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Gray Matter Volumes and Treatment Response of Psychotic Symptoms to Risperidone in Antipsychotic-Naïve Alzheimer's Disease Patients

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ABSTRACT

Objective: The purpose of this study was to determine whether gray matter volumes are associated with treatment response of psychotic symptoms in Alzheimer's disease (AD) patients.

Method: Risperidone, which is commonly used as an atypical antipsychotic drug, was administered in a clinical setting for 6 weeks from April 2012 to February 2013 to 25 antipsychotic-naïve AD patients with psychosis, diagnosed according to Jeste and Finkel's proposed diagnostic criteria for psychosis of Alzheimer's disease. Psychotic symptoms were rated with the Korean version of the Neuropsychiatric Inventory (K-NPI) at baseline and at 6 weeks, and treatment response was defined as the change in K-NPI score from baseline to 6 weeks. Gray matter volumes were measured with magnetic resonance imaging and voxel-based morphometry at baseline. Age, gender, years of education, total intracranial volume, apolipoprotein E genotype, dosage of risperidone, the baseline scores on the Korean version of the Mini-Mental State Examination, and the baseline psychotic and nonpsychotic symptoms scores on the K-NPI were measured as covariates of no interest.

Results: We found that treatment response of psychotic symptoms to risperidone in antipsychotic-naïve AD patients was positively associated with both left and right putamina, left parahippocampal gyrus, and left amygdala volume after controlling covariates of no interest (uncorrected $P < .001$, $K_E > 100$ voxels).

Conclusions: Therefore, we conclude that gray matter volumes of putamina, left parahippocampal gyrus, and left amygdala are associated with treatment response of psychotic symptoms after 6 weeks of treatment with risperidone in antipsychotic-naïve AD patients with psychosis. These results suggest that the volumes of specific gray matter regions probably contribute to treatment response of psychotic symptoms in AD patients.

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In patients with Alzheimer's disease (AD), psychotic symptoms, characterized by delusion or hallucinations, occur in approximately 30%–50% of patients^{1–5} and can develop throughout the course of illness. Untreated psychotic symptoms are distressing to both patients and caregivers, may worsen prognosis, and often result in institutionalization of the patients.^{6–8} Many nonpharmacologic and pharmacologic treatments may be used to ameliorate these psychotic symptoms. Antipsychotic drugs in particular have been shown to have a moderate benefit (approximately 18%–26%) over placebo in treating psychotic symptoms of AD patients.⁹

However, AD patients with psychosis have a variable treatment response to antipsychotic drugs^{4,9} and the factors associated with treatment response are unclear. One associating factor that has been suggested is gray matter volume including basal ganglia. Several studies^{10–13} of patients with schizophrenia have shown that gray matter volumes are associated with treatment response of psychotic symptoms. These studies reported that the putamen,^{10,12} caudate,^{11,12} and thalamus¹² are positively associated with treatment response of psychotic symptoms to antipsychotic drugs in patients with schizophrenia.

Many previous functional neuroimaging studies^{14,15} and postmortem studies¹⁶ support a shared etiology for psychosis in AD and schizophrenia. Therefore, it is possible that psychosis in AD and schizophrenia share the factors associated with treatment response to antipsychotic drugs. Because treatment with antipsychotic drugs can cause increases in gray matter volumes,¹¹ studies including only antipsychotic-naïve AD patients might be more suitable in order to avoid the confounding effects of previous antipsychotic exposure.

The purpose of this study was to determine whether gray matter volume in antipsychotic-naïve AD patients is associated with the treatment response of psychotic symptoms to antipsychotic drugs. For this purpose, risperidone, which is commonly used as an atypical antipsychotic drug, was administered for 6 weeks to antipsychotic-naïve AD patients with psychosis.

METHOD

Participants

Twenty-nine AD patients with psychosis who were receiving treatment from a memory impairment clinic at the Department of Psychiatry, Pusan National University

- Psychotic symptoms in patients with Alzheimer's disease (AD) are common, but the factors associated with treatment response to antipsychotic medication are unclear.
- If patients with AD have psychotic symptoms, consider that both putamina, left parahippocampal gyrus, and left amygdala volumes could be positively associated with treatment response to antipsychotic medication.

