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Frontolimbic atrophy is associated with agitation and aggression in mild cognitive impairment and Alzheimer's disease

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Abstract

Background—The neuroanatomy of agitation and aggression in Alzheimer's disease is not well understood.

Methods—We analyzed 24 months of Alzheimer's Disease Neuroimaging Initiative data for patients with Alzheimer's disease, mild cognitive impairment-stable, and mild cognitive impairment-converter (n = 462) using the Neuropsychiatric Inventory Questionnaire Agitation and Aggression subscale. Magnetic resonance imaging regions of interest that correlated with Neuropsychiatric Inventory Questionnaire Agitation and Aggression subscale raw scores were included in mixed-model, repeated-measures analyses of agitation and aggression over time with age, sex, apolipoprotein E ε4 status, education, and Mini-Mental State Examination score as covariates.

Results—Neuropsychiatric Inventory Questionnaire Agitation and Aggression subscale scores worsened in patients with Alzheimer's disease and in mild cognitive impairment-converter ($P <$ .05; trend for mild cognitive impairment, P =.0518). Greater agitation and aggression severity was associated with greater atrophy of frontal, insular, amygdala, cingulate, and hippocampal regions of interest ($P <$ .05). Mini-Mental State Examination score was significant in mixed-effect model repeated measures only in mild cognitive impairment-converters for posterior regions of interest. Demographics and apolipoprotein ε4 were not associated with agitation and aggression.

Conclusions—Agitation and aggression in Alzheimer's disease and mild cognitive impairment is associated with neurodegeneration affecting the anterior salience network that may reduce capacity to process and regulate behaviors properly.

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Keywords

MRI; Agitation and aggression; Alzheimer's disease; Mild cognitive impairment; Frontolimbic; Salience network

1. Introduction

Agitation and aggression are common neuropsychiatric symptoms (NPS) of Alzheimer's disease (AD) that result in caregiver distress, daily life disruption, and potential harm that affect the patient, family, and caregiver. These behaviors are likely to lead to caregiver distress and burden [1], and increased rates of institutionalization of community-dwelling patients with AD [2] where they continue to be problematic for caregivers in institutionalized settings. Cohen-Mansfield et al [3,4] described behavioral symptoms in AD as categories of verbal and physical agitation and aggression that involve a range of behaviors: motor restlessness, such as pacing and fidgeting; verbal agitation, such as repeating phrases and yelling out inappropriately; disinhibited and emotionally labile behaviors, such as irritability, temper outbursts, blurting embarrassing comments, and making inappropriate sexual advances; and hurtful behaviors such as belittling, cursing, pinching, punching, kicking, and biting. Rates of these symptoms vary with the measurement method, but have been reported to range from 48% to 80% of patients with AD [5], be persistent over months [6], and occur across all stages of AD [5,7,8]. Agitation and apathy are among the most common NPS to occur in mild cognitive impairment (MCI) compared with elderly control subjects [9], suggesting that noncognitive NPS begin during the earliest stages of this neurodegenerative disease process. Furthermore, agitation in MCI predicts earlier diagnosis of AD [10]. Symptoms of agitation and aggression may co-occur with other NPS such as psychotic or mood symptoms [7], although factor analyses report them as loading together, separate from other NPS [6,11]. An Alzheimer's Association research roundtable identified the need for further research into the biological underpinnings of NPS syndromes, including agitation, as a way to advance understanding and to target management efforts more effectively [12].

Neuroanatomic studies relevant to agitation and aggression are few, but point toward involvement of frontal and temporal areas. Hirono et al [13] compared dementia patient groups with and without agitation and aggression as measured on the Neuropsychiatric Inventory (NPI) using single photon-emission computed tomography (SPECT) neuroimaging and found hypoperfusion of left anterior temporal, bilateral dorsolateral prefrontal, and right superior parietal cortices in those with agitation and aggression. Autopsy of brains from patients with AD revealed that the burden of neurofibrillary tangles in the left orbitofrontal and left anterior cingulate correlated with A/A, and in the left orbitofrontal correlated with aberrant motor behavior as measured by NPI scores [14]. Aggression in patients with AD was associated with right medial temporal lobe (hippocampus, parahippocampus, and posterior amygdala) hypoperfusion on SPECT neuroimaging and also with greater motor agitation, as measured by the Behavioural Pathology in Alzheimer's Disease scale [15]. Magnetic resonance imaging (MRI) measures of medial temporal lobe atrophy using visual inspection of T1-weighted images and fluid attenuated inversion recovery-detected white matter hyperintensities did not correlate with any NPI score in patients with AD such that Staekenborg et al [16] concluded that other brain regions might be involved, such as amygdala or frontal cortex. Using fludeoxyglucose positron emission tomography scans, Sultzer et al [17] reported an association between agitation/disinhibition on the Neurobehavioral Rating Scale and hypometabolism in the frontal-temporal lobes. Bruen et al [18] found greater agitation in those with decreased gray matter density on MRI in the left insula and anterior cingulate bilaterally.

