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ORIGINAL ARTICLE

Reduced Gray Matter Volume in Subjective Cognitive Decline: A Voxel-Based Morphometric Study

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Background and Purpose   Subjective cognitive decline has been proposed as a potential indicator of the preclinical state of Alzheimer's disease (AD). The results of the studies of cortical atrophy on brain MRIs in subjects with subjective cognitive decline are inconsistent across the literatures. We investigated whether subjects with subjective cognitive decline had less gray matter volume compared to controls without subjective cognitive decline as per brain MRI.

Methods   Thirty-six subjects with subjective cognitive decline and thirty-three controls without subjective cognitive decline were recruited retrospectively from among the patients who had visited the department of neurology at Inha University Hospital between January 2008 and December 2010. All subjects had undergone a brain MRI scan including 3D T1-weighted spoiled gradient recalled echo imaging. We used voxel-based morphometry (VBM) to examine gray matter volumes between the two groups, after controlling for age, sex, education, and total intracranial volumes (TIV).

Results   There were no significant differences in age, gender, education, and TIV between the two groups. In comparison to controls without subjective cognitive decline, subjects with subjective cognitive decline showed gray matter atrophy in the left superior and medial frontal gyri, left superior and inferior parietal lobules, and right precuneus and insular in the VBM analysis.

Conclusions   Individuals with subjective cognitive decline encountered in clinical settings have greater similarity to an AD gray matter atrophy pattern compared with cognitively normal individuals without subjective cognitive decline.

Key Words   subjective cognitive decline, voxel based morphometry, gray matter, atrophy.

INTRODUCTION

Persons with subjective cognitive decline are reported to experience a decline in cognitive capacity without measurable cognitive deficits on objective testing.[1] In a meta-analysis, subjective cognitive decline was present in about 17% of healthy elderly.[2] The pathophysiological process of Alzheimer's disease (AD) is thought to begin many years before the diagnosis of AD dementia.[3] Subjective cognitive decline has been

proposed as a potential indicator of the preclinical state of AD.[3,4] Older people with subjective cognitive decline are twice as likely to develop dementia as individuals without subjective cognitive decline.[5] In a meta-analysis, approximately 2.3% and 6.6% of older people with subjective cognitive decline progressed to dementia and mild cognitive impairment (MCI) per year.[5]

The existence of subjective cognitive decline does not ascertain progression to clinical AD. Long-term studies, with a follow-up period of over 4 years, showed that 14% of individuals with subjective cognitive decline develop dementia and about 27% go on to develop MCI.[1] Subjective cognitive decline may be non-specific and may result from other causes

including attention difficulties, depression, sleep disorders, and drug side-effects.[1,6] Therefore, detection of sensitive markers of preclinical AD in individuals with subjective cognitive decline is critical before the introduction of a potential disease-modifying treatment. The underlying biological changes as assessed by biomarkers have been examined in subjects with subjective cognitive decline. A study on subjects with subjective cognitive decline found that cerebrospinal fluid (CSF) 42-mer amyloid β-protein (Aβ42) alone is a superior biomarker over total tau, hyperphosphorylated tau, or a combination of all three biomarkers in predicting progression to MCI or AD.[7] Previous studies also demonstrated brain atrophy through magnetic resonance imaging (MRI),[8-10] and increased hypometabolism, as revealed through positron emission tomography (PET), in characteristic brain regions affected by AD.[11] MRI-based methods have the advantage of being non-invasive and relatively cost-effective compared to PET neuroimaging and CSF analysis. Brain MRIs are also performed routinely for evaluating the cause of cognitive decline.