Hospital in Busan, Korea, were initially included in this study (NCT01198093) between April 2012 and February 2013. Written, informed consent was obtained from all participants, and this study was approved by the Pusan National University Hospital Institutional Review Board.

All the participants included in this study met the National Institute of Neurologic and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria¹⁷ for probable AD. Criteria¹⁸ for psychosis of AD required the presence of persistent or intermittent delusions, hallucinations, or both for at least 1 month, and scores of 6 or higher (severity \times frequency) on the sum of the delusion and hallucination items on the Korean version of the Neuropsychiatric Inventory (K-NPI).¹⁹ All participants had no previous history of taking any antipsychotic medication and had their first experience of psychotic symptoms.

Participants were excluded from participation in this study if they had (1) an Axis I diagnosis of delirium, schizophrenia, bipolar disorder, or mood disorder with psychotic features; (2) clinically active cerebrovascular disease or other conditions causally related to cognitive impairment (eg, severe organ failure, metabolic or hematologic disorders, clinically significant abnormal laboratory findings, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease, or epilepsy); (3) a score of <5 or >24 on the Korean version of the Mini-Mental State Examination (K-MMSE).²⁰

Study Design

To determine whether gray matter volume in antipsychotic-naïve AD patients is associated with the treatment response of psychotic symptoms, the atypical antipsychotic risperidone was administered for 6 weeks to 29 antipsychotic-naïve AD patients with psychosis. The initial dose of risperidone was 0.5 mg/d. Titration of dosing was conducted every 7 days depending on the patient's condition. The mean \pm SD dosage of risperidone was 0.93 ± 0.32 mg/d during the study period. Concomitant anticholinergics or benzodiazepines were not administered. Donepezil 5 mg/d as an acetylcholinesterase inhibitor also was taken by all 29 AD patients, and the dosage of donepezil was not changed during the study period.

Psychotic symptoms were rated with the K-NPI¹⁹ at baseline and at 6 weeks, and treatment response was defined as the change in K-NPI score from baseline to 6 weeks. Gray matter volumes were measured with magnetic resonance

imaging (MRI) and voxel-based morphometry (VBM) at baseline. Age, gender, years of education, total intracranial volume (TIV), apolipoprotein E (apoE) genotype, dosage of risperidone, the baseline K-MMSE scores, and the baseline K-NPI psychotic and nonpsychotic symptoms scores were measured as covariates of no interest.

Figure 1 shows the flow of patients through the study. A total of 4 AD patients with psychosis were dropped out of the study: 3 patients discontinued treatment because of intolerable adverse effects including rigidity ($n=2$) and dizziness ($n=1$), and 1 patient was excluded because the MRI data contained too much noise and could not be used for VBM analysis. This left a final group of 25 AD patients with psychosis who completed the study.

Clinical Evaluation and Neuropsychological Test

All participants underwent a comprehensive evaluation consisting of the following assessments: history taken from the patient and informant, medical and neurologic examinations, the K-MMSE²⁰ for general cognitive evaluation, the K-NPI for severity of behavioral and psychotic symptoms of dementia, and the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K)²¹ as a comprehensive neuropsychological battery.

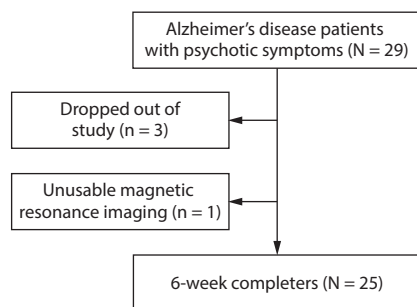
The K-NPI¹⁹ has been proven valid and reliable and has been used in clinical study in Korea. The K-NPI is a convenient instrument that evaluates both the severity and the frequency of abnormal behaviors including delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior and neurovegetative changes including nighttime behavior (eg, sleep disorders) and eating changes (eg, appetite disorders). We considered the sum of the delusion score (severity \times frequency) and hallucination score (severity \times frequency) on the K-NPI as the severity of psychotic symptoms of AD.