We studied measures of atrophy in selected anterior and posterior brain regions of interest (ROIs) using serial MRI data over 2 years from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study for patients with MCI and AD with symptoms of agitation and aggression. We assessed the relationship between gray matter volume and cortical thickness in selected ROIs, and severity of agitation and aggression symptoms as measured on a four-item subscale of the NPI Questionnaire version (NPI-Q).

2. Methods

2.1. Subjects and design

We analyzed the ADNI data set released in September 2010 (http://adni.loni.ucla.edu/). The ADNI is a multisite, multistudy program funded by public and private partnership to investigate whether the combination of neuroimaging, biological markers, and clinical and neuropsychological assessments can track accurately the disease progression in the Alzheimer's disease [19]. Data are publicly available to the scientific community for analyses. As of September 2010, 819 subjects had been recruited: 229 elderly control subjects, 402 subjects diagnosed with amnestic MCI, and 188 subjects with mild AD. Mini-Mental State Examination (MMSE) scores of patients with AD were between 20 points and 26 points (inclusive), Clinical Dementia Rating Scale scores of either 0.5 point or 1.0 point, and all met National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ ADRDA) criteria for probable AD. Mini-Mental State Examination scores of subjects with MCI were between 24 points and 30 points, and these subjects had a memory complaint, objective memory loss as measured by education-adjusted scores on the Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating Scale score of 0.5 point, an absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. All subjects underwent clinical/cognitive assessments and 1.5-T structural MRI at specified intervals (6 months or 12 months) for 2 to 3 years. At each visit, subjects with MCI were assessed to determine whether they had clinically progressed to AD (MCI-converters) or regressed to normal.

For the MCI population, we excluded patients whose complaints were attributed to other identifiable etiologies such as frontotemporal dementia, Parkinson's disease, Huntington's disease, and so forth, and separated out the patients with MCI who converted to AD during the initial 2-year follow-up as a separate subgroup. For the AD population, we excluded subjects who had Parkinson's disease. We collected demographic, genetic, and cognitive measurements, including age, sex, years of education, apolipoprotein E (APOE) epsilon (ε) allele status (ε2, ε3, and ε4 alleles), and NPI and MMSE [20] scores.

We selected patients with AD and MCI from the ADNI database who had any evidence of agitation and aggression symptoms (at least 1 point on the subscale) at one or more study visits during a 2-year follow-up period to analyze the relationship between these symptoms and particular MRI measurements. Longitudinal data were analyzed for study visits that occurred at 6-month intervals, from baseline to 24 months (maximum of five study visits).

2.2. Procedures

2.2.1. Neuropsychiatric Inventory—The NPI-Q [21] was used in the ADNI instead of the standard version of the NPI. Both have the same 12 symptoms, but the NPI-Q differs from the NPI in that it rates only severity and not frequency in the ratings, and it is reformatted to be a self-administered written questionnaire instead of an interview of the caregiver. The caregiver chooses a yes or no answer for every subquestion for each item, and if any are selected for a symptom domain then the item is rated for severity (from 0–3

points). The NPI-Q correlates highly with the standard NPI (0.91 for total scale scores, 0.71–0.93 for items) and its maximum score is 36 points. Four items from the NPI-Q were chosen to capture a full range of verbal and physical agitation and aggression symptoms (agitation and aggression [A/A], irritability and emotional lability, aberrant motor behavior, and disinhibition) to comprise the NPI-Q-4-A/A subscale, which was our symptom outcome measure. The NPI-4-A/A has content validity based on factor analyses [7,11] and has been validated in part in an independent study [22].

2.2.2. MRI measurements—To study brain structure and atrophy associated with agitation and aggression in the AD and MCI populations, we used Freesurfer (http://surfer.nmr.mgh.harvard.edu) volumetric parcellations of the structural magnetic resonance images provided by the University of California at San Francisco, one of the funded MRI analysis sites in the ADNI consortium. Data files from September 2010 comprising numerical MRI end points and patient clinical and demographic variables were downloaded from the LONI website and combined by the Lilly study team. (A full list of subjects analyzed in this study is provided in Supplemental Data.) The preselected MRI ROIs that we analyzed are listed in Table 1 and were sorted into anterior ROI areas thought to be potentially related to agitation and aggression symptoms and posterior ROIs thought to be impaired in most patients with AD regardless of whether they have behavioral symptoms. We analyzed the left and right hemispheres separately in this study, and used both volumetric and cortical thickness measures (when available) for the selected ROIs.

