Decreased gray matter volume is associated with the subtypes of psychotic symptoms in patients with antipsychotic-naïve mild or moderate Alzheimer's disease: A voxel-based morphometry study

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Abstract
The purpose of this study was to investigate the association between brain regional gray matter volume and two subtypes of psychotic symptoms, namely paranoid and misidentification subtypes, in antipsychotic-naïve mild or moderate Alzheimer's disease (AD) patients. Forty AD patients with psychotic symptoms and 25 AD patients without psychotic symptoms were assessed for cognitive and functional impairment. Presence and subtype of psychotic symptoms were assessed by using the delusion and hallucination subscale of the Korean Neuropsychiatric Inventory (K-NPI). Structural MRI images were acquired on a 3 T scanner, and were analyzed using voxel-based morphometry (VBM) for automated analysis. The misidentification subtype is associated with more severe gray matter atrophy, and paranoid subtype is associated with less severe gray matter atrophy compared to non-psychosis group. These results suggest that the misidentification, the paranoid subtype and the non-psychosis group have a distinct neural correlation.

1. Introduction
Psychotic symptoms, such as delusion or hallucination, occur in approximately 30–50% in patients with Alzheimer's disease (AD) (Wragg and Jeste, 1989; Mendez et al., 1990). Caring for such patients is often difficult. Untreated psychotic symptoms are distressing to both patients and caregivers (Ikeda et al., 2003), may worsen prognosis (Stern et al., 1997), and often result in institutionalization of the patients (Steele et al., 1990). Given the modest efficacy and high incidence of adverse effects associated with antipsychotic medication in AD patients with psychotic symptoms (Schneider et al., 2006), there is a need for research investigating the biological mechanism underlying psychotic symptoms to develop a better treatment for these distressing symptoms (Jeste et al., 2008).

Although many structural (Howanitz et al., 1995; Serra et al., 2010) and functional neuroimaging (Starkstein et al., 1994; Kotrla et al., 1995; Sultzer et al., 1995; Hirono et al., 1998; Staff et al., 1999; Sultzer et al., 2003; Nakano et al., 2006) studies have investigated the neurobiological correlations of psychotic symptoms in AD patients, there is a lack of consensus among the results of these studies. Some studies have shown a significant correlation between psychotic symptoms and neuroanatomical structures, such as the frontal cortex (Sultzer et al., 1995; Sultzer et al., 2003; Nakano et al., 2006), the right temporal (Starkstein et al., 1994; Nakano et al., 2006), the left temporal (Starkstein et al., 1994; Hirono et al., 1998), the right parietal (Nakano et al., 2006), and the occipital cortex (Hirono et al., 1998), while other studies (Howanitz et al., 1995; Kotrla et al., 1995; Staff et al., 1999; Serra et al., 2010) have failed to find any correlation. The lack of consensus may be related to the heterogeneity of psychotic symptoms among AD patients. Most of the previous AD psychosis studies (Starkstein et al., 1994; Howanitz et al., 1995;...
had had persistent or intermittent delusions, hallucinations or both. The subject was considered to have psychotic symptoms if he or she met the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer Disease and Related Disorders Association (NINCDS ADRDA) criteria for probable AD (McKhann et al., 1984); (2) had no previous history of any anti-psychotic medication; (3) were at least 60 years old at the first visits; (4) have 0.5, 1 or 2 in CDR score. The subjects were excluded in this study if they had: (1) an axis I diagnosis of dementia, schizophrenia, bipolar disorder, major depressive disorder with psychotic feature or other psychiatric illness; (2) clinically active cerebrovascular disease or other neurological and medical conditions that could affect cognitive function; (3) absence of a reliable informant. Written informed consents were obtained from all of the subjects and their relatives, and this study was approved by the Pusan National University Hospital Institutional Review Board.

2.2. Assessment of Clinical, Cognitive and Functional Status

A comprehensive evaluation was conducted with all subjects and their reliable informants to assess clinical, cognitive and functional status: (1) the K-NPI (Choi et al., 2000) for presence and severity of psychotic and other neuropsychiatric symptoms of dementia; (2) the K-MMSE (Han et al., 2008) for general cognitive evaluation; (3) CERAD-K (Lee et al., 2002) for comprehensive neuropsychological function; (4) the Korean version of the Frontal Assessment Battery (FAB-K) (Kim et al., 2010) for the frontal or executive function. (5) Seoul Instrumental Activities of Daily Living (SIADL) (HM KJ KE et al., 2004) for severity of functional impairment; (6) Clinical Dementia Rating Scales and Global Deterioration Scales for disease severity.

