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Association of Temporolimbic Volumes with Treatment Response to Antipsychotic Medication for Delusion in Patients with Alzheimer's Disease

ABSTRACT

Objective: This study investigated the association between gray matter volume and the treatment response to antipsychotic medication in patients with Alzheimer's disease (AD).

Methods: We included 26 AD patients with delusions from the Memory Impairment Center of the Pusan National University Hospital in South Korea. All participants underwent baseline brain magnetic resonance imaging and took risperidone as an antipsychotic medication for 6 weeks. Gray matter volumes were measured using voxel-based morphometry at baseline. Treatment response with respect to delusional symptoms was defined as the change in delusion item scores in the Korean version of the Neuropsychiatry Inventory (K-NPI), from baseline to 6 weeks later. A voxel-based multiple linear regression model integrated with statistical parametric mapping was used to investigate the association between gray matter volume and treatment response after controlling for covariates.

Results: The treatment response was significantly positively correlated with gray matter volume in the temporal lobe (both the fusiform gyri and the left superior and inferior temporal gyri) and the limbic system (the left parahippocampal gyrus and left amygdala) after controlling for age, sex, education level, total intracranial volume, risperidone dosage, baseline Korean version of the Mini-Mental Status Examination scores, and baseline K-NPI scores for the delusion and non-delusion domains ($P < .001$, uncorrected, $K_E > 100$ voxels).

Conclusion: Our findings suggest that specific gray matter volumes, including those of the temporal region and the limbic system, may affect treatment response to antipsychotic medication in terms of delusional symptoms in patients with AD.

Keywords: Gray matter, treatment, delusions, Alzheimer's disease

Introduction

Delusions are one of the common non-cognitive neuropsychiatric symptoms seen in patients with Alzheimer's disease (AD), and have been reported to occur in approximately 30% of patients.[1] Antipsychotic drugs have traditionally been used to control delusional symptoms in AD patients, but these drugs have limited efficacy,[2] have concerning side effects,[3] and can increase mortality.[4] Therefore, identifying the neuropathology related to the response to drug treatment is critical for developing effective interventions.

Many previous neuroimaging[5-7] and neuropathological[8,9] studies have shown that an alteration in gray matter may contribute to the incidence of delusions in patients with dementia. In AD patients, delusions are associated with exaggerated reductions in gray matter volume, including volumes of the prefrontal cortex,[5] the hippocampus,[7] and the entorhinal cortex.[6] Decreased soluble beta-amyloid (Aβ) 1-40 levels[8] and increased neurofibrillary tangle density[9] in the neocortical regions are associated with delusions in patients with AD. Longitudinal neuroimaging studies of schizophrenia have reported that gray matter volumes are associated with the outcomes and treatment response to antipsychotic

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medications in patients with schizophrenia.[10-13] Larger striatothalamic volume,[10] medial temporal gyral volume,[11] and dorsolateral prefrontal cortex volume[12] were correlated with good response to antipsychotic medications at the 1-year follow-up in patients with schizophrenia. Another study[13] that evaluated the relationship between brain structure and treatment response in the first 6 months of illness showed that parahippocampal volume was significantly larger in the remission group than in the non-remission group.

Although gray matter volumes in patients with schizophrenia contribute to the treatment response to antipsychotic medication with respect to delusions, little is known about this association in patients with AD. Considering that abnormalities in the prefrontal lobe, the medial temporal lobe, and the limbic system may render people vulnerable to delusional symptoms in the context of schizophrenia and AD,[14-16] it is plausible to assume that AD with delusions and schizophrenia may share factors associated with the treatment response to antipsychotic medication, with respect to delusions.

