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Associations Between Hyperactive Neuropsychiatric Symptoms and Brain Morphology in Mild Cognitive Impairment and Alzheimer's Disease

Lyna Mariam El Haffaf[a,b], Lucas Ronat[a,c], Adriana Cannizzaro[a,b] and Alexandru Hanganu[a,b,*] for the Alzheimer's Disease Neuroimaging Initiative[1]
[a]*Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, CIUSSS du Centre-Sud-de-l'Ile-de-Montreal, Montréal, QC, Canada*
[b]*Département de Psychologie, Faculté des Arts et des Sciences, Université de Montréal, Montréal, QC, Canada*
[c]*Département de Médecine, Faculté de Médecine, Université de Montréal, Montréal, QC, Canada*

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Abstract.
Background: Hyperactive neuropsychiatric symptoms (NPS) (i.e., agitation, disinhibition, and irritability) are among the most challenging symptoms to manage in Alzheimer's disease (AD). However, their underlying brain correlates have been poorly studied.
Objective: We aimed to investigate the associations between the total score of hyperactive NPS and brain structures in participants with AD, mild cognitive impairment (MCI), and cognitively normal older adults (CN).
Methods: Neuropsychiatric and 3T MRI data from 216 AD, 564 MCI, and 660 CN participants were extracted from the Alzheimer's Disease Neuroimaging Initiative database. To define NPS and brain structures' associations, we fitted a general linear model (GLM) in two ways: 1) an overall GLM including all three groups (AD, MCI, CN) and 2) three pair-wise GLMs (AD versus MCI, MCI versus CN, AD versus CN). The cortical changes as a function of NPS total score were investigated using multiple regression analyses.
Results: Results from the overall GLM include associations between 1) agitation and the right parietal supramarginal surface area in the MCI-CN contrast, 2) disinhibition and the cortical thickness of the right frontal *pars opercularis* and temporal inferior in the AD-MCI contrast, and 3) irritability and the right frontal *pars opercularis*, frontal superior, and temporal superior volumes in the MCI-CN contrast.
Conclusions: Our study shows that each hyperactive NPS is associated with distinct brain regions in AD, MCI, and CN (groups with different levels of cognitive performance). This suggests that each NPS is associated with a unique signature of brain morphology, including variations in volume, thickness, or area.

Keywords: Agitation, Alzheimer's disease, cognitively normal older adults, cortical structures, disinhibition, irritability, magnetic resonance imaging, mild cognitive impairment, neuropsychiatric symptoms

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

*Correspondence to: Alexandru Hanganu, Centre de Recherche de l'insitut Universitaire de Gériatrie de Montréal, 4545 Chemin Queen Mary, H3 W 1W4 Montréal, QC, Canada. Tel.: +1 514 340 3540; E-mail: alexandru.hanganu@umontreal.ca.

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disease and the leading cause of dementia. As of 2016, 6.9% of Canadians aged 65 and older are living with diagnosed dementia [1]. The prevalence of this disease increases with age and it affects more women than men [1].

Neuropsychiatric symptoms (NPS) are a heterogeneous group of symptoms that contribute to cognitive and functional changes and can accelerate disease progression [2]. In addition to the cognitive and functional impairment affecting AD patients, NPS are often associated with the disease [3]. In fact, 97% of patients experience at least one NPS and around half of them experience four or more symptoms [2, 4]. Peter et al. [5] showed that specific NPS including aggression, hallucination, delusions, depression, and anxiety are associated with shorter survival time from mild AD to severe dementia or death. Moreover, NPS are associated with a greater possibility of conversion to AD from mild cognitive impairment (MCI) [6, 7]. Thus, understanding the role of these NPS on brain morphology may be a lead in preventing disease progression.

Usually, NPS are quantified using the Neuropsychiatric Inventory (NPI), which outlines 12 symptoms. Nevertheless, the so-called hyperactive NPS seems to be of a particular importance. Drawing on the taxonomic concept commonly used in delirium [8], hyperactive symptoms of AD include agitation, disinhibition, and irritability. These symptoms represent one of the most difficult sets of symptoms to manage, causing an increase in institutionalization and a burden for caregivers [9]. From one perspective, hyperactive NPS can be grouped based on their onset. Both agitation and irritability appear at the MCI or pre-clinical stage of AD [10], while disinhibition is prone to appear in the last phase of NPS installment [11]. Another perspective is the clustering studies, which have suggested that there is a likelihood of common underlying molecular and cellular pathologies for symptoms that are being classified in the same cluster [9]. Specifically, Cheng et al. used a confirmatory factor analysis on the NPI data of participants with AD and proposed a four-factor clustering model which included behavioral problems (agitation, disinhibition, irritability, and aberrant motor behavior), mood disturbance (apathy, depression, anxiety, sleep, and appetite), psychosis (delusions and hallucinations), and euphoria [12]. Other clustering models combined agitation, disinhibition, and irritability under the hyperactive disturbance cluster [13, 14]. Finally, previous structural magnetic resonance imaging (MRI) studies in AD have reported associations between agitation and cortical atrophies in the frontal, cingulate, insular regions, as well as the subcortical amygdala and hippocampus [15–18]. Furthermore, the severity of agitation correlated with the atrophy score in the posterior brain regions [18]. Similarly, disinhibition in AD was associated with the atrophy of the anterior cingulate and middle frontal gyrus [6], while irritability was associated with decreased volume of the insula [19]. Also, hyperactive NPS were associated with a dysfunction of the orbitofrontal subcortical circuit [20, 21] and, in participants with AD, they exhibited a deficit in the appropriate brain regions associated with inhibition of action [9]. In sum, the three hyperactive NPS can occur concurrently, have been combined by different clustering-based studies and tend to have similar associations with brain regions.