We used K-NPI to assess psychotic symptoms and other non-psychotic neuropsychiatric symptoms. The K-NPI has been proven valid and reliable (Choi et al., 2000) and has been used in clinical study in Korea. The K-NPI (Choi et al., 2000) is a convenient instrument that evaluates both the severity and the frequency of abnormal behaviors including delusion, hallucination, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior and neurovegetative changes including night time behavior and eating change. We considered the sum of the delusion score (severity × frequency) and hallucination score (severity × frequency) on K-NPI as K-NPI psychotic score of AD. We considered the sum of the other non-psychotic scores as K-NPI non-psychotic score of AD.

We assessed cognitive function by using CERAD-K (Lee et al., 2002) to examine the functional capacity of several cognitive domains: (1) memory (word list delayed recall); (2) language (the Korean version of the Boston Naming Test [K-BNT]); and (3) visuospatial function (constructional apraxia). We also used FAB-K (Kim et al., 2010) to examine the frontal or executive function. The FAB-K was known as a valid and reliable instrument for evaluating frontal lobe function in the elderly (Kim et al., 2010).

We used Seoul instrumental activities of daily living (SIADL) (Hu HM KJ KE, 2004) which was validated in Korea as the standardized ADL scale to assess the severity of functional impairment. The SIADL consist 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 1 (no impairment) to 3 for all items. Thus, the maximum score of SIADL is 45 and scores of ≤ 7 indicate normal complex ADL.

2.3. Imaging data analysis

2.3.1. MRI data acquisition

All participants underwent MRI scans of T1-weighted images (T1WI) on a Siemens (Erlangen, Germany) Trio TIM 3 T scanner. T1WI were acquired using a 3D magnetization prepared rapid
gradient echo (3D MP-RAGE) sequence with 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 the same slice orientation paralleled to the anterior commissure and posterior commissure line.

2.3.2. Image pre-processing for Voxel Based Morphometry (VBM)

The VBM 8 toolbox (http://dbm.neuro.uni-jena.de/vbm) which is incorporated in statistical parametric mapping 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm) (Ashburner and Friston, 2000) was used to perform the analysis of brain structural imaging. In this process, all images were spatially normalized using combinations of affine linear transform and nonlinear registration to the standard Montreal Neurological Institute (MNI) template and segmented into gray matter, white matter and cerebrospinal fluid (Mazziotta et al., 2001). 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 corresponding voxel in template space. The modulated images were then smoothed with an 8-mm full width half maximum (FWHM) isotropic Gaussian kernel.

2.4. Statistical analysis

Pearson’s chi-square for categorical data and Kruskall-Wallis test for continuous variables were used to evaluate differences in demographic or clinical characteristics between the three groups (those with misidentification subtype, those with paranoid subtype, and those without psychotic symptoms) of AD patients. Analyses for demographic or clinical characteristics were performed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL).

Factorial analysis of covariance integrated in SPM was used to investigate the association between brain regional gray matter volume and two subtypes of psychotic symptoms in AD patients after controlling covariates of no interest (i.e. age, gender, education, total intracranial volume, CDR score and the K-NPI non-psychotic scores). Statistical significant level was considered at P < 0.001 uncorrected at voxel level with the extent threshold of contiguous 100 voxels (P < 0.001, uncorrected, Ke > 100 voxels).

3. Results

3.1. Demographic and clinical characteristics

Table 1 compares the demographic and clinical characteristics between the groups. There were no significant differences in age, gender, education, total intracranial volume (TIV) and K-MMSE scores between the groups. Those with misidentification subtype displayed more severe impairment on cognition, daily function and neuropsychiatric status than those without psychotic symptoms: 2 points lower on K-BNT; 1 point lower on word list delayed recall; 9 points higher on SIADL; 18 points higher on K-NPI non-psychotic score. Those with misidentification subtype displayed more severe impairment on daily function than those with paranoid subtype, although cognition and neuropsychiatric status did not differ significantly: 8 points higher on SIADL. There were no significant differences on cognition, daily function and neuropsychiatric status between those with paranoid subtype and without psychotic symptoms, except the score of K-BNT differs significantly: 4 points lower on K-BNT in those with paranoid subtype. Those with misidentification subtype displayed more severe impairment on global dementia severity than the other groups, although CDR-SOB and GDS did not differ significantly: 0.32 points higher on CDR than those with paranoid subtype; 0.34 points higher on CDR than those without psychotic symptoms. Age, gender, education, total intracranial volume, CDR score and the K-NPI non-psychotic scores were selected as covariates in analysis for the association between brain regional gray matter volume and two subtypes of psychotic symptoms in AD patients.

