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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 anti-psychotic-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 fail 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;

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Kotrla et al., 1995; Sultzer et al., 1995; Hirono et al., 1998; Staff et al., 1999; Sultzer et al., 2003; Nakano et al., 2006; Serra et al., 2010) considered the psychotic symptoms or delusions as a single entity, though many subtypes of psychotic symptoms have been described in AD. Some researchers (Cook et al., 2003) classified psychotic symptoms into paranoid (persecutory delusion) subtype and misidentification (misidentification delusion and/or hallucinations) subtype. They have argued that paranoia and misidentification may represent two distinct subtypes (Cook et al., 2003), characterized by different pathological and cognitive trajectories (Ismail et al., 2011). Some studies have reported that misidentification subtype, in particular, is a more impairing subtype cognitively (Forstl et al., 1994b), and has a wider involvement with the cerebral region (Lee et al., 2006).

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 AD patients. For this purpose, we hypothesized:

(1) More significantly decreased gray matter volume would be shown in misidentification subtype and paranoid subtype than non-psychotic AD.
(2) More significantly decreased gray matter volume would be shown in misidentification subtype than paranoid subtype.

2. Methods

2.1. Subjects

Forty AD patients with psychotic symptoms and 25 AD patients without psychotic symptoms matched for age, gender and year of education were included from a cohort of AD patients who regularly follow up at the Memory Impairment Clinic at the Department of Psychiatry, Pusan National University Hospital in Busan, Korea between June 2013 and December 2014. All candidate subjects and their reliable informants were interviewed by a psychiatrist with advanced training in geriatric psychiatry according to the protocol of the Korean Version of the Consortium to Establish a Registry for Alzheimer's disease Assessment Packet (CERAD-K) (Lee et al., 2002). Psychiatric, physical, neurological examinations and routine laboratory tests were performed to exclude secondary causes of cognitive deficits. A panel consisting of two psychiatrists and one neurologist with expertise in dementia research made clinical decisions, including clinical diagnosis and Clinical Dementia Rating Scale (CDR).

We assessed the presence of psychotic symptoms by using the delusion and hallucination subscale of the Korean Neuropsychiatric Inventory (K-NPI), a caregiver-based rating scales, which was proven reliable and valid in a previous study (Choi et al., 2000). A subject was considered to have psychotic symptoms if he or she had had persistent or intermittent delusions, hallucination or both for at least one month (Jeste and Finkel, 2000), and those without any kind of psychotic symptom to the non-psychotic group. For subtype analysis, subjects with psychotic symptoms were classified into two subtypes according to the classification used by Cook and colleagues (Cook et al., 2003): (1) the paranoid subtype was defined by the presence of persecutory delusions including theft, persecutory, infidelity and abandonment; (2) The misidentification subtype was defined by the presence of misidentification delusion or hallucination including Capgras, phantom boarder, reduplication place, TV sign and mirror sign. The subjects ($n=7$) who met both paranoid and misidentification subtype were excluded in this study to increase comparability between group.

All subjects included in this study also met the following inclusion criteria: (1) 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 delirium, 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) (Ku 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