Nevertheless, recent scientific advances have outlined significant limitations of previous results that require further investigations. Specifically, it has been shown that the volume of the cortex is ultimately determined by surface area and thickness, which are correspondingly influenced by different factors [22]. As such, only the analysis of all three measurements would allow a correct understanding of the potential underlying pathology, since volumetric brain changes can be explained either by thickness, surface area or both. In fact, it has been outlined that all three features, cortical volume, thickness and surface area are key features in the diagnosis of MCI and AD [23].

To address the outlined limitations, we investigated the associations between the hyperactive symptoms total score and the cortical morphology in AD, MCI, and cognitively normal older adults (CN). Specifically, we aimed to explore the cortical volume differences from the perspective of cortical surface area and thickness between each of the three groups: AD versus MCI, MCI versus CN, and AD versus CN. We hypothesized that hyperactive symptoms would share common cortical brain structures and yet the underlying measurements of thickness and surface area would be different.

MATERIALS AND METHODS

Participants

Participants' MRI and clinical data were extracted from the Alzheimer's Disease Neuroimaging

Initiative (ADNI) database (https://adni.loni.usc.edu) (ADNI-2 and ADNI-3) [24]. 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 MRI, positron emission tomography, other biological markers as well as clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

We extracted the structural MRI data of 1440 participants, consisting of 216 with AD, 564 with MCI, and 660 CN. Eligibility criteria for CN participants include: 1) a Mini-Mental State Examination (MMSE) score between 24 and 30, 2) a global Clinical Dementia Rating of 0, 3) being non-depressed, 4) being non-MCI, and 5) being non-demented [25, 26]. Entry criteria for participants with amnestic MCI include: 1) a MMSE score of 24 to 30 and 2) a Memory Box score of at least 0.5. All participants with AD met the National Institute of Neurological and Communication Disorders/Alzheimer's Disease and Related Disorders Association criteria for probable AD: 1) a MMSE score between 20 and 26, 2) a global Clinical Dementia Rating of 0.5 or 1, and 3) a sum-of-boxes Clinical Dementia Rating of 1.0 to 9.0. Therefore, all AD participants were only mildly impaired.

Exclusion criteria were: 1) abnormal MRI brain scan, 2) contraindications for MRI studies (presence of cardiac pacemakers, metal fragments or foreign objects in the body), 3) presence of psychiatric history prior to inclusion in the ADNI study (major depression, schizophrenia, bipolar disorder, substance abuse, post-traumatic stress, obsessive-compulsive disorder), 4) presence of neurological history (stroke, head injury, brain tumor, anoxia, epilepsy, alcohol dependence and Korsakoff, neurodevelopmental disorder), 5) prematurity, 6) diagnostic criteria in favor of other neurodegenerative or neurological etiology (Parkinson's disease, frontotemporal degeneration, progressive supranuclear paralysis, corticobasal degeneration, Lewy body dementia, amyotrophic lateral sclerosis, multiple sclerosis, multi-system atrophy, vascular dementia), 7) clinically significant abnormalities in B12 or thyroid function tests that might interfere with the study, and 8) taking a pharmacological treatment (antidepressant or neuroleptics with anti-cholinergic properties; regular use of narcotics analgesics; chronic use of other medications with significant central nervous system anticholinergic activity; use of anti-parkinsonian medication; or participating in any other investigational drug study). In the case of CN, this group of participants has been screened for the presence of prior psychiatric history, yet we cannot exclude that these are older adults with primary psychiatric disease, since their NPS evaluation presented changes in multiple domains. All data are available on the ADNI websites upon demand (http://adni.loni.usc.edu/data-samples/access-data/). Ethics committee approval and individual participant consent were received by the corresponding registration sites according to ADNI rules (http://adni.loni.usc.edu/methods/documents/). This study was approved by the Comité d'éthique de la recherche vieillissement-neuroimagerie CER VN 19-20-06.

For each participant, demographic data as well as 3T MRI scans were collected during the screening visit, while a neuropsychiatric assessment using the NPI was carried out during the baseline visit. The baseline visit must occur within 28 days of the screening.

Neuropsychiatric assessment

Each participant's primary caregiver completed a neuropsychiatric assessment via the NPI. The NPI is a clinical questionnaire that assesses 12 behavioral and psychological symptoms of dementia (i.e., delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime behavior disorders, and appetite disorders) [26]. The 12 NPI domains are rated according to their frequency and severity. The presence or absence, frequency, and severity of each NPS are rated by the participant's primary caregiver. Based on our hypothesis, we extracted the NPS required for our study: agitation/aggression, disinhibition, and irritability. For each NPS, frequency and severity scores were multiplied to obtain a total score ranging from 0 to 12.