3.2. The difference in gray matter volumes between the groups

Table 2 and Fig. 1 compare gray matter volumes between the groups by using volumetric MRI scans of T1-weighted images. In factorial analysis of covariance (ANCOVA) model, significant differences in gray matter volume between the groups was found (P < 0.001, uncorrected, Ke > 100 voxels). Patients with misidentification subtype, compared with those without psychotic symptoms, showed a more significant decrease in the right middle frontal gyrus, the right middle temporal gyrus, the right inferior
Table 2
The regions of more significantly decreased gray matter volume between three subtypes (paranoid subtype, misidentification subtype and non-psychosis subtype) in AD patients.

<table>
<thead>
<tr>
<th>Anatomical region</th>
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<th>MNI coordinates (mm)</th>
<th>Cluster size</th>
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<td>Misidentification vs Non-psychosis&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>R inferior parietal lobe</td>
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<td>4.75</td>
<td>53</td>
<td>–35</td>
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<td>R lingual gyrus</td>
<td>4.79</td>
<td>4.33</td>
<td>9</td>
<td>–85</td>
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<tr>
<td>L cuneus</td>
<td>4.41</td>
<td>4.03</td>
<td>–10</td>
<td>–85</td>
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<tr>
<td>R middle frontal gyrus</td>
<td>4.37</td>
<td>4.01</td>
<td>30</td>
<td>29</td>
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<tr>
<td>R superior occipital gyrus</td>
<td>4.13</td>
<td>3.81</td>
<td>38</td>
<td>–77</td>
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<tr>
<td>R middle temporal gyrus</td>
<td>3.99</td>
<td>3.70</td>
<td>46</td>
<td>–60</td>
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<td>Misidentification vs Paranoid&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>R middle frontal gyrus</td>
<td>6.48</td>
<td>5.50</td>
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<td>R medial frontal gyrus</td>
<td>6.30</td>
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<td>L middle frontal gyrus</td>
<td>5.81</td>
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<td>L medial frontal gyrus</td>
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<td>4.98</td>
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<td>L superior frontal gyrus</td>
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<td>4.80</td>
<td>–20</td>
<td>28</td>
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<tr>
<td>L inferior frontal gyrus</td>
<td>5.41</td>
<td>4.77</td>
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<tr>
<td>R middle occipital gyrus</td>
<td>5.22</td>
<td>4.64</td>
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<td>–93</td>
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<tr>
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<td>4.58</td>
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<td>21</td>
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<tr>
<td>R middle temporal gyrus</td>
<td>4.84</td>
<td>4.36</td>
<td>42</td>
<td>–75</td>
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<td>Non-psychosis vs Paranoid&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>R middle frontal gyrus</td>
<td>5.36</td>
<td>4.74</td>
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<td>21</td>
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<tr>
<td>R lateral frontal gyrus</td>
<td>4.96</td>
<td>4.45</td>
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<td>L middle frontal gyrus</td>
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<td>R middle frontal gyrus</td>
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<td>L cuneus</td>
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<td>3.88</td>
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<tr>
<td>L middle frontal gyrus</td>
<td>4.16</td>
<td>3.84</td>
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<tr>
<td>R superior frontal gyrus</td>
<td>4.11</td>
<td>3.88</td>
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<td>47</td>
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<tr>
<td>L lingual gyrus</td>
<td>4.09</td>
<td>3.78</td>
<td>–17</td>
<td>–96</td>
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</table>

<sup>a</sup> Regions of atrophy in Misidentification subtype compared to Non-psychosis subtype.