Fasting samples were collected and immediately sent to the biochemical laboratory for processing, and apoE genotyping was performed using the restriction enzyme isoform genotyping method.²²

We also measured the cognitive function of the AD patients with 7 neuropsychological tests included in the CERAD-K²¹: verbal fluency, animal category; 15-item Boston Naming Test; word list memory; word list recall; word list recognition; constructional praxis; and constructional recall. We also used the Korean version of the Frontal Assessment Battery (FAB-K)²³ to examine the frontal or executive function; the FAB-K is known as a valid and reliable instrument for evaluating frontal lobe function in the elderly. We used the Seoul Instrumental Activities of Daily Living (SIADL),²⁴ which was validated in Korea as the standardized ADL scale. The SIADL consists of 15 items that address an individual's ability to engage in more complex tasks, such as shopping or using the telephone, and impairment severity is scored from 0 to 3 (0: no impairment, 1: slight impairment, 2: moderate impairment, 3: severe impairment) for all items. Thus, the maximum score of SIADL is 45, and scores of ≤ 7 indicate normal, complex activities of daily living.

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Figure 1. Flowchart of Alzheimer's Disease Patients Through the Study



Imaging Data Analysis

MRI data acquisition. All participants underwent MRI scans of T1-weighted images (T1WI) on a Siemens Trio TIM 3T scanner (Siemens Healthcare GmbH, Erlangen, Germany). T1WI were acquired using a 3-dimensional magnetization prepared rapid gradient echo (3D MP-RAGE) sequence with the following parameters: repetition time (TR) = 1800 ms, echo time (TE) = 2.07 ms, inversion time (TI) = 900 ms, flip angle = 12°, acquisition matrix = 256 × 256, field of view (FOV) = 250 × 250 mm², slice thickness = 1 mm, total number of slices = 256. All image acquisitions were ensured to have the same slice orientation paralleled to the anterior commissure and posterior commissure line.

Image preprocessing for VBM. The VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm>) that is incorporated in statistical parametric mapping 8 (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>)²⁵ was used to perform the analysis of brain structural imaging. In this process, all images were spatially normalized using combinations of affine linear transformation and nonlinear registration to the standard Montreal Neurologic Institute (MNI) template and segmented into gray matter, white matter, and cerebrospinal fluid.²⁶ Segmented gray matter images were modulated to compensate the volumetric effects of expansion or shrinking employed in spatial normalization by multiplying the voxel intensity with the Jacobian determinants reflecting the parameters for fitting a voxel in native space to a corresponding voxel in template space. The modulated images were then smoothed with an 8-mm full-width half-maximum isotropic Gaussian kernel.

Statistical Analysis

A voxel-based simple regression model integrated in SPM was used to determine whether gray matter volume in antipsychotic-naïve AD patients was associated with the treatment response of psychotic symptoms to risperidone. A voxel-based multiple regression model was used to control covariates of no interest (ie, age, gender, years of education, TIV, apoE genotype, dosage of risperidone, the baseline K-MMSE scores, and the baseline K-NPI psychotic and nonpsychotic symptoms scores). Statistical significance level was considered at $P < .001$ uncorrected at voxel level with

Table 1. Demographic and Clinical Characteristics of Antipsychotic-Naïve Alzheimer's Disease Patients (N = 25) With Psychosis^a

Characteristic	Mean ± SD
Age, y	76.28 ± 8.21
Female, n (%)	19 (76.0%)
Education, y	5.56 ± 5.01
Total intracranial volume (mm ³)	1,490.72 ± 143.87
K-MMSE	16.84 ± 5.11
Baseline K-NPI psychotic symptoms score	9.48 ± 3.99
Baseline K-NPI nonpsychotic symptoms score	28.76 ± 21.52
Dosage of risperidone (mg/d)	0.93 ± 0.32

^aAll values are mean ± SD unless otherwise stated.