2.3. Statistical analyses

Data were analyzed using SAS (version 9.1) and JMP (version 8). Demographic, clinical, and scale data are reported as mean and standard deviation, and are reported for three subgroups: MCI-stable, MCI-converter, and AD.

2.3.1. Longitudinal modeling of NPI-Q-4-A/A—To understand the progression of the NPI-Q-4-A/A scores over time and its dependence on baseline covariates—age, MMSE score, sex, and ApoE genotype (binary variable)—we built longitudinal models separately for the AD, MCI-converter, and MCI-stable groups during a period of 2 years. For each ADNI subject, there were at most five time points during the 2-year follow-up (baseline and every 6-month visit). We implemented a linear model to capture the rate of NPI-Q-4-A/A changes in each group, as shown in equation 1.

$$NPI4_{ij}=b_0+\gamma_{i0}+(b_t+\gamma_{it})\times t_{ij}+b_{age}\times\mathrm{age}+b_{mmse}\times\mathrm{mmse}+b_{apoe}\times\mathrm{apoE}+b_{sex}\times\mathrm{sex}+\varepsilon_{ij} \quad (1)$$

where $NPI4_{ij}$ is the sum of NPI-Q-4-A/A scores for subject i at visit j; t_{ij} is the corresponding time elapsed since the baseline visit in years (0, 0.5, 1, 1.5, and 2 years); b_0, b_t, γ_{i0}, and γ_{it} are the fixed intercept, fixed slope, random intercept, and random slope; b_{age}, b_{mmse}, b_{apoe}, and b_{sex} are the weights of corresponding covariates, and ε_{ij} is the individual error term with $\varepsilon_{ij}\sim N(0, \sigma^2)$.

None of theseÞvariables were normalized. We examined the initial models built for the AD, MCI-converter, and MCI-stable groups and reduced these models further by leaving out variables that were not found to be significant (at a P value of .05) in any group. The final model includes significant variables only.

2.3.2. Correlation analysis of MRI measurements and NPI-Q-4-A/A—Next, to identify brain ROIs that are related to A/A symptoms in patients diagnosed with AD or MCI, we conducted nonparametric correlation analyses using the NPI-Q-4-A/A scores and MRI measurements in the selected brain ROIs across all longitudinal study visits using all

subjects with AD and MCI. Volume/cortical thickness measurements of these brain ROIs, divided into primary and secondary functional groups as listed in Table 1, were used in this study. We used Spearman's ρ to calculate these correlations because the NPI-Q-4-A/A score is an ordinal variable. The correlation coefficients were calculated using raw measurements of brain ROIs (volume/cortical thickness) at each time point of the visit. An adjustment of raw MRI measurements using total intracranial volume did not generate significantly different results.

Based on these calculated correlation coefficients, we selected only MRI measurements with an absolute correlation coefficient greater than 0.09 across any visit as input to our subsequent mixed-effect model, repeated-measures (MMRM) analyses of the association between brain ROIs and A/A. These ROIs had *P* values ≤.15 to ensure we captured those with trends but also to delimit from those ROIs with correlations that were in a much lower range. Regions of interest clustered together clearly at ρ values either greater than 0.09 or much less than 0.09, so this value was chosen as the cutoff to select ROIs for the subsequent analyses. The method retains important features in the data set while avoiding issues such as multicolinearity and overfitting.

2.3.3. Association between brain ROIs and NPI-Q-4-A/A with MMRM modeling

—Last, using the reduced set of MRI measurements, we modeled the association between NPI-Q-4-A/A and these selected brain ROIs during the period of 2 years with an MMRM approach. The model was built separately for each of the AD, MCI-converter, and MCI-stable subgroups, and for each of the MRI ROI groups. In each model, we assessed the degree to which the change in NPI-Q-4-A/A scores over time could be explained by the reduced set of MRI measurements over time, together with baseline covariates such as age, sex, MMSE score, ApoE genotype (binary as presence or absence of an ε4 allele), and patient educational level (measured in years of formal education). The MRI measurements were coded as percentage changes from baseline for normalization, and raw values were used for all other variables. In sum, using this model we attempted to determine which brain regions are associated with change in NPI-Q-4-A/A over an extended period of time in the AD and MCI populations.