<sup>b</sup> Regions of atrophy in Misidentification subtype compared to Paranoid subtype.

parietal lobe, the right inferior parietal lobe and the occipital lobe (right lingual gyrus, left cuneus and right occipital gyrus). Patients with misidentification subtype, compared with those with paranoid subtype, showed a more significant decrease in the frontal lobe (both middle frontal and medial frontal, both superior frontal and left inferior frontal), the right middle temporal gyrus and the right middle occipital gyrus. Patients without psychotic symptoms, compared with those with paranoid subtype, showed a more significant decrease in the frontal lobe (both medial frontal, both middle frontal, left inferior frontal and right superior frontal), the left middle temporal gyrus and the left occipital lobe (left cuneus and left lingual gyrus). No other supra-threshold clusters of increased areas were found between the groups Figs. 2 and 3.

4. Discussion

The present study examined the association between brain regional gray matter volume and two subtypes of psychotic symptoms, namely paranoid and misidentification subtypes, in antipsychotic-naïve mild or moderate AD patients. In this study, we found that there are significant differences on gray matter volume between the groups (paranoid subtype, misidentification subtype and non-psychosis group) in AD. The misidentification subtype is associated with more severe gray matter atrophy, and paranoid subtype is associated with less severe gray matter atrophy compared to non-psychosis group.

Compared with those without psychotic symptoms, the patients with the misidentification subtype showed a more significantly decrease in the right middle frontal gyrus, the right middle temporal gyrus, the right inferior parietal lobe and the occipital lobe (right lingual gyrus, left cuneus and right superior occipital gyrus). This finding is consistent with the findings in previous studies that the misidentification subtype is associated with deficits in the right cerebral hemisphere (Forstl et al., 1994a; Devinsky, 2009). Several researchers have demonstrated relationships between delusional misidentification and the right cerebral hemisphere deficits (Forstl et al., 1994a). For example, Forstl and colleagues reported that compared to non-delusional AD patients, AD patients with delusional misidentification had a decreased volume in the right frontal lobe and an increase in EEG delta and theta power over the central and right cerebral hemisphere (Forstl et al., 1994a). Serra and colleagues found that delusional misidentification was associated with decreased gray matter volume in the right medial temporal lobe in AD patients (Serra et al., 2010). Nakano and colleagues used SPECT to examine the correlation between neuroanatomical structures and delusional misidentification in AD (Nakano et al., 2006). They found that in the misidentification subtype, there was decreased perfusion in the left lingual gyrus and right middle occipital gyrus (Nakano et al., 2006). The right inferior temporal lobe is associated with emotional familiarity with people (Gainotti, 2007), the right posterior temporoparietal regions are associated with emotional familiarity with places (Gainotti, 2007), the right parieto-occipital lesions may produce dysmorphic distortions (Nakano et al., 2006) and the right frontal lobe is associated with monitoring of the appropriateness of familiarity decisions (Gainotti, 2007). Thus, the deficits in the right cerebral hemisphere cause a sense of unfamiliarity concerning places and people, which lead to misperception and self-corrective dysfunction (Malloy and...
continuum of abnormality of familiarity (Sno, 1994). Thus, the agnosia. However, delusional misidenti
cation may result from elaboration of these misperceptions and self-corrective dysfunction. Delu-
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In this study, we found that the misidentification subtype, compared with paranoid subtype, is associated with a more significantly decrease in the frontal lobe (both middle frontal and medial frontal, both superior frontal and left inferior frontal), the right middle temporal gyrus and the right middle occipital gyrus. This finding is broadly consistent with the findings in previous studies that misidentification subtype is associated with a wider involvement of the cerebral region (Lee et al., 2006), usually frontal (von Gunten et al., 2005; Gainotti, 2007) with variable temporal (von Gunten et al., 2005; Gainotti, 2007), parietal (Nakano et al., 2006) or occipital involvement (Nakano et al., 2006). It is unclear whether misidentification subtype and paranoid subtype represent two distinct subtypes, or are a part of the same continuum, manifesting at different time points because mis-
identification subtype appears at a somewhat later age compared to the paranoid subtype, and shows lower MMSE scores at onset (Forstl et al., 1994b). In this study, those with misidentification subtype also displayed more severe impairment on CDR score representing global dementia severity than those with the other subtypes. Thus, in order to correct the effect of global dementia severity on gray matter volume between the groups, we selected CDR scores as covariates. After controlling the effects of CDR and other variables (i.e. age, gender, education, total intracranial vo-