Abbreviations: K-MMSE = Korean version of the Mini-Mental State

Examination, K-NPI = Korean version of the Neuropsychiatric Inventory.

Table 2. Voxel-Based Simple Regression Analysis for Regions With Positive Significant Association^a Between Gray Matter Volume and Treatment Response of Psychotic Symptoms After 6 Weeks of Treatment With Risperidone in Antipsychotic-Naïve Alzheimer's Disease Patients (N = 25) With Psychosis

Anatomic Region	Cluster Size ^b	MNI Coordinates (mm)			T Value
		x	y	z	
Left putamen	1,690	-25	-5	-5	5.84
Right putamen	612	30	-3	-1	4.36

^aUncorrected $P < .001$, $K_E > 100$ voxels.

^bFull width at half maximum (FWHM) isotropic Gaussian kernel used for smoothing.

Abbreviations: K-MMSE = Korean version of the Mini-Mental State

Examination, K-NPI = Korean version of the Neuropsychiatric Inventory,

MNI = Montreal Neurologic Institute.

the extent threshold of contiguous 100 voxels (uncorrected $P < .001$, $K_E > 100$ voxels).

RESULTS

Demographic and Clinical Characteristics

Table 1 shows the demographic and clinical characteristics of the antipsychotic-naïve AD patients with psychosis analyzed in this study. Our study consisted mostly of female subjects (76%). The mean scores of baseline K-NPI psychotic symptoms was 9.48, and the mean dosage of risperidone was 0.93 mg/d.

Correlations Between Gray Matter Volume and Treatment Response in AD Patients With Psychosis

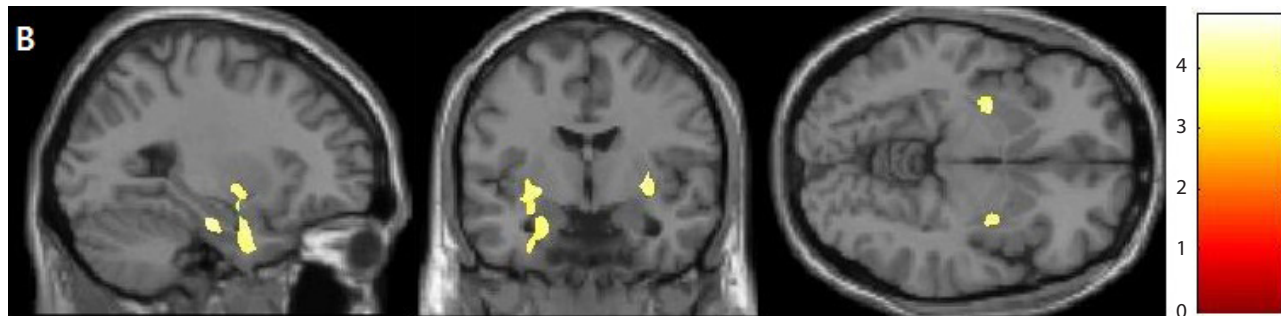
To determine whether gray matter volume in antipsychotic-naïve AD patients is associated with the treatment response of psychotic symptoms, we analyzed volumetric MRI scans of T1WI acquired using a 3D MP-RAGE (uncorrected $P < .001$, $K_E > 100$ voxels). In a simple regression model, treatment response of psychotic symptoms to risperidone was positively associated with both left and right putamen volume (Table 2, Figure 2). After controlling age, gender, years of education, TIV, apoE genotype, dosage of risperidone, the baseline K-MMSE scores, and the baseline K-NPI psychotic and nonpsychotic

Figure 2. Regions With Positive Significant Association^a Between Gray Matter Volumes and Treatment Response of Psychotic Symptoms After 6 Weeks of Treatment With Risperidone in Antipsychotic-Naïve Alzheimer's Disease Patients (N = 25) With Psychosis^b

A. Voxel-Based Simple Regression Model



B. Voxel-Based Multiple Regression Model^c



^aUncorrected $P < .001$, $K_E > 100$ voxels.