Studies have reported volume reductions of the entorhinal cortex and the hippocampus in subjects with subjective cognitive decline compared to healthy controls without subjective cognitive decline.[1,8] However, the results of the studies of cortical atrophy in subjects with subjective cognitive decline are inconsistent across the literatures.[9,10] In a recent study, subjects with subjective cognitive decline showed gray matter atrophy in the left frontal gyrus, right calcarine gyrus, precuneus, lingual gyrus, temporal gyrus, and cingulate areas, compared to normal controls without subjective cognitive decline.[9] In another study, measures of cortical thickness showed no significant difference between subjects with subjective cognitive decline and cognitively healthy controls without subjective cognitive decline.[10] We investigated whether subjects with subjective cognitive decline had less gray matter volume compared to healthy controls without subjective cognitive decline as per brain MRI.

METHODS

Subjects

Thirty-six subjects with subjective cognitive decline and thirty-three healthy controls without subjective cognitive decline were recruited retrospectively from among the patients who had visited the department of neurology at Inha University Hospital between January 2008 and December 2010. The subjects with subjective cognitive decline were 50 years or older and were diagnosed by the criteria of the Subjective Cognitive Decline Initiative.[4] They complained of self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and had scores more than 1.0 standard deviation below age and education-adjusted normative means on all subtests of the Seoul Neuropsychological Screening Battery-Dementia version.[12] They had undergone a brain MRI scan including 3D T1-weighted spoiled gradient recalled echo (SPGR) imaging. The normal control subjects without subjective cognitive decline were selected from among the patients who had visited the neurology clinic because of chronic headache or dizziness and had undergone a brain MRI scan including 3D T1-SPGR imaging between January 2008 and December 2010. The control subjects were at least 50-years-old and did not complain of self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and any impairment in activities of daily living. They also did not have any of 28 diseases or a history suggestive of a decrease in cognitive function.[13] They included the following: stroke or transient ischemic attack, seizures, Parkinson's disease, multiple sclerosis, cerebral palsy, Huntington's disease, encephalitis, meningitis, brain surgery, surgery to clear arteries to the brain, diabetes that required insulin for control, hypertension that was not well controlled, cancer other than skin cancer diagnosed within the past three years, shortness of breath while sitting still, use of home oxygen, heart attack with changes in memory, walking, or solving problems lasting at least 24 hours, kidney dialysis, liver disease, hospitalization for mental or emotional problems in the past five years, current use of medications for

Table 1. Demographics and clinical characteristics of the subjects

	Subjects with subjective cognitive decline (*n*=36)	Controls (*n*=33)	*p* value
Age, years	64.6 (7.7)	63.9 (7.5)	0.69
Female	29 (81%)	29 (88%)	0.52
Education, years	7.9 (5.1)	6.8 (5.0)	0.56
TIV, mm³	1717406.9 (330201.7)	1631883.7 (307984.0)	0.91
Total gray matter volumes, mm³	765458.7 (248230.9)	778729.6 (308368.0)	0.84

Values are given as mean (standard deviation) or number (%).
TIV: total intracranial volume.

mental or emotional problems, alcohol consumption greater than three drinks each day, abuse of drugs in the past five years, treatment for alcohol abuse in the past five years, unconsciousness for more than one hour other than during surgery, overnight hospitalization because of a head injury, illness causing a permanent decrease in memory or other mental functions, trouble with vision that impairs reading ordinary print even with glasses on, and difficulty understanding conversations because of hearing problems even if wearing a hearing aid. They were matched randomly for age, gender, and education with subjects with subjective cognitive decline.

Table 2. Neuropsychological findings in the subjects with subjective cognitive decline

Cognitive domain	Subtest	Score
Attention	Digit span forward	7.2 (1.2)
	Digit span backward	4.5 (1.7)
Language	Short form of K-BNT (A form)	12.6 (1.7)
Visuospatial function	RCFT copy	32.46 (6.50)
Memory	SVLT, immediate recalls	19.2 (3.5)
	SVLT, delayed recall	6.3 (1.8)
	SVLT, recognition	8.7 (1.5)
	RCFT, immediate recall	15.6 (7.6)
	RCFT, delayed recall	16.0 (7.3)
	RCFT, recognition	7.6 (2.2)
Executive function	Animal fluency	15.8 (3.9)
	Phonemic word generation (ㄱ)	8.4 (4.2)
	Stroop test-color reading	92.6 (17.9)