This study investigated the effect of the baseline gray matter volume on the treatment response to antipsychotic medication with respect to delusions, in AD patients with delusions. Delusions are often accompanied by hallucinations, but we only included patients with delusions in this study because hallucinations are likely to have a neurobiological mechanism which is different from that of delusions.[17]

Based on previous findings,[10-13] we hypothesized that the regional volumes of gray matter were positively correlated with a good treatment response with respect to delusions, after 6 weeks of antipsychotic medication use in patients with AD. To test this hypothesis, we applied a voxel-based multiple linear regression model analysis integrated with statistical parametric mapping (SPM) to simultaneously assess the association between treatment response and specific gray matter volumes throughout the brain.

Methods

Participants

We included 26 AD patients with delusions from the Memory Impairment Center of the Pusan National University Hospital in South Korea from July 2015 to May 2017. The diagnostic evaluation for AD with delusions consisted of recording the psychiatric history, and performing a neurological examination, laboratory tests, comprehensive neuropsychological tests, and magnetic resonance imaging (MRI) of the brain. All patients with AD were diagnosed based on the National Institute on Aging-Alzheimer's Association workgroup (NIA-AA) core clinical criteria for probable AD dementia.[18]

The diagnosis of delusions in AD patients was made using the Jeste and Finkel criteria:[19] (1) diagnosis of AD dementia; (2) occurrence of psychosis after the diagnosis of dementia; (3) persistent or intermittent delusions or both for at least 1 month; (4) severe delusional symptoms that disrupt functioning; and (5) exclusion of schizophrenia and related psychotic disorders (e.g., schizoaffective disorder, delusional disorder, or psychotic mood disorder), delirium, and other causes of psychotic symptoms (e.g., substance use and other general medical conditions).

The exclusion criteria for all participants were as follows: (1) significant psychiatric conditions (e.g., delirium, bipolar disorder, major depressive disorder, schizophrenia and other psychotic disorders, or substance abuse); (2) significant cerebrovascular or intracranial disease (severe white matter hyperintensity with a Fazekas scale score of 3, multiple [more than 5] lacunes, hemorrhages, or tumors); (3) significant other neurodegenerative disorders (e.g., behavioral variant frontotemporal dementia,[20] semantic variant of primary progressive aphasia,[21] non-fluent variant of primary progressive aphasia,[21] dementia with Lewy bodies,[22] or Parkinson's disease[23]); (4) significant medical conditions causally related to cognitive impairment (e.g., severe organ failure, metabolic or hematologic disorders, clinically significant abnormal laboratory findings); (5) a score of <10 or >24 on the Korean version of the Mini-Mental State Exam (K-MMSE);[14] and (6) history of taking antipsychotic medications within the past 1 year.

Figure 1 shows a flowchart of the participant exclusion process. Four participants dropped out due to intolerable side effects, including dizziness (n = 1) and rigidity (n = 3), and one participant was excluded because the MRI data were too noisy. Finally, the analysis included 21 patients with AD and delusions. The phenomenology of delusions in these patients involved theft (n = 11), morbid jealousy (n = 5), harm (n = 4), and phantom border (n = 1). None of the AD patients with delusions had mood disorders or other psychiatric diseases that would cause delusions. Considering the average scores of the K-MMSE (mean = 16.52 [SD = 5.23]) and the Seoul Instrumental Activities of Daily Living (SIADL) scale[25] (mean = 23.60 [SD = 11.55]) in the study group, the participants appeared to have dementia of moderate severity (Table 1). The Institutional Ethical Review Board of Pusan National University Hospital approved this study (1908-006-081), and the participants and their caregivers provided written informed consent.

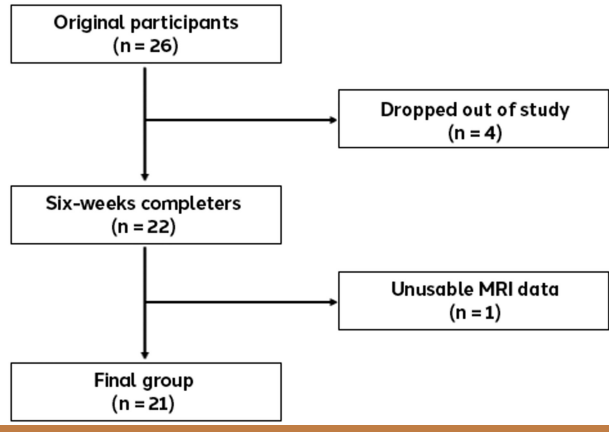

Figure 1. Flowchart showing the criteria used to exclude participants from the study and reach final sample size.