3. Results

3.1. Subjects

During the 2-year study period, 139 of the 356 patients with MCI converted to AD, producing three study groups: AD (n = 179), MCI-converters (n = 139), and MCI-stable (n = 217). Of these subjects, 163 with AD, 122 MCI-converters, and 177 MCI-stable subjects whose NPI-Q-4-A/A score was nonzero for at least one time point during the 24-month follow-up were used in the analyses. Summary statistics of these three groups are shown in Table 2. There was no significant difference in age, but there were significant differences for sex, education, and MMSE score across groups. Note that there are 2 AD and 1 MCI-converter subjects whose MMSE scores did not meet the ADNI–specified inclusion criteria. Because they were assigned to clinical groups by the ADNI I study investigators and their MMSE scores were only slightly out of range, we still included them in this analysis.

As expected, mean MMSE score was the lowest in the AD group, with a range from 18 to 27 points at baseline that decreased at 2 years. At baseline, the AD group had the highest NPI-Q-10 and NPI-Q-4-A/A mean scores compared with the MCI-converter and MCI-stable groups. All groups' NPI mean scores were in the mild severity range, although some individuals had high scores. Both the NPI-Q-10 and NPI-Q-4-A/A scores increased from baseline to 24 months, indicating worsening NPS with progression of the neurodegenerative process.

3.2. Longitudinal modeling of NPI-Q-4-A/A

In Table 3, we summarize the parameters estimated with the reduced longitudinal model for NPI-Q-4-A/A scores for each group. The NPI-Q-4-A/A score increase significantly over time ($P < .05$) for all groups, with annual point increases of 0.37, 0.24, and 0.11 point for the AD, MCI-converter, and MCI-stable groups, respectively. Among all baseline covariates (age, MMSE score, sex, and ApoE genotype), the only one that was associated significantly with NPI-Q-4-A/A, after adjusting for progression over time, was sex in the MCI-converter group, in which females had less progression.

3.3. Correlation among MRI ROIs and NPI-Q-4-A/A scores

Twenty-three ROIs had Spearman correlations of at least 0.09 with the NPI-Q-4-A/A score at any visit (Table 4). Of the anterior ROIs that correlated with the NPI-Q-4-A/A score, 10 were volume measures (left and right insula, left and right rostral anterior cingulate, left and right amygdala, left and right pallidum, right caudal anterior cingulate, and left superior frontal), whereas four were cortical thickness measures (left rostral middle frontal, left superior frontal, medial orbitofrontal, and right superior frontal). Of the posterior ROIs that correlated with the NPI-Q-4-A/A score, six were volume measures (left and right fusiform, left and right hippocampus, left precuneus, and left superior parietal) whereas three were cortical thickness measures (left and right fusiform, and right posterior cingulate).

3.4. Associations with NPI-Q-4-A/A in MMRM modeling

Baseline variables for demographics, ApoE ε4 allele status, and MMSE score were not related to agitation and aggression in MMRM modeling analyses with the exception that lower baseline MMSE scores were significant in the posterior ROIs analysis for the MCI-converter group (Table 5). In contrast, change over time for MRI structural measures from a number of brain regions was associated with change over time in agitation and aggression symptoms. These were predominantly frontolimbic regions rather than posterior ROIs and comprised many components of the salience network (Fig. 1).

Increasing atrophy of two posterior regions—the left hippocampus in subjects with AD and MCI-converters, and the right posterior cingulate in MCI-converters—was associated with increasing agitation and aggression symptoms. Increasing atrophy of many frontal ROIs was associated with increasing agitation and aggression symptoms: left rostral middle frontal in MCI-stable, right superior frontal in AD, and right medial orbitofrontal, left rostral anterior cingulate, and left superior frontal in MCI-converters.

Atrophy of limbic structures—bilateral insula in the AD group, left insula in the MCI-stable group, and right amygdala in both the AD and MCI-converter groups—was related significantly to agitation and aggression. Amygdala atrophy (right sided) associations were contralateral to that of the hippocampus (left-sided).

4. Discussion

We investigated the relationship between agitation and aggression symptom severity over time and regional brain atrophy on MRI using longitudinal data in patients with MCI and AD from the ADNI database during a 2-year period. Our MMRM modeling analyses found a significant relationship for greater atrophy of frontolimbic regions, right posterior cingulate, and left hippocampus with greater severity of agitation and aggression. Volumetric and/or cortical thickness atrophy findings overshadowed educational, cognitive, and ApoE allele variables, suggesting that regional neurodegeneration was the dominating factor underlying these symptoms. There were more anterior ROI group relationships revealed by MMRM modeling than posterior. The frontolimbic ROIs are among those that

represent components of the salience network [23] implicated in processing and reacting to complex social situations. Our findings suggest an important role for frontolimbic neural networks in the generation of agitation and aggression behaviors in each of our groups, although the specific components of these networks were affected variably at different disease stages. That these areas are affected early is supported by findings of decreased cortical thickness, decreased fractional anisotropy, and increased diffusivity in frontal and temporal regions in amnestic patients with MCI [24]. Our findings, taken in conjunction with the neuroimaging and autopsy literature [13–15,17,18], strongly support that neuroanatomic changes underlie abnormal behaviors in MCI and AD, even at early stages of the neurodegenerative disease process.

