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Correlation between gray matter volume in the temporal lobe and depressive symptoms in patients with Alzheimer's disease

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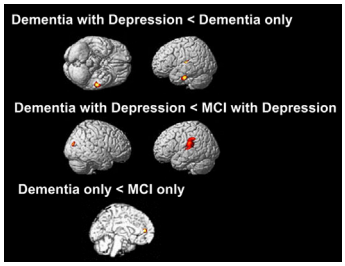
HIGHLIGHTS

- Depression might be an aggravating factor in Alzheimer's disease.
- Left inferior temporal volume was decreased in AD patients with depression.
- Depressive symptoms may accelerate cognitive decline and brain volume changes.

GRAPHICAL ABSTRACT

Depressive symptoms may be associated with the volume changes of frontal and temporal lobe in patients with Alzheimer's disease.



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ABSTRACT

Recent studies have suggested that depression might be an aggravating factor in Alzheimer's disease (AD). The aim of the study was to compare depressive symptoms and gray matter volume between AD patients with comorbid depression and patients with dementia only. Forty-nine patients with AD, 57 with mild cognitive impairment (MCI), and 50 healthy control subjects were assessed using the Consortium to Establish a Registry for Alzheimer's disease (CERAD) and the Geriatric Depression Scale (GDS). All magnetic resonance imaging (MRI)s were analyzed using voxel-based morphometry (VBM). Seventeen AD patients with depression versus 32 patients with dementia only showed decreased immediate recall for a word list (8.7 ± 1.1 vs. 10.1 ± 1.5, $z = 3.6$, $p < 0.01$) and constructional praxis scores (3.7 ± 0.9 vs. 5.3 ± 2.1, $z = 2.5$, $p = 0.01$). Compared to 32 patients with dementia, seventeen AD patients with depression showed decreased gray matter volume in the left inferior temporal gyrus ($-56, -19, -31$; $K_E = 578$, $t = 3.80$, $P_{uncorr} < 0.001$). The MCI group showed decreased gray matter volume in the right hippocampal gyrus compared to healthy control group. Our results suggest that depressive symptoms may be associated with the volume changes of frontal and temporal lobe in patients with AD.

1. Introduction

Depression is a common comorbid symptom in elderly patients suffering from Alzheimer's disease (AD). Recent studies have suggested that the presence of depression may accelerate the rate of cognitive decline in patients with AD [17,18]. In adults with depressive symptoms, functional neuroanatomy studies reveal subcortical ischemic changes, diminished activity of dorsolateral prefrontal cortex, and contractions in the dorsoanterior region of the subiculum and lateral posterior of the CA1 subfield in the left hippocampus [1,2]. However, other studies have suggested that depression may not be a causal factor of AD [11]. Compared with early-life depression, late-life depression might be an early manifestation rather than a risk factor for dementia and AD [15].

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An epidemiologic study of 136 participants with AD and depressive symptoms found that depression corresponds with accelerated cognitive decline and neuropathological changes within the hippocampus [19]. Previous structural magnetic resonance imaging (MRI) studies examining depressed elderly people found that those with small left hippocampal volumes were at a higher risk for later dementia [16,20]. Additionally, some studies have compared the hippocampal thinning in elderly people and suggested that most intense changes localized in the right hippocampal head according to the degree of cognitive decline [4].

Collectively, these findings suggest that depressive symptoms may contribute to cognitive impairment and dementia in AD. The aim of this study was to compare gray matter volume in AD with and without comorbid depression. Additionally, we compared the cerebral correlates of neuropsychological deficits in healthy subjects, those with MCI, and those with AD.

2. Methods

2.1. Participants

From March 2011 to September 2012, 350 old people visited Keum-cheon Center for Dementia in Seoul, South Korea. Of 350 old people, 195 old people agreed to participate in current research. Thirty-nine people were excluded due to the history of psychiatric treatment including schizophrenia, major depression, and anxiety disorder. Forty-nine patients with AD and 57 subjects with MCI, and 50 healthy control subjects were recruited. All subjects were assessed using the Korean version of the Mini Mental State Examination (K-MMSE) and the clinical dementia rating score (CDR). Cognitive functioning in all subjects was assessed by a psychologist using the Korean version of the test battery of the Consortium to Establish a Registry for Alzheimer's disease (K-CERAD) test battery. Depressive symptoms were evaluated using the Geriatric Depression Scale (GDS) [22]. All subjects underwent a brain MRI scan and blood tests including measurements of hemoglobin, white cell count, serum electrolytes, glucose, urea, creatinine, liver function, and thyroid hormone at Chung-Ang University Hospital. A clinical evaluation included a confirmation of personal and family history and physical and neurological examinations. No participants had a history of or current evidence of neurological or psychiatric illness, head injury, or substance abuse. All subjects provided written informed consent, and this study was approved by the Chung-Ang University Hospital Institutional Review Board.