MAIN POINTS

- *Gray matter volume was associated with the treatment response for delusion in patients with AD.*
- *Temporal gray matter regions were positively associated with the treatment response for delusion.*
- *Limbic gray matter regions were positively associated with the treatment response for delusion.*

Table 1. Demographic and Clinical Characteristics of 21 AD Patients with Psychosis

	Mean (SD), (N = 21)
Age, years	72.42 (7.38)
Gender, female, n (%)	15 (71.4)
Education, years	5.78 (4.82)
TIV (cm^3)	1510.42 (138.72)
K-MMSE	16.52 (5.23)
CERAD-K	
K-BNT	6.22 (2.82)
Constructional apraxia	6.40 (3.01)
Word list delayed recall	0.18 (0.58)
FAB-K	7.77 (3.96)
SIADL	23.60 (11.55)
Baseline K-NPI delusion scores	9.48 (3.99)
The change in K-NPI delusion item score from baseline to 6 weeks	2.40 (3.60)
Baseline K-NPI non-delusion scores	25.65 (19.42)
Dosage of risperidone (mg/day)	1.06 (0.41)

AD, Alzheimer's disease; TIV, total intracranial volume; K-MMSE, the Korean version of the Mini-Mental State Exam; CERAD-K, the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease; K-BNT, the Korean version of the Boston Naming Test; FAB-K, the Korean version of the Frontal Assessment Battery; SIADL, Seoul Instrumental Activities of Daily Living; K-NPI, the Korean version of the Neuropsychiatry Inventory.

Study Design and Clinical Evaluation

This study was a pre-post treatment, single-arm, prospective longitudinal study of AD patients with delusions. Risperidone was administered to AD patients with delusions for 6 weeks. The initial dosage of risperidone was 0.5 mg/day, and the doses were titrated every 7 days according to the patient's clinical condition. AD patients received 5 mg of donepezil daily, and the dosage did not change during the study period.

All participants underwent comprehensive assessment consisting of the following: a psychiatric interview with both the patient and an informant, physical and neurologic examinations, K-MMSE[24] and SIADL[25] evaluations, administration of the Korean version of the Neuropsychiatric Inventory (K-NPI),[26] and brain MRI.

The SIADL was validated in Korea as a standardized scale for activities of daily living (ADL). The SIADL consists of 15 items that address an individual's ability to engage in more complex tasks, such as shopping and using the telephone, and impairment severity is scored from 1 (no impairment) to 3 (severe impairment) for all items. Thus, the maximum SIADL score is 45, and scores of ≤ 7 indicate normal complex ADLs.

The Korean version of the Consortium to Establish a Registry for AD[27] was used to examine the functional ability of multiple cognitive domains: (1) word list delayed recall for memory; (2) the Korean version of the Boston Naming Test for naming ability; and (3) the constructional apraxia test for visuospatial function. We also used the Korean version of the Frontal Assessment Battery (FAB-K)[28] to measure executive function. The FAB-K is a valid and reliable instrument for evaluating frontal lobe function in elderly people.

Treatment Response with Respect to Delusions

The primary outcome measure was the treatment response to risperidone with respect to delusional symptoms in AD patients. We used the delusion item scores (severity × frequency) of the K-NPI[26] to assess the severity of delusional symptoms. The severity of delusional symptoms was assessed using the K-NPI at baseline and after the administration of risperidone for 6 weeks. Treatment response was defined as the change in the K-NPI delusion item score from baseline to 6 weeks. The K-NPI is a valid and reliable tool that evaluates the severity and frequency of abnormal behaviors, including delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, and neurovegetative changes including night-time behavior, and changes in eating habits.