Using Freesurfer and voxel based morphometry analyses of atrophy per se via serial MRI data in the ADNI cohort, Risacher et al [25] reported larger percent changes for atrophy of frontal, temporal, and parietal ROIs in AD and MCI-converter groups but did not report behavioral indices. Furthermore, they reported that presence of one or more ApoE-4 alleles was associated significantly with higher annual mean rates of atrophy for various hippocampal and entorhinal cortex indices. In contrast, we did not find a relationship with ApoE-4 alleles in our models, and the literature on whether the ApoE4 allele is associated with agitation and aggression in AD is mixed [26–31]. This is interesting because in normal individuals the presence of the ApoE4 allele is associated with a faster breakdown of white matter integrity in late-myelinating regions (frontal and corpus callosal genu) than early-myelinating regions (splenium) [32,33], and the volume of the prefrontal callosal region shrinks faster with aging [34], which could be expected to affect neural signaling in frontolimbic brain regions implicated in behavioral changes in AD more in those with ApoE4. However, Agosta et al [35] found differentially more atrophy of gray matter in patients with AD with ApoE4-positive status in posterior ROIs than anterior ROIs. Although common in AD, agitation and aggression symptoms may only occur in those whose neurodegeneration affects certain anterior brain regions and circuitry regardless of ApoE allele status.

Our longitudinal model findings are consistent with cross-sectional reports of an association between agitation and aggression in AD with brain changes in frontal and limbic regions including amygdala, cingulate cortex, and insula [13–15,17]. Amygdaloid nuclei generate negative emotions like fear, disgust, and anxiety as well as affective memory, the latter occurring in close conjunction with the hippocampus, and become atrophied in AD. Amygdala outputs to insula may be abnormal in AD.

The dorsolateral prefrontal cortex subserves insight and executive functions and provides oversight and regulation over limbic outputs. Our findings of atrophy of superior frontal ROIs (ie, dorsolateral) is consistent with prior reports of impaired insight and executive functioning in patients with AD with agitation and aggression symptoms [36–38] and behavioral impairment. The orbitofrontal cortex (OFC) is important for social intelligence and comportment, and integrates limbic drives with social context. Dysfunctional OFC results in disinhibition, irritability, and other socially inappropriate behaviors, in part because limbic structures are dysregulated [39]. That right medial OFC atrophy was associated with agitation and aggression severity in MCI-converters suggests that impaired regulation of the amygdala by the OFC contributes to these symptoms. The OFC and rostral middle frontal cortices have a white matter connection to the amygdala via the uncinate fasciculus. Diffusion tensor imaging including tractography found significant abnormalities in the uncinate fasciculus in patients with AD compared with control subjects [40–42], consistent with disrupted connectivity that would exacerbate the neural communications between frontal–limbic regions where gray matter is also atrophied. Late- but not early-myelinating fibers, including uncinate, inferior, and superior longitudinal fascicule, stria

terminalis, cingulum, and splenium, have significantly lower fractional anisotropy in patients with AD vs control subjects [43], supporting connectivity problems between frontal–limbic regions.

Our findings of bilateral insular atrophy associated with agitation and aggression are consistent with the report of Bruen et al [18] of left insular atrophy with agitation in AD and the occurrence of severe agitation with insular seizures. Furthermore, AD is associated with greater neurofibrillary tangle density in the agranular layer of the insula on autopsy, which is a more cytoarchitecturally primitive portion of the insula and interconnected reciprocally with the entorhinal region. The insula receives broad sensory inputs, has strong connections with the autonomic and limbic systems, and integrates external and internal sensations with emotion and memory such that it contributes to an awareness of oneself and how one feels [44]. The insula plays a fundamental role in human awareness and may contain interoceptive representations that link somatic and emotional feelings, whereas the anterior insula activates jointly with the anterior cingulate to integrate sensory, motor, and limbic inputs [45]. Therefore, insular pathology in AD may contribute to a disordered social sense of self and dysregulated social interactions evident in those with agitation and aggression in AD.