Procedure

MRI data were processed on the *Graham* cluster of the *Digital Research Alliance of Canada* (http://www.alliancecan.ca), on the CentOS Linux version 7, with FreeSurfer 7.3.2 (http://surfer.nmr.mgh.harvard.edu) centos_7.0_x86_64 version [27, 28] and automatically managed and verified by an in-house pipeline (github.com/alexhanganu/nimb). The cortical thickness was computed as the average of 1) the distance from each white surface vertex to

Table 1
Demographic characteristics and NPI hyperactivity subscales scores

Variables	CN ($N=660$)	MCI ($N=564$)	AD ($N=216$)	p
Female, n (%)	389 (58.9%)	256 (45.4%)	90 (41.7%)	<0.001
Male, n (%)	271 (41.1%)	308 (54.6%)	126 (58.3%)	
Age (y)	71.1 ± 6.68	71.8 ± 7.38	74.56 ± 8.17	<0.001
Education (y)	16.66 ± 2.37	16.30 ± 2.54	15.69 ± 2.59	<0.001
MMSE, score	29.03 ± 1.24	27.80 ± 1.89	22.97 ± 2.30	<0.001
Agitation, total score	0.08 ± 0.5	0.41 ± 1.18	0.94 ± 1.99	<0.001
Disinhibition, total score	0.02 ± 0.15	0.23 ± 0.92	0.44 ± 1.25	<0.001
Irritability, total score	0.16 ± 0.69	0.59 ± 1.45	1.06 ± 2.16	<0.001

CN, cognitively normal older adults; MCI, mild cognitive impairment; AD, Alzheimer's disease; p, p-value; total score, severity * frequency. Values are given in mean and standard deviation, except for the sex distribution.

their corresponding closest point on the pial surface (not necessarily at a pial vertex) and 2) the distance from the corresponding pial vertex to the closest point on the white surface [29]. Cortical surface area was computed based on the triangular face of the surface representation with corresponding vertex coordinates *abc* of the corresponding triangle corner and dividing by two the vector norm of the cross product x of the differences between vertex coordinates: $|(a\text{-}c) \times (b\text{-}c)| /2$ [30]. Cortical volume was based on defining oblique truncated triangular pyramids which were divided into three irregular tetrahedra and their volumes were calculated [31]. Each voxel in the normalized brain volume was assigned to one of 40 labels of the Desikan atlas, using a probabilistic atlas obtained from a manually labeled training set [32]. We extracted the region-based measurements of cortical volume, thickness, and surface area. Cortical brain volumes were corrected using the Estimated Total Intracranial volume which is a metric computed from the amount of scaling based on the MNI305 space Talairach transformation [33]. We used the regression-based correctional method, which was shown to provide advantages over the proportion method [34].

Managing missing data

Missing NPI data were found for one CN participant and one participant with AD. Scores based on the mean of each group were assigned. Each averaged NPI subscale score was rounded to the nearest integer and their sum was used to estimate the total score for these participants.

Statistical analysis

Firstly, Python 3.9 with Pandas 1.1.2 library was used to compile data of participants. Descriptive analyses were performed using SPSS version 26 software. Differences among the three groups were assessed by a one-way ANOVA for continuous variables (age, years of education, MMSE score, and NPI total score) and by a contingency χ^2 analysis for categorical variables (sex distribution). *Post-hoc* comparisons were performed using a Bonferroni correction for statistically significant differences observed in the one-way ANOVA (Table 1).

Subsequently, we performed a whole-brain analysis using a General Linear Model (GLM) with FreeSurfer mri_glmfit for each NPS of interest to assess their association with the brain's morphology. The total score of each NPI subscale was included as a fixed factor, while brain metrics (cortical volume, thickness, and surface area) were regarded as dependent variables. For each NPS of interest and for each brain metric, we fitted the GLM in two ways: 1) an overall GLM model that included all three groups (AD, MCI, CN), in order to adjust for a potential multiple comparison issue and 2) three pair-wise GLMs, one for each pair of groups (AD versus MCI, AD versus CN, and MCI versus CN), in order to explore the two-group contrasts. The main effect of groups is also presented. Each GLM included the groups, the NPS of interest and the three covariates (age, sex, and years of education). Results underwent a Monte-Carlo correction at a threshold of $p<0.05$, with the p-value adjusted for the two hemispheres. Clusters that survived the Monte-Carlo correction were attributed to specific Desikan atlas regions based on the vertex with the maximum p-value. Each cluster represents a group of neighboring voxels of the brain that shows statistically significant differences for the analyzed contrast. The mean partial correlation coefficient was also performed for each contrast.

Finally, using multiple regression analyses, we plotted the results to evaluate the cortical change as a function of the total score of each NPS subscale with

Table 2
Overall general linear model analysis of hyperactive NPS including AD, MCI, and CN participants

Brain Area	Measure	Talairach coordinates			F	p (log(p))	r
		x	y	z			
			AD-MCI				
Disinhibition							
Frontal pars opercularis R	Thick	53.9	14.9	11.2	17.06	< 0.001 (3.1)	–0.15
Temporal Inferior R	Thick	45.5	–51.0	–7.9	17.13	< 0.001 (3.5)	–0.16
			MCI-CN				
Agitation							
Parietal supramarginal R	Area	57.6	–19.4	22.3	1.12	< 0.001 (3.0)	–0.18
Irritability							
Frontal pars opercularis R	Vol	42.4	6.6	18.5	18.34	< 0.001 (–4.6)	–0.15
Frontal superior R	Vol	15.4	14.1	54.3	1.51	< 0.001 (–5.4)	–0.15
Temporal superior R	Vol	44.9	8.8	–20.5	11.15	< 0.001 (–3.5)	–0.16

x/y/z, coordinates of the maximum vertex using the Talairach atlas x/y/z axis; L, left; R, right; Thick, cortical thickness; Area, cortical surface area; Vol, cortical volume; F, F-value; r, mean partial correlation coefficient. The log(p) value indicates the level of significance in the difference in slope of cortical volume, thickness and surface area relative to NPS total score for the overall GLM with three groups, (e.g., log(p) of 3 corresponds to a $p = 0.001$).

the same covariates (age, sex, years of education). For each significant cluster, we utilized the brain metrics of the corresponding atlas-based region. The p-values added in the regression plots represent the significance of increase or decrease for each corresponding slope for the atlas-based region.