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In this study, those without psychotic symptoms, compared with those with paranoid subtype, showed a significantly decreased volume of gray matter in the frontal lobe (both medial frontal, both middle frontal, left inferior frontal and right superior frontal), the left middle temporal gyrus, and the left occipital lobe (left cuneus and left lingual gyrus). In terms of patients with the paranoid subtype showing a decrease in gray matter volume, compared to patients without psychotic symptoms, this finding was not in accordance with our expectations. Many of the previous functional neuroimaging studies have shown a significant neuroanatomical correlations to psychotic symptoms, such as the frontal cortex (Sultzer et al., 1995; Sultzer et al., 2003; Nakano et al., 2006), the right temporal (Starkstein et al., 1994; Nakano et al., 2006), the left temporal (Starkstein et al., 1994; Hirono et al., 1998), the right parietal (Nakano et al., 2006), and the occipital cortex (Hirono et al., 1998). However, most of these studies considered the psychotic symptoms or delusions as a single entity. There are a few structural neuroimaging studies showing the association of brain regional gray matter volume with paranoid subtype, although many structural neuroimaging studies have been conducted. One structural neuroimaging study (Whitehead et al., 2011) showed that in female paranoid subjects, there was cortical thinning in the left medial orbitofrontal cortex and the left superior temporal cortex. However, in multivariate analysis including cognitive scores, the findings lost significance in the paranoid group (Whitehead et al., 2011). Our finding that those without psychotic symptoms showed more of a significant decrease in gray matter volume compared with those with the paranoid subtype suggests that paranoid delusion is not likely to only occur due to decreased gray matter volume. In a functional neuroimaging study, Geroldi and his colleagues (Geroldi et al., 2000) reported that AD patients without psychotic symptoms had symmetrical enlargement of the temporal and frontal horns. However, the paranoid subtype had asymmetrical enlargement of the right temporal horn and left frontal horn. While the left hemisphere is an activator of mentation and behaviour, the right hemisphere is an inhibitor of mentation and behavior (Ismail et al., 2011). The two hemispheres compete and cooperate with one another to maintain a balance of two fundamentally opposed dispositions (Ismail et al., 2011). Therefore, it is possible that the
abnormal asymmetric pattern of brain atrophy in the paranoid subtype may be associated with the development of paranoid delusion. In this study, although those with the paranoid subtype appeared to have a more preserved gray matter volume than those without psychotic symptoms, cognition and function in those with the paranoid subtype is not preserved than those without psychotic symptoms. One possible interpretation for such discrepancies is the negative effects of delusion to cognition (Ismail et al., 2011) and function (Fischer et al., 2012) in AD patients. Many previous studies (Ismail et al., 2011) showed greater cognitive impairment, especially the executive function, in AD patients with delusion, including those who present only with persecutory delusion. These greater cognitive impairments in AD patients with delusion may have mediated worse social function (Fischer et al., 2012).

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, we used caregiver rated NPI to assess the presence and subtype of psychosis, which is likely to be less reliable than a full clinical interview. Third, there is an increased risk for false positive results because we used uncorrected (p < 0.001) thresholds for VBM analysis due to small sample size. Fourth, we classified AD patients with hallucination into misidentification subtype because some previous studies (Cook et al., 2003; Perez-Madrinan et al., 2004) using factor and cluster analysis on AD patients with psychosis indicated that misidentification and hallucination were loaded into the same group of factor. Some factor analysis studies (Nagahama et al., 2007; Nagahama et al., 2010), however, reported that misidentification and hallucination were classified into different groups of factor. Therefore, further multimodal neuroimaging studies are needed to investigate associations between regional structural brain atrophy and hallucination in AD patients.

Despite these limitations, to our knowledge, this is the first report of showing the association of brain regional gray matter volume with two subtypes of psychotic symptoms, namely the paranoid and the misidentification subtypes, in antipsychotic-naïve mild or moderate AD patients after controlling covariates of no interest (i.e. age, gender, education, total intracranial volume, CDR score and the K-NPI non-psychotic scores).

In conclusion, we found that there are significant differences in gray matter volume between the groups (paranoid subtype, misidentification subtype and non-psychosis group), independent of disease severity, in antipsychotic-naïve mild or moderate AD patients. The misidentification subtype is associated with more severe gray matter atrophy, and the paranoid subtype is associated with less but severe gray matter atrophy compared to non-psychosis group. These results suggest that the misidentification, the paranoid subtype and non-psychosis group have a distinct neural correlation.

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