^bThe multiple regression model included age, gender, years of education, total intracranial volume, apolipoprotein E genotype, dosage of risperidone, the baseline K-MMSE scores, the baseline K-NPI psychotic and nonpsychotic scores as covariate of no interest.

^cColor bar indicates the range of T values.

Abbreviations: K-MMSE = Korean version of the Mini-Mental State Examination scores, K-NPI = Korean version of the Neuropsychiatric Inventory.

symptoms scores by multiple regression model, treatment response of psychotic symptoms to risperidone was positively associated with both left and right putamina, left parahippocampal gyrus, and left amygdala (Table 3, Figure 2).

DISCUSSION

In this study, we found by a simple regression model that treatment response was positively associated with both left and right putamina volumes. Even after controlling variables (ie, age, gender, years of education, TIV, apoE genotype, dosage of risperidone, the baseline K-MMSE scores, and the baseline K-NPI psychotic and nonpsychotic symptoms scores) by multiple regression model, treatment response was positively associated with both putamina, left parahippocampal gyrus, and left amygdala.

Our finding that putamina are associated with the treatment response of psychotic symptoms in antipsychotic-naïve AD patients is similar to the results of previous studies^{10–13} that have investigated the association between basal ganglia volumes and treatment response of psychotic symptoms in patients with schizophrenia. These studies reported that putamen,^{10,12} caudate,^{11,12} and thalamus¹² are positively associated with treatment response of

Table 3. Voxel-Based Multiple Regression Analysis^a for Regions With Positive Significant Association^b Between Gray Matter Volume and Treatment Response of Psychotic Symptoms After 6 Weeks of Treatment With Risperidone on Antipsychotic-Naïve Alzheimer's Disease Patients (N = 25) With Psychosis

Anatomic Region	Cluster Size	MNI Coordinates (mm)			T Value
		x	y	z	
Right putamen	450	31	-2	1	4.85
Left parahippocampal gyrus	1,630	-29	-20	-24	4.76
Left amygdala	1,630	-28	-1	-28	4.37
Left putamen	661	-27	-5	-5	4.25

^aMultiple regression model included age, gender, years of education, total intracranial volume, apolipoprotein E genotype, dosage of risperidone, K-MMSE scores, baseline K-NPI psychotic and nonpsychotic symptoms scores as covariates of no interest.

^bUncorrected $P < .001$, $K_E > 100$ voxels.

Abbreviations: K-MMSE = Korean version of the Mini-Mental State Examination, K-NPI = Korean version of the Neuropsychiatric Inventory, MNI = Montreal Neurologic Institute.

psychotic symptoms to antipsychotic drugs in patients with schizophrenia.

According to contemporary theories of psychosis,^{27–29} a variety of pathological processes, including neonatal hypoxia, cholinergic denervation, and cortical and subcortical lesions, may lead to the sensitization of striatal dopaminergic neurons and the expression of psychotic symptoms. In

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schizophrenia, deficits in cortical development leave striatal dopaminergic neurons more responsive to dopamine-releasing stimuli, including psychostimulants.³⁰ A similar process of sensitization may be occurring in AD, as studies of rodents have shown that cholinergic denervation increases striatal dopamine release in response to amphetamine challenge and is accompanied by psychotic-like behavior.³¹

One postmortem study¹⁶ reported that in AD patients with psychosis, striatal dopamine (D₂/D₃) receptor availability is increased to an extent comparable to that observed in drug-naïve patients with schizophrenia. Another postmortem study³² has shown that an increase in mineralization (especially iron) of the basal ganglia has a modulatory effect on the dopamine receptor and its role as a cofactor for tyrosine hydroxylase, which might lead to an increased manifestation of psychosis in AD patients. Several functional neuroimaging studies of AD patients with psychosis reported altered perfusion within left and right striata.^{15,33,34}