RESULTS

Descriptive analyses showed significant differences between groups for demographic variables. Regarding the sex distribution, the AD and MCI groups included more males than females, while the CN group had more females than males. The AD group had a lower mean number of years of education, a lower mean MMSE score and were older compared to both MCI and CN groups (Table 1). When analyzing each NPS based on their total score in each group, irritability had the highest mean total score among AD, MCI, and CN participants. (Table 1).

GLM analysis

Differences between groups

The GLM analysis revealed significant differences in certain structures among the three groups. In fact, the left frontal superior surface area and volume ($F = 9.35$, $p < 0.001$; $F = 11.42$ $p < 0.001$, respectively), the right frontal rostral middle surface area and volume ($F = 13.88, p < 0.05$; $F = 11.78, p < 0.001$, respectively) and the right orbitofrontal lateral volume ($F = 14.63, p < 0.05$) were significantly different among the three groups (Supplementary Table 1 and Fig. 1). The same structures were also significantly different when comparing the CN and MCI groups to the AD group. The left temporal superior surface area ($F = 1.49, p < 0.001$) as well as the right temporal superior sulcus surface area and volume ($F = 10.72$, $p < 0.001$; $F = 2.23$, $p < 0.001$, respectively), the left parietal inferior thickness and volume ($F = 2.76$, $p < 0.001$; $F = 2.43$, $p < 0.001$, respectively), right the parietal precuneus ($F = 2.66$, $p < 0.001$), and the right occipital pericalcarine surface area ($F = 1.43$ $p < 0.001$) were also significantly different among the three groups. The temporal superior gyrus and sulcus as well as the parietal inferior and precuneus regions were also significantly different when comparing the CN and MCI groups to the AD groups. Furthermore, the right temporal inferior surface area ($F = 25.60$, $p < 0.05$) was significantly different when comparing the CN and MCI groups to the AD groups.

Agitation

The agitation score was shown to have significant associations in both GLMs. The overall GLM with three groups showed a significant association between agitation and the parietal supramarginal surface area ($F = 1.12$, $p < 0.001$, $r = –0.18$) in the MCI versus CN contrast (Table 2, Fig. 1). In the pair-wise GLM of the AD versus MCI contrast, agitation was more strongly associated with the cortical thickness of the left temporal superior and fusiform ($p < 0.001$, $r = –0.12$; $p < 0.001$, $r = –0.11$, respectively) in AD compared to MCI (Table 3). Agitation was also more strongly associated with the left temporal

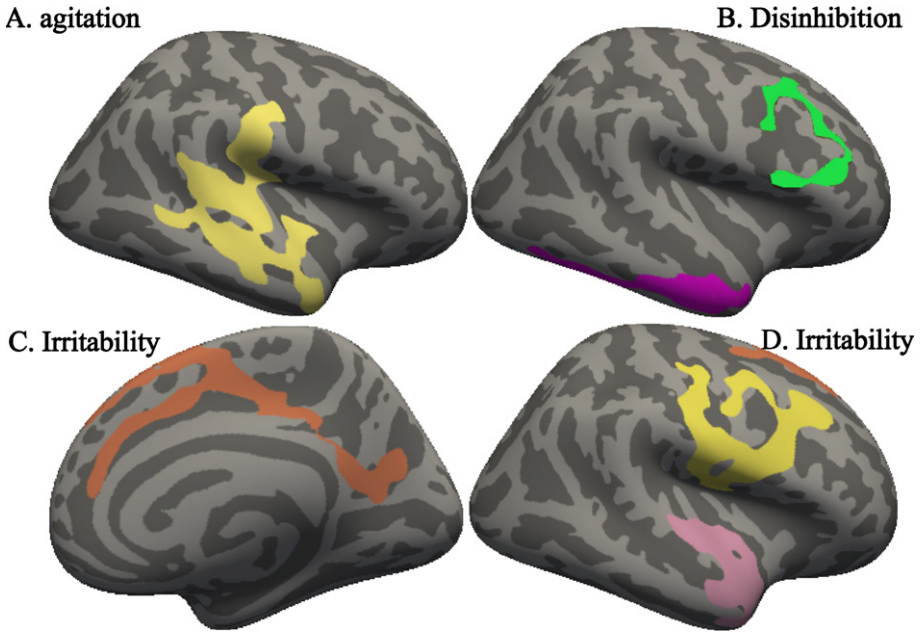

Fig. 1. Regions of significant correlations between NPS and significant brains regions. Agitation (A) and the surface area of the right temporal supramarginal (yellow); Disinhibition (B) and the thickness of the right frontal *pars opercularis* (green) and temporal inferior (pink) region; Irritability (C) and the volume of right frontal and temporal superior (orange) regions; Irritability (D) and volume of the right frontal superior (burnt orange), frontal *pars opercularis* (yellow) and temporal superior (light pink) regions.