Values are given as mean (standard deviation).
K-BNT: Korean-Boston Naming Test, RCFT: Rey-Complex Figure Test, SVLT: Seoul Verbal Learning Test.
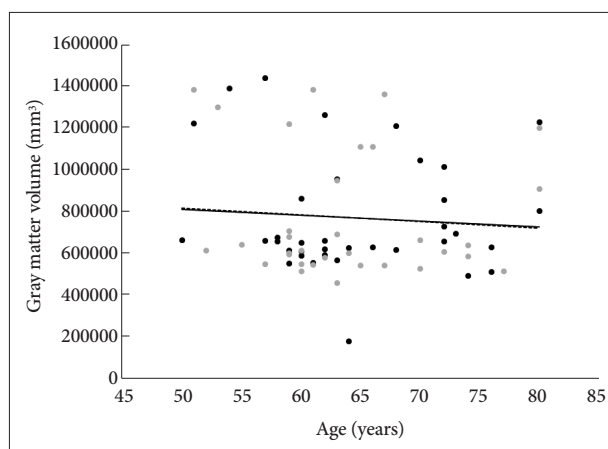
Fig. 1. The distribution of total gray matter volumes according to the age in subjects with subjective cognitive decline (black dots, solid line) and those without subjective cognitive decline (gray dots, broken line). The total gray matter volumes were not significantly associated with age and the presence of subjective cognitive decline.

Patients with the following diseases or conditions were excluded: severe or unstable systemic diseases; abnormal laboratory tests such as vitamin B_{12} or folate deficiency, positive syphilis serology, and uncontrolled thyroid disease; a major neurological disease such as Parkinson's disease, normal pressure hydrocephalus, seizure, and stroke; alcoholism or drug abuse; the Korean version of Geriatric Depression Scale score above 18,[14] major depression, or psychiatric diseases; and severe white matter hyperintensities (Fazekas scale 3),[15] any lacunes, cerebral hemorrhages, cortical stroke, or brain tumors on brain MRI. This study was approved by the Institutional Review Board of Inha University Hospital.

Voxel based morphometry

SPGR imaging was performed using a 1.5-T GE Signa MRI scanner (signal HDX, General Electric, Milwaukee, WI, USA) with the following imaging parameters: repetition time=11.2 ms, echo time=4.9 ms, field of view=240×240 mm, slice thickness=1.2 mm, no interslice gap, number of excitation=1, and acquisition matrix=250×160.

All images were saved in Digital Imaging and Communications in Medicine format and changed to an appropriate format for voxel based morphometry (VBM) using MRIcro. VBMs were performed using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). We used the standard template that was provided by the Montreal Neurological Institute to perform spatial normalization with non-linear transformation. The purpose of performing this step was to correct for global differences in brain shape. Normalized images for each subject were segmented into gray and white matter and CSF using the default SPM brain tissue prior probability maps. After normalization and segmentation, smoothing was performed with a 12-μL full-width at half-maximum Gaussian kernel for preprocessing. After image processing, voxel-based comparisons between the two groups were made using two-sample t-tests. Age, gender, educational levels, and total intracranial volume (TIV), obtained automatically using SPM5, were used as covariates. Only the regions that differed in more than 100 voxels between the two groups were analyzed. Areas with voxel levels of $p<0.005$, uncorrected, were regarded as significant. The x, y, z coordinates of the areas of significant correlation obtained from the analyses were first converted into Talairach coordinates and then the specific anatomy region and the Brodmann area were identified using the Talairach Daemon Client.