Gray Matter Volume Estimation: MRI Data Acquisition and Image Analysis

Structural T1-weighted MRI was performed for each participant during the baseline clinical evaluation. All images were collected at the Pusan National University Hospital Imaging Center using a Siemens 3-T Trio scanner (Erlangen, Germany). For the estimation of gray matter volume, three-dimensional high-resolution magnetization-prepared rapid gradient-echo sequences were obtained using the following imaging parameters: slice thickness = 1 mm, total number of slices = 256, acquisition matrix = 256 × 256, flip angle = 12°, field of view = 250 × 250 mm^2, echo time = 2.07 ms, and repetition time = 1800 ms. All images were acquired with the same slice orientation (parallel to the anterior and posterior commissure lines). During brain imaging, movement of the patient's head was limited using an expandable cushion. Imaging data with motion or any other artifacts that were difficult to analyze were excluded.

Structural MRI analysis was performed using the voxel-based morphometry toolbox (VBM8) integrated into statistical parametric mapping 8 (SPM8).[29] First, all images were spatially normalized to the Montreal Neurologic Institute template using affine linear transformation and nonlinear registration, and then segmented into cerebrospinal fluid, white matter, and gray matter.[30] After segmentation, a modulation process was performed by multiplying the voxel intensity by the Jacobian determinant representing the parameters for fitting native voxel space to a corresponding voxel in the template space, to minimize the volume effect of expansion or contraction occurring during the normalization process.[30] The modulated gray matter images were smoothed with a half-maximum isotropic Gaussian kernel of 8 mm full width.

Statistical Analysis

Voxel-based multiple linear regression analysis in SPM8[29] was used to explore the effect of gray matter volume on the treatment response throughout the brain. In this model, the factors known to affect gray matter volume (age, sex, education level, risperidone dose, total intracranial volume [TIV], baseline K-MMSE scores, and baseline K-NPI delusion item scores) were included as covariates. We also included the K-NPI non-delusion score (the sum of scores of K-NPI items other than the delusion item) as a covariate because the non-delusional symptoms included in the K-NPI, such as depression,[31] apathy,[32] and agitation,[33] are known to be associated with decreased brain volume in the prefrontal and temporolimbic regions. Statistical significance was set at an uncorrected P value of $< .001$, at a threshold level of 100 voxels (uncorrected $P < .001$, $K_E >$

Table 2. Regions with Positive Significant Association Between Gray Matter Volume and Treatment Response of Delusion After 6 Weeks of Treatment with Risperidone on Voxel-based Multiple Regression Analysis in 21 AD Patients with Delusion (P < .001, Uncorrected, K_E > 100 voxels)

Anatomical region	Cluster size	MNI coordinates (mm) x	y	z	*T*
L inferior temporal gyrus	4553	−29	−4	−41	6.19
L superior temporal gyrus	4553	−33	0	−23	5.03
L parahippocampal gyrus	4553	−27	−19	−25	4.98
L fusiform gyrus	4553	−31	−4	−34	4.83
L amygdala	4553	−30	0	−25	4.62
R fusiform gyrus	266	33	−4	−35	4.40

The multiple regression model included age, gender, years of education, total intracranial volume, K-MMSE scores, baseline K-NPI delusion scores, and K-NPI non-delusion scores as covariate of no interest.
AD, Alzheimer's disease; MNI, Montreal Neurologic Institute; L, left; R, right; K-MMSE, the Korean version of the mini-mental status examination; K-NPI, the Korean version of the neuropsychiatry inventory.

100 voxels). SPM8 (Wellcome Department of Imaging Neuroscience, London, United Kingdom) was used for the statistical analysis.

Results

Demographic and Clinical Characteristics

Table 1 presents the clinical information of the study participants. The average age was 72.42 years, and 71.4% of participants were female. The baseline K-NPI delusion score was 9.48 [SD = 3.99]. The average dose of risperidone was 1.06 mg (SD = 0.41) per day during the study period.