Table 3
Pair-wise (AD-MCI) general linear model analysis of hyperactive NPS

Brain Area	Measure	Talairach coordinates			p (log(p))	r
		x	y	z		
AD-MCI						
Agitation						
Temporal Fusiform L	Thick	–26.3	–51.7	–10.6	<0.01 (3.7)	–0.12
Temporal superior L	Thick	–59.0	–8.0	–1.8	<0.001 (3.1)	–0.11
Temporal superior sulcus L	Thick	–51.4	–34.5	2.7	<0.005 (–2.7)	–0.11
Disinhibition						
Frontal middle caudal L	Thick	–32.6	26.2	38.3	<0.001 (4.6)	–0.18
Frontal pars opercularis L	Thick	–43.5	21.8	16.9	<0.001 (3.0)	–0.15
Frontal pars opercularis R	Thick	53.9	14.9	11.2	<0.01 (2.8)	–0.15
Temporal middle L	Thick	–51.7	–59.6	1.1	<0.001 (3.7)	–0.18
Temporal inferior R	Thick	45.7	–50.4	–8.2	<0.001 (3.0)	–0.15
Parietal superior L	Thick	–36.2	–42.9	54.5	<0.05 (5.3)	–0.17
Occipital lateral L	Thick	–13.8	–89.0	–2.2	<0.001 (5.5)	–0.18
Irritability						
Temporal superior R	Thick	44.2	13.3	–21.7	<0.001 (3.3)	–0.096

x/y/z, coordinates of the maximum vertex using the Talairach atlas x/y/z axis; L, left; R, right; Thick, cortical thickness; Area, cortical surface area; Vol, cortical volume; r, mean partial correlation coefficient. The log(p) value indicates the level of significance in the difference in slope of cortical volume, thickness and surface area relative to NPS total score for the pair-wise analysis, (e.g., log(p) of 3 corresponds to a $p = 0.001$).

superior sulcus thickness ($p < 0.005$, $r = –0.11$) in MCI compared to AD. Additionally, agitation showed a stronger association with the surface area of the right temporal middle ($p < 0.001$, $r = –0.19$), right parietal supramarginal ($p < 0.05$, $r = –0.096$), left parietal inferior ($p < 0.001$, $r = –0.18$), and right occipital lateral ($p < 0.05$, $r = –0.19$) regions in AD compared to CN. Conversely, within the same contrast, CN had a stronger association between agitation and the left occipital lingual thickness compared to AD. Finally, agitation was more strongly associated with the left parietal inferior volume ($p < 0.05$,

Table 4
Pair-wise (MCI-CN and AD-CN) general linear model analyses of hyperactive NPS

Brain Area	Measure	Talairach coordinates			p (log(p))	r
		x	y	z		
MCI-CN						
Agitation						
Parietal inferior L	Vol	–38.8	–66.3	38.2	< 0.05 (2.7)	–0.18
Frontal precentral R	Thick	55.8	–0.1	22.9	< 0.05 (–3.7)	0.18
Temporal inferior R	Thick	49.4	–13.2	–23.4	< 0.05 (–3.7)	0.21
Parietal inferior L	Area	–30.9	–66.8	41.1	< 0.001 (3.0)	–0.18
Parietal supramarginal R	Area	57.6	–19.4	22.3	< 0.001 (3.1)	–0.18
Occipital lingual L	Thick	–9.0	–74.6	0.0	< 0.05 (–5.8)	0.20
Disinhibition						
Frontal pars opercularis R	Thick	51.4	16.2	16.3	< 0.005 (–3.4)	0.63
Frontal precentral R	Thick	30.4	–23.1	44.5	< 0.05 (–2.4)	0.58
Irritability						
Frontal superior R	Vol	15.4	14.1	54.3	< 0.001 (–5.5)	0.15
Frontal pars opercularis L	Vol	–41.4	7.5	17.7	< 0.001 (–5.0)	0.16
Frontal pars opercularis R	Vol	41.8	6.8	18.8	< 0.001 (–4.5)	0.16
Temporal superior R	Vol	44.9	8.8	–20.5	< 0.001 (–3.6)	0.16
Frontal superior L	Area	–12.1	–2.1	38.6	< 0.01 (–4.8)	0.15
Frontal pars opercularis L	Area	–39.6	9.5	19.7	< 0.005 (–4.2)	0.16
Frontal pars opercularis R	Area	34.7	12.8	21.4	< 0.01 (–4.0)	0.16
Frontal paracentral R	Area	8.3	–9.0	47.7	< 0.005 (–3.6)	0.14
Temporal superior R	Area	48.4	11.5	-19.7	< 0.05 (–3.3)	0.15
AD-CN						
Agitation						
Temporal middle R	Area	46.9	–32.2	–4.7	< 0.001 (3.4)	–0.19
Parietal supramarginal R	Area	57.2	–19.8	22.4	< 0.05 (3.1)	–0.096
Parietal Inferior L	Area	–34.5	–67.6	45.5	< 0.001 (3.4)	–0.18
Occipital lateral R	Area	25.2	–78.5	–2.9	< 0.05 (2.4)	–0.19
Occipital lingual L	Thick	–8.5	–74.3	0.9	< 0.005 (–5.7)	0.19
Disinhibition						
Frontal Pars triangularis R	Thick	49.1	29.1	–2.3	< 0.05 (–2.5)	0.59
Irritability						
Frontal superior L	Vol	–16.5	45.6	32.4	< 0.001 (–3.8)	0.15
Frontal superior R	Vol	16.6	15.3	54.6	< 0.001 (–4.8)	0.16
Frontal pars opercularis L	Vol	–38.6	9.3	20.1	< 0.01 (–5.3)	0.16
Frontal pole L	Area	–6.0	56.3	–17.6	< 0.05 (–3.8)	0.15
Frontal superior R	Area	12.7	20.4	52.5	< 0.005 (–3.3)	0.14
Frontal pars opercularis L	Area	–39.2	10.0	20.0	< 0.05 (–4.3)	0.15

x/y/z, coordinates of the maximum vertex using the Talairach atlas x/y/z axis; L, left; R, right; Thick, cortical thickness; Area, cortical surface area; Vol, cortical volume; r, mean partial correlation coefficient. The log(p) value indicates the level of significance in the difference in slope of cortical volume, thickness and surface area relative to NPS total score for the pair-wise analysis, (e.g., log(p) of 3 corresponds to a $p = 0.001$).