Statistical analysis

Demographic and clinical characteristics were compared using student t-tests for continuous variables and a chi-square

Table 3. Brain regions showing significant gray matter atrophy in subjects with subjective cognitive decline compared with controls without subjective cognitive decline in global voxel-based morphometry analysis, after controlling for age, gender, education, and total intracranial volume

Brain area	T score	p value	Cluster extent	Coordinates (mm)			BA
				x	y	z	
R precuneus	3.41	0.001	356	20	-58	42	7
L superior frontal gyrus	3.41	0.001	220	-26	48	4	10
L inferior parietal lobule	3.31	0.001	241	-50	-58	56	40
L medial frontal gyrus	3.29	0.001	228	-20	26	26	9
L superior parietal lobule	2.98	0.001	289	-24	-56	42	7
R insular	2.62	0.004	115	30	28	18	13

BA: Brodmann area, L: left, R: right.
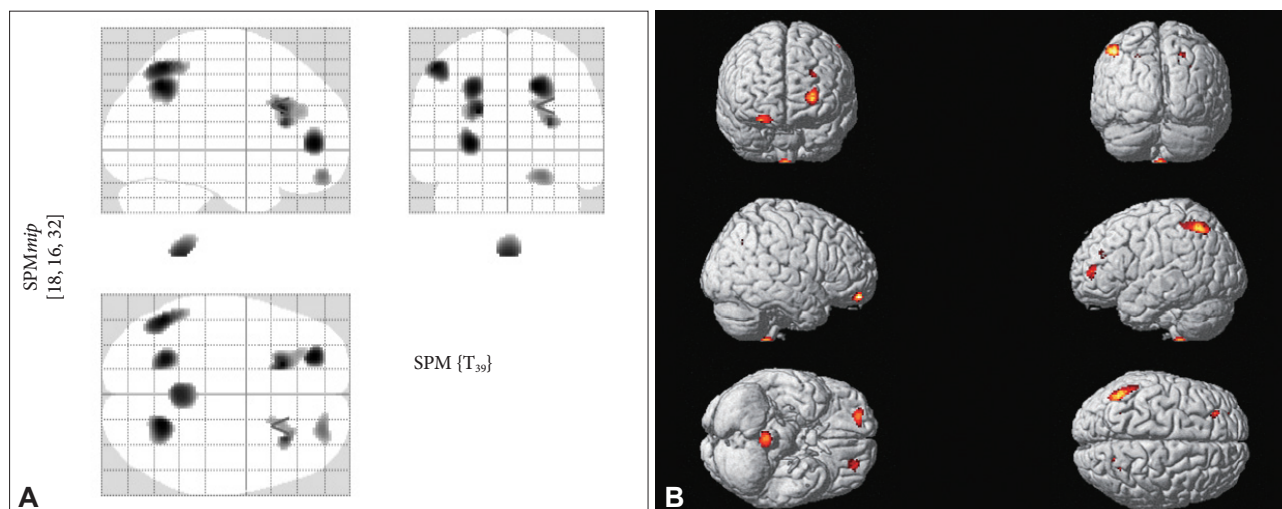
Fig. 2. Statistical parametric maps (SPM) (A) and three dimensional rendering (B) of gray matter atrophy in subjects with subjective cognitive decline compared to controls without subjective cognitive decline. Meaningfully reduced gray matter distributions were located in the right precuneus and insular, left superior and inferior parietal lobules, and left superior and medial frontal gyri. Results were considered statistically significant at $p<0.005$, cluster level, uncorrected.

test for categorical variables. The effect of age and subjective cognitive decline on the gray matter volumes was tested by multiple linear regression method. Significance for all tests was set at α=0.05, two-tailed. All statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

There were no significant differences in age, gender, education, TIV, and total gray matter volumes between subjects with subjective cognitive decline and controls without subjective cognitive decline (Table 1). The neuropsychological findings in subjects with subjective cognitive decline are presented in Table 2. The distribution of total gray matter volumes according to age in both groups is shown in Fig. 1. The total gray matter volumes were not significantly associated with age (p=0.49) and the presence of subjective cognitive decline (p=0.78). However, in comparison to controls without subjective

cognitive decline, subjects with subjective cognitive decline showed gray matter atrophy in the left superior and medial frontal gyri, left superior and inferior parietal lobules, and right precuneus and insular in the VBM analysis (Table 3, Fig. 2).