Related to insula function are Von Economo neurons (VENs). Von Economo neurons are only found in frontal–insular–anterior cingulate circuitry in primates and cetaceans that have large brains and live in complex social structures, and are most numerous in humans. Von Economo neurons are long, thin bipolar neurons that are larger than pyramidal neurons. They are implicated in mediating fast neurotransmission to support rapid, intuitive decision making and adjustment of behaviors, and thereby appear to subserve behavioral regulation in social contexts [46,47]. They are especially common in layer V of anterior cingulate and right frontoinsular cortices, as well as in the dorsolateral prefrontal cortex [48]. This anterior circuitry involving VENs is called the salience network [49], the activation of which is anticorrelated with activation of the posterior default mode network that is involved in introception [45]. Histopathology finds VENs to be dystrophic and atrophied in behavioral variant frontotemporal dementia, but not in AD [49], although patients with AD with agitation and aggression have not been studied separately. If VENs are preserved in patients with AD with agitation and aggression, then perhaps they are transmitting misinformation among atrophied amygdala and salience network regions, and may represent the altered neuroanatomy for the proposed frontal variant in AD [50].

Our data support that decreased prefrontal regulation of a dysfunctional amygdala that is receiving disrupted hippocampal inputs provides misinformation to an atrophied insula with an outflow for emotional information integration and autonomic stimulation that results in a range of agitated and aggressive behaviors in patients with MCI and AD. The prefrontal cortex loses its behavior-regulating capacity, which results in behavior and personality changes. These findings are consistent with a large body of neuropsychiatry literature describing a complex brain network of prefrontal, subcortical, and mesolimbic circuitry that mediates and regulates social behaviors and the frontoinsular circuitry that plays a crucial role in the processing of more complex social emotions such as empathy, compassion, and fairness.

Limitations of our study include its exploratory nature that used a low threshold for correlations between ROIs with symptoms to select ROIs initially for modeling. Our findings using longitudinal data did have consistency with prior cross-sectional literature, however, and contribute meaningfully to this poorly understood but common condition. Although agitation and aggression may co-occur with other NPS such as mood or psychosis, we did not covary for those in our multivariate analyses so as not to dilute the signal for our target symptoms, which are observable in a way that subjective symptoms are not. We

selected an NPS phenotype measure based on face validity and results of large factor analyses [7,11,22]. The NPI-Q was the only measure of NPS available in the ADNI database.

5. Conclusions

An impaired modulatory interface of prefrontal regions with dysfunctional amygdalar–hippocampal and amygdalar–insular networks may result in disrupted behavioral control in a subset of patients with MCI and AD that expresses itself as symptoms of agitation and aggression. Magnetic resonance imaging indices of volumetric or cortical thickness found the left hippocampus and posterior cingulate as the only posterior ROIs associated with agitation and aggression, and these areas have important connectivity with amygdala and prefrontal cortex. These frontolimbic regions of the brain are known to subserve a range of functions such as insight, facial emotion recognition, and expression of negative emotions that are impaired in AD. Our exploratory MRI findings are consistent with other studies' findings of regional brain pathology in AD that affects both white and gray matter in more anterior brain areas and plausibly associated with agitation and aggression symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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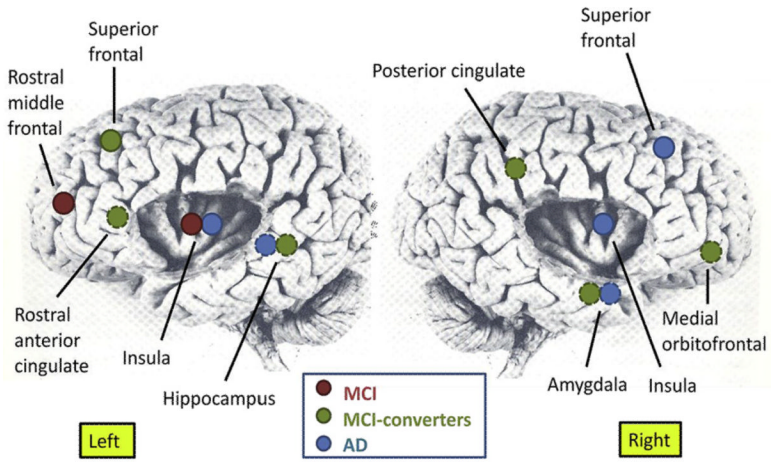

Fig. 1.