$r = –0.18$) as well as left parietal inferior and the right supramarginal surface area ($p < 0.001$, $r = –0.18$) in MCI compared to CN (Table 4). In the same contrast however, CN had a stronger association with the cortical thickness of the right frontal precentral ($p < 0.05$, $r = 0.18$), right temporal inferior ($p < 0.001$, $r = 0.21$), and the right occipital lingual ($p < 0.05$, $r = 0.20$) regions compared to MCI.

Disinhibition

Disinhibition was significant in the overall GLM with three groups. Specifically, disinhibition score was more strongly associated with the cortical thickness of the right frontal *pars opercularis* and temporal inferior regions ($F = 17.06$, $p < 0.01$, $r = –0.15$; $F = 17.13$, $p < 0.001$, $r = –0.16$, respectively) in AD compared to MCI. In the pair-wise GLM, disinhibition was also associated with the same two regions ($p < 0.01$, $r = –0.15$; $p < 0.001$, $r = –0.15$) in the AD versus MCI contrast, as well as the cortical thickness of the left frontal middle caudal ($p < 0.001$, $r = –0.18$), the left frontal *pars opercularis* ($p < 0.001$, $r = –0.15$), the left temporal middle ($p < 0.001$, $r = –0.18$), the parietal superior ($p < 0.05$, $r = –0.17$), and occipital lateral ($p < 0.001$, $r = –0.18$)

regions. Specifically, there was a stronger association between disinhibition and these regions in AD compared to MCI. Also, disinhibition was more strongly associated with the right frontal *pars triangularis* thickness ($p < 0.05$, $r = 0.59$) in CN compared to AD, as well as the cortical thickness of the right frontal *pars opercularis* ($p < 0.005$, $r = 0.63$) and right frontal precentral ($p < 0.05$, $r = 0.58$) regions in CN compared to MCI.

Irritability

Irritability was also depicted in the overall GLM with three groups. It showed a stronger association with the cortical volumes of the right frontal (*pars opercularis* and superior) ($F = 18.34$, $p < 0.001$, $r = 0.15$; $F = 1.51$, $p < 0.001$, $r = 0.15$, respectively) and the temporal superior regions ($F = 11.15$, $p < 0.001$, $r = 0.16$) in CN compared to MCI. The pair-wise GLM of the AD versus MCI contrast showed that irritability had a stronger association with the right temporal superior thickness ($p < 0.001$, $r = –0.096$) in AD compared to MCI. In the AD versus CN contrast, the volumes of the left frontal superior ($p < 0.001$, $r = 0.15$), right superior ($p < 0.001$, $r = 0.16$), *pars opercularis* ($p < 0.01$, $r = 0.16$), and surface areas of the left frontal pole ($p < 0.05$, $r = 0.15$), right frontal superior ($p < 0.005$, $r = 0.14$) and left *pars opercularis* ($p < 0.05$, $r = 0.15$) had a stronger association in CN compared to AD. Finally, irritability was more strongly associated with the volumes and areas of the right frontal superior ($p < 0.001$, $r = 0.15$, $p < 0.01$, $r = 0.15$), bilateral frontal *pars opercularis* ($p < 0.001$, $r = 0.16$; $p < 0.005$, $r = 0.16$; $p < 0.01$, $r = 0.16$), right temporal superior ($p < 0.001$, $r = 0.16$, $p < 0.05$, $r = 0.15$), and the surface area of the right paracentral ($p < 0.005$, $r = 0.14$) regions in CN compared to MCI.

Multiple regression analysis

Multiple regressions are presented for results from the overall GLM (Fig. 2). Our results revealed that the increase in agitation scores were associated with decreased surface area in the temporal supramarginal region in the CN group ($p = 0.54$, $r^2 = 0.12$) (Fig. 2A). For MCI participants, increased disinhibition scores were associated with decreased thickness of the temporal inferior ($p = 0.55$, $r^2 = 0.03$) and frontal *pars opercularis* regions ($p = 0.74$, $r^2 = 0.02$). For AD participants, increased disinhibition scores were associated with increased thickness of the temporal inferior ($p = 0.08$, $r^2 = 0.04$) and frontal *pars opercularis* regions ($p = 0.03$, $r^2 = 0.03$). Finally, increased irritability scores were associated with an increase in corresponding cortical volumes for CN participants ($p = 0.13$, $r^2 = 0.17$; $p = 0.03$, $r^2 = 0.18$; $p = 0.23$, $r^2 = 0.07$) as well as decreasing volumes for the MCI participants ($p = 0.001$, $r^2 = 0.14$; $p = 0.02$, $r^2 = 0.15$; $p = 0.02$, $r^2 = 0.07$) (Fig. 2B-D).

DISCUSSION

With this study, we investigated the associations between the NPS of agitation, disinhibition and irritability based on the NPI assessment and cortical morphology in AD, MCI, and CN participants from the perspective of cortical volume, through the lens of surface area and thickness. We found that each hyperactive NPS had associations with brain regions as well as specific types of brain change (volume, thickness, or area).

Significant differences were observed among the frontal superior, rostral middle, and orbitofrontal lateral regions as well as the temporal superior region and sulcus, the parietal inferior and precuneus regions between the three groups and when comparing the CN and MCI groups to AD group.