Association Between Gray Matter Volume and Treatment Response

The voxel-based multiple linear regression analysis showed that the treatment response to risperidone was significantly positively associated with the gray matter volumes of the temporal lobe (both fusiform gyri, the left superior temporal, and the left inferior temporal gyri) and the limbic system (the left amygdala and the left parahippocampal gyrus) after controlling for age, sex, education level, risperidone dose, TIV, and baseline K-MMSE, K-NPI delusion, and K-NPI non-delusion scores (uncorrected P < 0.001, KE > 100 voxels; Table 2, Figure 2).

Discussion

This study aimed to explore the association between baseline gray matter volumes and the treatment response to antipsychotic medication with respect to delusions in patients with AD. We used a voxel-based multiple linear regression model integrated with SPM for this purpose. The main finding of this study was that specific regions of gray matter were associated with the treatment response to antipsychotic medication for delusional symptoms in AD patients with delusions. Our results demonstrated that a stronger treatment response was significantly associated with a larger volume of gray matter in the temporal lobe (both fusiform gyri, the left superior temporal and left inferior temporal gyri) and the limbic system (the left amygdala, the left parahippocampal gyrus).

Our findings are consistent with those of previous studies on schizophrenia that investigated the association between gray matter volume and treatment response in terms of psychotic symptoms. They reported that the volumes of gray matter in the frontal lobe,[12] temporal lobe,[11] limbic system,[13] and basal ganglia[10] were positively associated with treatment response in terms of psychotic symptoms.

In particular, alterations in gray matter volume in the temporolimbic region are commonly reported in patients with AD with psychotic symptoms. AD patients with psychosis have a significantly decreased gray matter volume[34,35] and glucose metabolism[36,37] in medial temporal structures. Our study showed that the temporolimbic regions may be involved in treatment response and in the onset of delusional symptoms in patients with AD. The prefrontal region, temporolimbic region, and striatum are known to be associated with the development of psychotic symptoms.[14,38,39] These regions are not independent of each other. They are highly interconnected, and integrated frontal-temporolimbic-striatal networks mediate many important realities, memory, and emotional processes.[14]

In this study, the gray matter volume of the temporolimbic region, but not the frontal or basal ganglia, was found to be significantly correlated with the treatment response to risperidone with respect to delusions. This may be due to the difference in the developmental mechanism of delusions between schizophrenia and AD.[40] The top-down theory has been proposed in schizophrenia, according to which the initial abnormality is due to frontal lobe dysfunction.[40] Frontal-temporolimbic disconnection due to the dysfunction of top-down modulation can cause failure in reality testing and

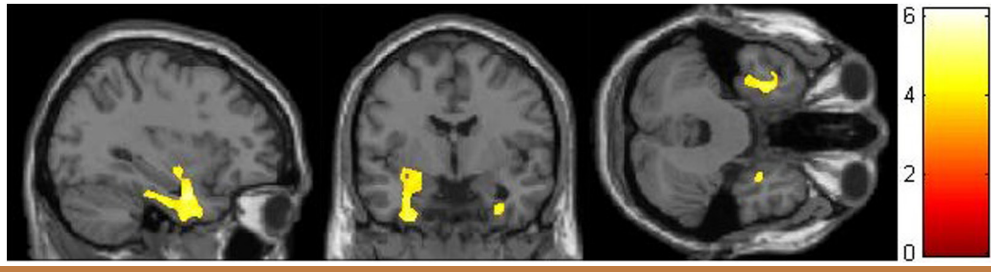

Figure 2. Regions with positive significant association between gray matter volumes and treatment response of delusion after 6 weeks of treatment with risperidone in 21 AD patients with psychosis (P < .001, uncorrected, KE > 100 voxels). The multiple regression model included age, gender, years of education, total intracranial volume, K-MMSE scores, baseline K-NPI delusion scores, and K-NPI non-delusion scores as covariate of no interest.
AD, Alzheimer's disease; K-MMSE, the Korean version of the Mini-Mental State Exam; K-NPI, the Korean version of the Neuropsychiatry Inventory.