Neuroanatomic areas showing significant associations using mixed-effect model, repeated-measures modeling between increasing agitation and aggression as measured by the Neuropsychiatric Inventory Questionnaire Agitation and Aggression with increasing magnetic resonance region of interest atrophy (see text for details regarding volume or cortical thickness) during a 2-year period in Alzheimer's Disease Neuroimaging Initiative patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI; n = 535). Dotted circles denote deep regions.

Table 1

Magnetic resonance imaging regions of interest are divided into two functional areas, include left and right hemispheres, and are modeled separately

MRI anterior group ROIs	MRI posterior group ROIs
Volume	Volume
R and L ventral pallidum	R and L hippocampus
R and L insula	R and L splenium
R and L amygdala	R and L thalamus
R and L rostral anterior cingulate	R and L fusiform
R and L caudal anterior cingulate	R and L posterior cingulate
R and L medial orbitofrontal	R and L superior parietal
R and L lateral orbitofrontal	R and L precuneus
R and L rostral middle frontal	
R and L superior frontal	
Cortical thickness average	Cortical thickness average
R and L insula	R and L fusiform
R and L rostral anterior cingulate	R and L posterior cingulate
R and L caudal anterior cingulate	R and L superior parietal
R and L medial orbitofrontal	R and L precuneus
R and L medial orbitofrontal	
R and L rostral middle frontal	
R and L superior frontal	

Abbreviations: MRI, Magnetic resonance imaging; ROI, region of interest; R, right; L, left.

Table 2

Demographic and rating scale data for the three diagnostic groups

Variable	Visit	AD (n = 163)	MCI converters (n = 122)	MCI stable (n = 177)
Age	Baseline	75.3 ± 7.5 (57–91)	74.6 ± 6.9 (55–89)	74.4 ± 7.8 (55–88)
Sex, % male*	Baseline	52.6%	65.5%	67.0%
Education, y†	Baseline	14.7 (4–20)	15.7 (6–20)	15.7 (4–20)
MMSE‡	Baseline	23.3 ± 2.1 (18–27)	26.6 ± 1.7 (23–30)	27.2 ± 1.8 (24–30)
NPI-Q-4-A/A*	Baseline	1.5 ± 1.6 (0–7)	1.2 ± 1.8 (0–10)	1 ± 1.5 (0–9)
NPI-Q-10‡	Baseline	3.2 ± 2.9 (0–13)	2.2 ± 2.8 (0–15)	1.8 ± 2.3 (0–15)
MMSE‡	24 mo	18.4 ± 6.2 (0–28)	22.4 ± 3.7 (8–30)	27.1 ± 2.9 (8–30)
NPI-Q-4-A/A‡	24 mo	2.2 ± 2.2 (0–11)	1.7 ± 2.2 (0–11)	1.2 ± 1.5 (0–7)
NPI-Q-10‡	24 mo	4.8 ± 4.5 (0–25)	3.6 ± 3.3 (0–15)	2.4 ± 2.5 (0–10)

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI-Q-4-A/A, Neuropsychiatric Inventory Questionnaire Agitation and Aggression; NPI-Q-10, Neuropsychiatric Inventory Questionnaire-10.

NOTE. Values are expressed as mean ± standard deviation unless otherwise specified. Ranges are in parentheses. *P* values are from one-way analysis of variance across all groups.

*$P \leq .05$.

†$P \leq .01$.

‡$P \leq .001$.

Table 3

Coefficients that showed significance for relationships with Neuropsychiatric Inventory Questionnaire Agitation and Aggression scores over the 2-year period in the reduced longitudinal model are listed by group

Variable	MCI stable	MCI converter	AD
Intercept	1.33‡	1.58‡	1.54‡
Sex (female)	−0.29	−0.39*	0.01
Time	0.11	0.24†	0.37*

Abbreviations: MCI, Mild cognitive impairment; AD, Alzheimer's disease.

*$P \leq .05$.

†$P \leq .01$.

‡$P \leq .001$.

Table 4

All anterior and posterior group region of interest values (Table 1) were entered into a correlation analysis with Neuropsychiatric Inventory Questionnaire Agitation and Aggression individual scores