DISCUSSION

We discovered significant macrostructural gray matter loss in the brains of subjects with subjective cognitive decline compared to normal controls without subjective cognitive decline. This suggests that subjects with subjective cognitive decline are neuroanatomically different from controls without subjective cognitive decline. Of special note, there was significant gray matter atrophy of the right precuneus and insula, left superior and medial frontal gyri, and left superior and inferior parietal lobules in subjects with subjective cognitive decline compared to controls without subjective cognitive decline. In another study, subjects with subjective cognitive de-

cline showed gray matter atrophy in the left frontal gyrus and right precuneus compared to normal controls, which is similar to the results of this study.[9] In a recent study, individuals with subjective cognitive decline showed greater similarity to an AD gray matter atrophy pattern compared to control subjects without subjective cognitive decline.[16]

In a previous study, the regions which were vulnerable to early deposition of amyloid β protein included the precuneus, posterior cingulate, lateral parietal region, and medial and lateral prefrontal regions.[17] The areas were also compatible with the regions within the default mode network. The impaired default mode network has been reported in AD and longitudinal data showed a correlation with clinical symptoms worsening.[18] Non-demented adults carrying a familial AD gene mutation also showed decreased connectivity in the default mode network.[19] The brain regions showing gray matter atrophy in subjects with subjective cognitive decline in this study are compatible with the areas vulnerable to early amyloid deposition. This suggests that subjects with subjective cognitive decline may be in the preclinical stage of AD. Subjects with subjective cognitive decline in this study may be in stage 2 of preclinical AD with amyloid deposition and early neurodegeneration.[3]

Atrophy of the insular cortex observed in the subjects with subjective cognitive decline is an interesting finding of this study. Many studies have reported that the insular cortex is involved in a variety of processing events, including interoceptive awareness, multimodal sensory integration, emotional processing, and regulation.[20,21] The insular cortex is associated with neuropsychiatric symptoms, changes in cardiovascular and autonomic control, and mortality in AD.[22] A recent study showed that atrophy of the insular cortex was detected in patients with mild AD.[23] The insular cortex is connected to the hippocampus and entorhinal cortex.[23] Atrophy of the insular cortex in subjective cognitive decline may indirectly reflect neuronal degeneration in the hippocampus and entorhinal cortex.

There are some limitations to our study. The first limitation regarding the study design was that this was not a prospective study. Therefore, we could not obtain any information on risk factors such as the presence of apolipoprotein E ε4 and a family history of dementia. Second, the control subjects without subjective cognitive decline were not evaluated with extensive neuropsychological tests. Some control subjects with MCI might have been included. Third, there is a possibility that we may not have obtained more significant findings because of the small sample size of this study. Fourth, biomarkers that reflect the presence of cerebral Aβ deposits were not evaluated in the subjects. The causes of subjective cognitive decline are heterogeneous. We may not have obtained more significant findings because some subjects without cerebral Aβ deposits might have been included in the subjective cognitive decline group. In future, we need to investigate brain atrophy patterns in individuals with subjective cognitive decline, in whom the presence of cerebral Aβ deposits is confirmed with a biomarker.

Despite these limitations, our study has some strengths; we observed that persons with subjective cognitive decline encountered in clinical settings have greater similarity to an AD gray matter atrophy pattern compared to cognitively normal individuals without subjective cognitive decline. Therefore, clinicians should follow-up patients with subjective cognitive decline longitudinally and administer pharmacological and non-pharmacological treatments whenever necessary.

Conflicts of Interest

The authors have no financial conflicts of interest.

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