits that are relevant to specific neuropsychiatric symptoms occur in some, but not all individuals with AD and predispose to the manifestation of the symptoms. The findings contribute to the understanding of the neuroanatomical pathology of the disturbing and burdensome neuropsychiatric symptoms in AD.

CONFLICT OF INTEREST

The data we used in this report are downloaded from the ADNI database (National Institutes of Health Grant U01 AG024904), which is funded by a large variety of sources. ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. 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 Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles, and it was also supported by NIH grants P30 AG010129 and K01 AG030514.

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The data we used are downloaded from the ADNI database, and 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. Data analysis: XH, BN, DM. Manuscript preparation: XH & FJ.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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