When analyzing agitation independently, our results are in line with previously reported data. The association observed in our study in the right parietal inferior surface area, appears to be consistent with a previous report [18] of an association between agitation and the atrophy score in the right posterior brain regions (which included the parietal lobe). Furthermore, in a longitudinal study, Rafii et al. [35] found an association between psychotic symptoms, including agitation, and the atrophy rate of the lateral frontal and parietal regions. However, no association was found between this NPS and frontal regions as did other studies [36]. A dysfunction between the frontal and parietal regions may underlie the agitation symptom, although this hypothesis was not tested in the present study. Moreover, while previous neuroimaging studies in AD found agitation to be associated with the anterior and posterior cingulate cortex, the insula, the amygdala, and the hippocampus, we did not replicate these findings [15, 16, 36]. Therefore, the association between agitation and corresponding cerebral change remains unclear.

As for disinhibition, most studies found that it was associated with the orbitofrontal region [37, 38]. Also, Finger et al. [39] found disinhibition to be associated with reduced cortical thickness of the right

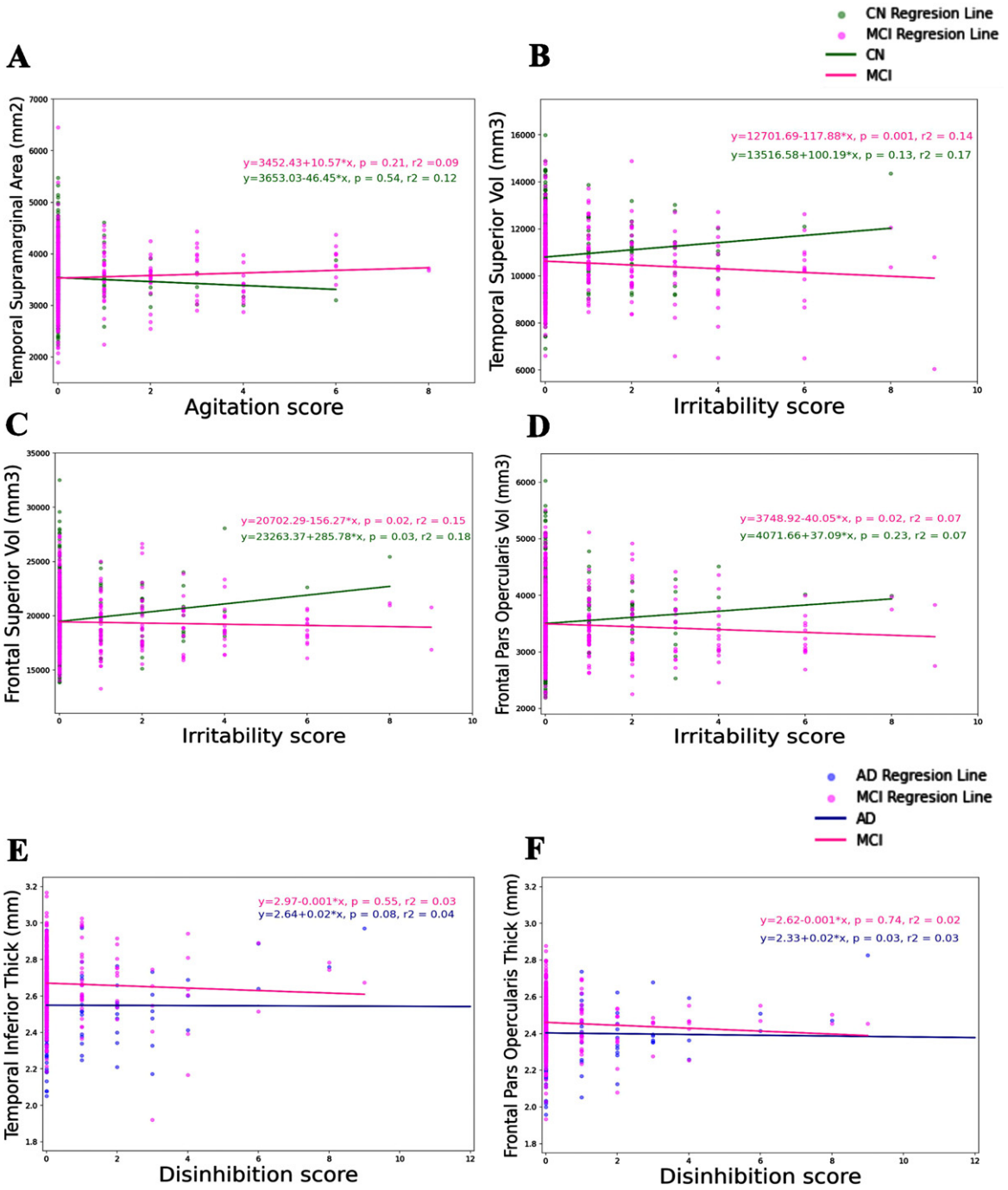

Fig. 2. Multiple regressions for the overall GLM with three groups. CN in green; MCI in pink; AD in blue; (A) surface area of the right temporal supramarginal region as a function of agitation; (B) volume of the right temporal superior (C) frontal superior and (D) frontal *pars opercularis* regions as a function of irritability; (E) cortical thickness of the right temporal inferior and (F) frontal *pars opercularis* regions as a function of disinhibition.

frontal pole. We did not find these associations in our study. Rather, we found the cortical thickness of the right frontal *pars opercularis* region to be associated with disinhibition which is similar to the results of Cajanus et al. [40]. The right frontal inferior region is important for behavioral inhibition and it has been

suggested that damage to this region can decrease performance on executive control tasks by disrupting inhibition processes [41]. This could explain the role of this region in disinhibition. We also found disinhibition to be associated with the cortical thickness of the right temporal inferior region. An interaction between the orbitofrontal cortex and the temporal region has been previously reported through the uncinate fasciculus [37], which is crucial for maintaining normal behavior and inhibitory performance. Since our cohort is composed of participants in the early stage of the disease, the reported disinhibition may be due to damage to the uncinate fasciculus, reflected by the temporal inferior region being significantly associated with disinhibition.