These findings of postmortem studies and functional neuroimaging studies reveal that psychosis in AD and schizophrenia have a shared etiology,^{14–16} and excessive dopamine activity in basal ganglia is the final common pathway in the development of psychosis. The association between the basal ganglia volume and treatment response of psychotic symptoms to antipsychotic drugs in AD patients with psychosis might be supported by the increase of both perfusion in functional neuroimaging and postsynaptic dopamine (D₂/D₃) receptor availability located in this region.³⁵

In addition to the volume of the putamina, we found that the volume of the left parahippocampal gyrus and left amygdala are positively associated with the treatment response of psychotic symptoms after controlling variables by multiple regression model. Although there are few studies that have shown the association between treatment response of psychotic symptoms and volumes of the parahippocampal gyrus and amygdala, previous published studies reported that these regions are associated with psychotic symptoms. The parahippocampal gyrus, which is referred to as a critical site for episodic memory and unpleasant emotional processing, has also been shown to be involved in persecutory delusion.³⁶ Mégevand and colleagues³⁷ found that hallucination could be evoked by direct electrical stimulation of the parahippocampal area. Harding and colleagues³⁸ showed an association between hallucinations and high densities of Lewy bodies in the parahippocampal gyrus. The amygdala is known to be important for processing emotions, especially fear and anxiety.³⁹ Sumi and colleagues⁴⁰ reported that presenile dementia with psychosis is associated with a high density of neurofibrillary tangle and neuronal loss in the amygdala. In a previous single photon emission computed tomography study of correlation between content-based categorization of delusional ideas and dysfunction of category-specific brain regions, Nakatsuka and colleagues⁴¹ showed that cerebral blood flow decreased at the amygdala contributed to the delusion that a patient's residence was not

his or her home. A recent study⁴² of correlation between gray matter volumes and treatment response in patients with bipolar disorder reported that decreased amygdalae volumes are associated with nonresponse to lithium. According to our finding, parahippocampus and amygdalae volumes in AD patients with psychosis also seem to be positively related to risperidone treatment response.

A recent retrospective case-control study⁴³ reported that the absolute effect of antipsychotics on mortality in elderly patients with dementia may be higher than previously reported and increases with dose. Thus, the decision to use such antipsychotic medication is generally in response to profoundly distressing and potentially dangerous behaviors of patients.⁴⁴ Most clinical practice guidelines^{45,46} suggest that people with dementia who develop psychotic symptoms can be offered an antipsychotic medication in the first instance only if they are severely distressed or there is an immediate risk of harm to the person or others.

The results in this study have several limitations to be interpreted with caution. First, this study was limited by a relatively small sample size. Although we were able to detect effects with this sample size, a larger sample would be optimal for VBM analysis. Second, there is an increased risk for false positive results because we used uncorrected ($P < .001$) thresholds for VBM analysis due to small sample size. Third, to reflect real geriatric treatment settings, we did not exclude the patients who take other medications such as drugs for diabetes and hypertension, which are common in elderly populations. However, these other medications might affect treatment response of psychotic symptoms in AD patients. Fourth, it is possible that delusion and hallucination may have different neurobiological and neuroimaging substrates, characterized by different pathological and cognitive trajectories.^{36,47} Therefore, in further study, clearly distinguishing between these 2 psychotic symptoms might be needed to investigate whether gray matter volume is associated with treatment response of psychotic symptoms in AD patients.

Despite these limitations, our results are significant in the sense that, to the best of our knowledge, this is the first study to investigate whether gray matter volume is associated with the treatment response of psychotic symptoms to antipsychotic drugs in antipsychotic-naïve AD patients.

In conclusion, we found that gray matter volumes of putamina, left parahippocampal gyrus, and left amygdala are associated with the treatment response of psychotic symptoms after 6 weeks of treatment with risperidone in antipsychotic-naïve AD patients with psychosis. These results suggest that the volumes of specific gray matter regions probably contribute to treatment response of psychotic symptoms in AD patients.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Helen Lavretsky, MD, MS, at hlavretsky@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.