MRI ROI	Baseline ρ	6-Month ρ	12-Month ρ	18-Month ρ	p 24-Month ρ
Anterior group					
R insula	0.056	0.019	−0.013	−0.015	**−0.090**
L insula	0.055	0.047	0.000	−0.006	**−0.164**
R rostral anterior cingulate	0.085	**0.093**	−0.003	0.011	−0.034
L rostral anterior cingulate	−0.010	0.045	−0.061	−0.012	**−0.132**
R caudal anterior cingulate	0.032	0.047	−0.048	−0.070	**−0.117**
R amygdala	0.057	0.061	0.016	0.063	**−0.130**
L amygdala	0.013	0.041	−0.018	0.004	**−0.126**
R pallidum	0.021	**0.146**	0.070	−0.001	**0.120**
L pallidum	0.014	**0.128**	0.026	0.012	0.042
R superior frontal*	−0.006	**−0.091**	−0.011	0.002	−0.035
L superior frontal	0.044	0.009	0.008	0.017	**−0.092**
L superior frontal*	−0.010	**−0.100**	−0.033	−0.017	−0.061
L rostral middle frontal*	−0.020	**−0.107**	**−0.098**	−0.017	**−0.091**
R medial orbitofrontal*	0.008	**−0.106**	−0.072	−0.032	−0.040
Posterior group					
R fusiform	**0.094**	0.049	0.001	0.015	**−0.096**
R fusiform*	−0.008	−0.053	−0.023	0.012	**−0.094**
L fusiform	0.059	0.053	0.016	−0.072	**−0.138**
L fusiform*	−0.042	−0.060	−0.041	−0.040	**−0.136**
L precuneus	−0.002	0.025	−0.022	0.069	**−0.111**
R hippocampus	0.024	0.005	−0.050	**0.112**	−0.090
L hippocampus	−0.020	0.007	−0.073	0.065	**−0.104**
R posterior cingulate*	−0.017	−0.063	−0.070	**−0.094**	−0.041
L superior parietal	0.012	0.043	0.032	**0.111**	−0.011

Abbreviations: MRI, Magnetic resonance imaging; ROI, region of interest; R, right; L, left.

NOTE. Those with Spearman correlation coefficients (ρ) values that were ≥0.09 at any visit over 2 years are listed. Regions of interest in bold type were then entered into the mixed-effect model, repeated-measures model (see Table 5). All patients with Alzheimer's disease and mild cognitive impairment were included in this analysis. Volumes are reported except when indicated by an asterisk.

* Cortical thickness average.

Table 5

Mixed-effect-model, repeated-measures modeling was performed for each diagnostic group for anterior and posterior group magnetic resonance imaging regions of interest

MMRM model variable*	MCI stable *P* value	MCI converters *P* value	AD *P* value
Anterior group ROI			
Age	NS	NS	NS
ApoE ε4+ status	NS	NS	NS
Sex, male	NS	NS	NS
Intercept	NS	NS	NS
Baseline MMSE	NS	.08	NS
Education, y	NS	NS	NS
R pallidum	.06	NS	NS
L pallidum	NS	NS	NS
R rostral anterior cingulate	NS	NS	NS
L rostral anterior cingulate	NS	**.00003**	NS
R caudal anterior cingulate	NS	NS	NS
R superior frontal†	NS	NS	**.01**
L superior frontal	NS	**.04**	NS
L superior frontal†	NS	NS	NS
L rostral middle frontal†	**.04**	NS	NS
R medial orbitofrontal†	.07	**.04**	NS
R insula	NS	NS	**.01**
L insula	**.02**	NS	**.01**
R amygdala	NS	**.02**	**.0007**
L amygdala	NS	NS	NS
Posterior group ROI			
Age	NS	NS	NS
ApoE ε4+ status	NS	NS	NS
Sex (male)	NS	NS	NS
Intercept	NS	NS	NS
Baseline MMSE	NS	**.02**	NS
Education, y	NS	NS	NS
R posterior cingulate†	NS	**.000005**	NS
R fusiform	NS	NS	NS
R fusiform†	NS	NS	NS
L fusiform	NS	NS	NS
L fusiform†	NS	NS	NS
R hippocampus	NS	NS	NS
L hippocampus	NS	**.03**	**.02**
L precuneus	NS	NS	NS
L superior parietal	NS	NS	NS

Abbreviations: MMRM, Mixed-effect model repeated measures; MCI, mild cognitive impairment; AD, Alzheimer's disease; ROI, regions of interest; NS, not significant; ApoE, apolipoprotein E; MMSE, Mini-Mental State Examination; R, right; L, left.

NOTE. Mixed-effect-model, repeated-measures modeling was analyzed within each group and included age, sex, educational level, MMSE score, and binary ApoE ε4 allele status (heterozygous or homozygous) along with the ROIs. Regions of interest with significant *P* values are in bold type, trends are not in bold type, and nonsignificant values are denoted as NS. Volumes are reported unless followed by an dagger.

*These ROIs were chosen for MMRM analyses if they showed a correlation of ≥0.09 with the Neuropsychiatric Inventory Questionnaire Agitation and Aggression subscale score at any time point during the 2-year study period (see Table 4).

†Cortical thickness average.