2.2. Subjects classification

Inclusion criteria in this study were 55–85 years of age, complete demographic information (age, sex, and education), and an accelerated AD diagnosis per Diagnostic and Statistical Manual of Mental Disorders Forth edition Text Revision (DSM IV-TR) criteria. MCI was defined as a condition in which a person has problems with memory and language which are not severe enough to interfere with daily life. At the screening, two psychiatrists (B.S. Kee and J.H. Son) assessed and diagnosed subjects as having dementia and comorbid diseases based on DSM IV-TR criteria. The inclusion criteria include the subjects who visited Keum-Cheon Center for Dementia, aged 55–85 years old. Exclusion criteria include (1) subjects with history or current episode of other Axis I psychiatric disease; (2) patients with other substance abuse/dependence (except for smoking and social drinking), and (3) patients with claustrophobia. Subjects were categorized based on K-MMSE score (less than 20 for AD, between 20 and 25 for MCI, and greater than 25 for the control group) [18]. After screening test, we also evaluated their cognitive function using the K-CERAD, which assesses verbal fluency, naming, immediate/delayed recall, constructional praxis, and constructional praxis recall, and this measure was also used to identify AD or MCI in dividing line patients, such as K-MMSE score 20 or 25 [5]. Those subjects were further categorized into each group based on K-CERAD score: one item failure MCI group, and more than two item failures AD group. Final diagnoses were confirmed at a clinical consensus discussion with more than two psychiatrists. Furthermore, we defined 'depression' as a GDS score greater than 20, which had been satisfactory scale (sensitivity = 0.91 and specificity = 0.82) [12]. No participants had diabetes mellitus or other concurrent diseases able to cause cognitive decline.

2.3. MRI data acquisition and analysis

All MRI data was obtained at Chung-Ang University Hospital with an Achieva 3.0 T scanner (Philips: Amsterdam, Netherlands). Acquisitions consisted of a set of 180 axial cuts parallel to the anterior commissure – posterior commissure line, slices 1 mm thick and voxel sizes of 1 mm × 1 mm × 1 mm, using the SPGR sequence (TR = 10 ms TE = 4 ms; image matrix = 256 × 256). Images were analyzed using MATLAB 7.5.0 (Mathworks, Natick, MA, USA) and SPM5 software. Images were reconstructed using a standard optimized VBM protocol. Each structural MRI was normalized to the template provided by the International Consortium for Brain Mapping template for East Asian Brains and nonlinear algorithms. The normalized images were segmented into gray matter, white matter and cerebrospinal fluid and were smoothed with an 8 mm full-width half maximum (FWHM) Gaussian kernel for the subsequent statistical analysis.

Voxel-wise comparisons of gray matter volume were performed between the groups using a two-sample *t*-test with SPM5. For the significant level of group difference, uncorrected $p \leq 0.001$ was set after false discovery rate (FDR) $p < 0.05$ with the cluster size >400 voxels.

2.4. Statistical analysis

SPSS 19 for Windows was used for statistical analysis. Results with $p < 0.05$ were considered significant. The distributions of age, sex, and education level were analyzed using ANOVA and χ^2-tests. Post hoc Duncan's test for variance was calculated to compare demographic and clinical data in healthy subjects and MCI and AD groups.

3. Results

3.1. Demographic characteristics

Subjects with dementia and MCI and healthy controls did not differ regarding sex, age, education years. They did differ on all sub-items of the K-CERAD. Subjects with comorbid dementia and depression versus those with dementia only showed decreased immediate recall for word list (8.7 ± 1.1 vs. 10.1 ± 1.5, $z = 3.6$, $p < 0.01$) and constructional praxis scores (3.7 ± 0.9 vs. 5.3 ± 2.1, $z = 2.5$, $p = 0.01$). There were no significant differences on K-CERAD sub-item scores between patients with comorbid dementia and depression versus patients with dementia only (Table 1).

3.2. Comparison of gray matter volume between patients with dementia, patients with MCI, and healthy controls

Compared to healthy control group, the dementia group showed decreased gray matter volume in the left middle temporal gyrus (−53, −12, −16, BA21; $K_E = 14{,}102$ (>400), $t = 4.02$, $P_{FDR\text{-}corr} = 0.016$), left middle frontal gyrus (−39, 28, 31, BA9; $K_E = 11{,}972$ (>400), $t = 4.77$, $P_{FDR\text{-}corr} = 0.016$), left superior frontal gyrus (−9, 12, 55,