self-monitoring.[41] Such failure of reality testing and self-monitoring can make it impossible for people with delusions to recognize their own thoughts as self-generated.[41] The temporolimbic regions can act as a gateway for the flow of information from the frontal lobe to the ventral striatum, thus facilitating frontostriatal input of emotional and contextual importance, respectively, while inhibiting non-salient frontostriatal information flow.[42] Therefore, a primary alteration in the temporolimbic region could cause secondary dyscontrol of frontostriatal interactions; this bottom-up theory suggesting temporolimbic dysfunction as the primary abnormality has been proposed for the development of delusions in AD.[43-45] This hypothesis is supported by functional imaging studies in patients with AD with delusions, showing that temporolimbic metabolism decreases in the early stages of the disease, and prefrontal metabolism decreases as the disease progresses.[45]

Another possible reason is that depending on the type of psychotic symptoms of schizophrenia, specific areas may be more involved in the treatment response.[46] Higher gray matter volume in the prefrontal cortex was associated with the improvement of negative symptoms, and the improvement of positive symptoms was related to greater gray matter volume in the temporal cortex.[47] Since our study only evaluated delusional symptoms in AD, which are similar to the positive symptoms in schizophrenia, it is likely that the temporolimbic region was more involved in the treatment response.

This study had several methodologic limitations, and our findings should be interpreted with caution. First, the sample size was small. Considering the relatively large number of covariates (age, sex, education level, risperidone dose, TIV, and baseline K-MMSE, K-NPI delusion and K-NPI non-delusion scores), a larger sample would be optimal for voxel-based morphometry and for finding an association. Second, in this study, voxel-based morphometry was performed using uncorrected ($P < .001$) thresholds due to the small sample size. The use of such uncorrected ($P < .001$) thresholds could have increased the likelihood of false positives in this study. Third, self-reported data, including data on the history of using antipsychotic drugs, may have caused recall bias. In addition, we did not verify the history of use of other medications (e.g., antidepressants, anti-hypertensive drugs, and anti-diabetic drugs) that can affect gray matter volume.[48] Finally, donepezil, used with risperidone, has been reported to be effective in treating delusions. Many previous studies[49,50] have reported the effects of donepezil on delusional symptoms in patients with AD. Thus, it should be considered that in addition to risperidone, donepezil may have affected the improvement in delusions, even if the donepezil dose was maintained at 5 mg to minimize the effect of donepezil on delusion treatment.

Despite these limitations, to the best of our knowledge, this is the first study on AD with delusions to investigate the association between gray matter volume in the temporolimbic region and the response to antipsychotic treatment.

We found that gray matter volume in the temporolimbic region is associated with the treatment response to risperidone in patients with AD. Considering that the temporolimbic region has been reported to contribute to the development of delusional symptoms,[14,38,39] our findings suggest that the temporolimbic region may play an essential role in the pathophysiological mechanism of delusions.

Ethics Committee Approval: *Ethics committee approval was received for this study from the Institutional Review Board of Pusan National University Hospital (Approval Date: May 21, 2015; Approval Number: 1908-006-081).*

Informed Consent: *Written informed consent was obtained from the participants and their caregivers.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - H.J.J., H.S., Y.M.L., H.J.K., K.P., K.U.C., Y.I.C.; Design - H.J.J., Y.M.L.; Data Collection and/or Processing - H.J.J., H.S., Y.M.L., H.J.K., K.P., K.U.C., Y.I.C.; Analysis and/or Interpretation - H.J.K.; Writing - H.J.J., Y.M.L.; Critical Review - H.J.J., H.S., Y.M.L., H.K.P., H.J.K., K.P., K.U.C., Y.I.C.*

Conflict of Interest: *The authors have no conflict of interest to declare.*

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