In our study, irritability total score was significantly associated with the volume of the right frontal *pars opercularis*, frontal superior and temporal superior regions. Trzepacz et al. [16] also showed a correlation between irritability and the frontal superior volume and thickness. Similar associations have been demonstrated in other clinical populations at different ages. In particular, in adolescents with severe irritability and participants with bipolar disorder, the frontal superior and inferior regions were associated with inhibitory control as well as affective response modulation [42, 43]. A model of cognitive control of emotion suggests that temporal regions including the temporal superior gyrus play an intermediate role between the frontal region and the amygdala during emotion regulation. Thus, damage to the temporal superior region may disrupt normal emotion regulation and underlie the symptom of irritability [44]. Other studies found associations between irritability and the insula as well as with lower fractional anisotropy of the anterior cingulate region [19, 45]. Also, irritability was usually associated with the anterior cingulate and the orbitofrontal-subcortical circuit [20, 45]. We did not find these results in our study. This could be due to differences in how irritability was quantified, as well as the fact that these regions did not survive the stringent correctional method applied in our study.

Another potential result of interest that emerged from our overall GLM analysis was that all hyperactive NPS were mostly associated with changes in frontal regions of the right hemisphere. While the relation between the regulation of behavior and the right hemisphere is not completely established, our results are in line with studies showing the role of the right hemisphere in the regulation of social and emotional behavior [46].

Based on the results from the multiple regression analyses, we found that as disinhibition scores increased, the thickness of corresponding brain regions increased in AD, while it decreased in MCI. This is a surprising finding, considering that most studies find that with increasing NPS severity, there is a decrease in the brain structure associated with it. From functional MRI (fMRI) studies, it has been hypothesized that brain activation forms an inverse U-shape, with hyperactivation in the early phase of AD [47]. In fact, Billette et al. [47] found an increased precuneus activity for participants with subjective cognitive decline and MCI. Furthermore, in participants with subjective cognitive decline, fMRI studies found increased task-related frontal and parietal activity [48, 49]. The underlying mechanisms regarding these findings remain unclear. In fact, it is still debated whether increased activity in prodromal AD represents compensation for early AD pathology or brain atrophy, or whether abnormal activity causes protein accumulation [47]. This explanation should be taken with caution, as no fMRI studies have investigated the association between this hypothesis and NPS in AD. For the MCI-CN contrast, our results revealed that with increasing irritability score there was a greater increase in the corresponding brain regions for CN compared to MCI. However, the opposite relationship is observed for agitation where an increase in agitation score is associated with an increase in the corresponding brain region for MCI compared to CN. To our knowledge, few studies have shown this relationship between hyperactive NPS and brain changes in CN. It may be that the positive associations are more specific to CN but this remains to be studied.

Strengths and limitations

This study provides insight on the involvement of hyperactive symptoms in neuroanatomical correlates in AD using a large sample size. These analyses revealed that distinct brain structures were associated with each hyperactive NPS in AD, MCI, and CN participants, contributing to a better understanding of these symptoms in AD, which have been poorly studied. Our study contains several strengths including the use of the NPI which is highly validated across several populations including demented patients and cognitively intact older adults. In addition, we performed our analyses on whole brains, used Monte-Carlo simulations for a more stringent correctional method and

added covariates to the models which are important methodological strengths. Finally, we compared two GLM models allowing us to address the importance of the multiple comparison problem.

A few limitations to our study need to be addressed. First, the small number of CN participants with NPS may have influenced the results pertaining to this group. Second, the age of disease onset was not included as a covariate in the model. Third, while we do not know the exact time point at which each participant was included in the study, all participants underwent screening to ensure that they met the inclusion and exclusion criteria before being enrolled. Fourth, the mean total score of each hyperactive NPS is low which can affect current results and limit the generalizability of our findings. Finally, our study is cross-sectional and thus, no causal relationship can be concluded from the significant associations. In fact, the results observed could be due to the pathophysiological decline of AD which is correlated with symptom scores; as disease progresses, NPS are more likely to become more severe. Conversely, it is possible that with increasing NPS score, the decline is greater and, therefore, the probability of belonging to the AD group rather than the MCI group is also greater.

Conclusion and implication of the current study

Our study shows that hyperactive NPS are associated with distinct brain regions morphology in AD, MCI, and CN participants. As opposed to the initial hypothesis, hyperactive NPS seem to have only some regions in common, while the overall associations with brain morphology is specific for each of them, both for the regions involved as well as the type of association, surface area or thickness. Specifically, agitation is primarily associated with the parietal region, disinhibition is associated with the frontal *pars opercularis* and temporal inferior regions, predominantly through changes in cortical thickness. Irritability, on the other hand, is associated with the frontal superior and inferior and temporal superior regions, mainly through volume changes. These results imply that even if hyperactive NPS tend to be clustered together, they are associated with different brain morphological signatures both with respect to the regions as well as the type of brain metric (thickness or area) in AD and MCI participants. As such, they should be assessed individually and in combination with cognitive evaluations. It is crucial to keep in mind that predominantly mild neuropsychiatric symptoms were noted in each group, requiring careful consideration of these conclusions.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

All data are available on the Alzheimer's Disease Neuroimaging Initiative (ADNI) website upon demand (http://adni.loni.usc.edu/data-samples/access-data/).

SUPPLEMENTARY MATERIAL

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