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Decreased Cortical Thickness and Local Gyrification in Individuals with Subjective Cognitive Impairment

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Objective: Subjective cognitive impairment (SCI) is associated with future cognitive decline. This study aimed to compare cortical thickness and local gyrification index (LGI) between individuals with SCI and normal control (NC) subjects.
Methods: Forty-seven participants (27 SCI and 20 NC) were recruited. All participants underwent brain magnetic resonance imaging scanning and were clinically assessed using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery of tests. We compared cortical thickness and LGI between the two groups and analyzed correlations between cortical thickness/LGI and scores on CERAD protocol subtests in the SCI group for region of interests with significant between-group differences.
Results: Cortical thickness reduction in the left entorhinal, superior temporal, insular, rostral middle frontal, precentral, superior frontal, and supramarginal regions, and right supramarginal, precentral, insular, postcentral, and posterior cingulate regions was observed in the SCI compared to the NC group. Cortical thickness in these regions correlated with scores of constructional praxis, word list memory, word list recall, constructional recall, trail making test A, and verbal fluency under the CERAD protocol. Significantly decreased gyrification was observed in the left lingual gyrus of the SCI group. In addition, gyrification of this region was positively associated with scores of constructional praxis.
Conclusion: Our results may provide an additional reference to the notion that SCI may be associated with future cognitive impairment. This study may help clinicians to assess individuals with SCI who may progress to mild cognitive impairment and Alzheimer's dementia.

KEY WORDS: Alzheimer disease; Cognitive decline; Mild cognitive impairment; Brain cortical thickness; Local gyrification index; Lingual gyrus.

INTRODUCTION

Subjective cognitive impairment (SCI) is defined by cognitive deficits subjectively perceived by individuals who have normal performance in objective neuropsychological examinations [1]. Evidence that SCI is associated with an increased risk for future cognitive decline and Alzheimer's disease (AD) dementia is rapidly increasing [1-6].

Many studies have investigated associations between individuals with SCI and AD-related biomarker abnormalities and have revealed that SCI is associated with an increased likelihood of biomarker abnormalities consistent with AD [3,7,8]. Eliassen *et al.* [9] and Rami *et al.* [8] have reported that there was no significant difference between SCI and mild cognitive impairment (MCI) in terms of cerebrospinal fluid (CSF) β-amyloid, total tau, and phosphorylated tau pathology. In several neuroimaging studies, greater SCI severity was related to a greater β-amyloid

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burden [10,11]. Kryscio *et al.* [12] and Barnes *et al.* [13] also reported higher levels of neuritic β-amyloid plaques in post-mortem brain tissue of individuals with SCI. In addition, some studies have conducted fluorodeoxyglucose (FDG)-positron emission tomography (PET) analyses in individuals with SCI. Vannini *et al.* [14] revealed that increased SCI severity correlated with decreased glucose metabolism in the bilateral precuneus, bilateral inferior parietal lobes, right inferior temporal lobe, right medial frontal gyrus, and right orbitofrontal gyrus. Song *et al.* [15] also showed periventricular hypometabolism in individuals with SCI as compared with healthy controls. Moreover, previous structural magnetic resonance imaging (MRI) has shown a reduced volume of the medial temporal lobe, including the hippocampus and the entorhinal cortex in individuals with SCI [7,16].

Cortical thickness analysis may reveal biomarkers of SCI; cortical thickness is the distance between the white/gray matter border and the pial surface [17]. Ashburner [18] reported that analyses of cortical thickness could reveal more significant differences than analyses of volume in this disease, which is thought to cause cortical thinning. Cortical thinning has been observed in various conditions, such as normal aging, Huntington's disease, corticobasal degeneration, amyotrophic lateral sclerosis, and schizophrenia [17]. Additionally, in AD pathology, cortical thickness is of great interest [17,19]. Previously, measurements of the cortical thickness of individuals with SCI [9,20,21] have been shown to be related to future cognitive decline and AD dementia [1-6]. However, these studies only conducted a region of interest (ROI) analyses. Therefore, in this study, we analyzed the cortical thickness of the whole brain in SCI with a sub-regional resolution.

Several studies have previously shown that decreased cortical gyrification could occur during the normal aging process [22]. Moreover, cognitive abilities localize to specific regions on the cortical folds of the brain; therefore, folding pattern changes in the brain may also represent the underlying pathology of neurodegenerative disease [23]. Hence, estimation of gyrification may be helpful in assessing the potential for development of neurodegenerative pathologies, such as AD [23]. We considered that this might be particularly important in SCI, as this condition is related to future cognitive decline and AD dementia [1-6]. The degree of folding of the cortical surface is quantified by the local gyrification index (LGI) [23]. Despite several published studies on brain MRI, only a few studies have assessed cortical folding using the LGI in individuals with SCI.

In this context, we aimed to compare cortical thickness and LGI based on brain MRI between individuals with SCI and normal control (NC) subjects. Additionally, we analyzed the correlation between cortical thickness/LGI and the score of cognitive measures in the SCI group for the ROIs where group differences were significant.

METHODS

Participants

Participants were recruited from the psychiatric clinic at the Korea University Guro Hospital and the Guro-gu Center for Dementia. The inclusion criteria for NC subjects were: 1) individuals at least 60 years of age; 2) individuals who subjectively reported that there was no abnormality in their cognitive function; and 3) individuals whose scores on all subtests of a neuropsychological battery of tests were within 1.5 standard deviations (SDs) below the mean. The inclusion criteria for SCI patients were: 1) individuals at least 60 years of age; 2) individuals who subjectively complained about their cognitive impairment; and 3) individuals whose scores on all subtests of a neuropsychological battery of tests were within 1.5 SDs below the mean. Subjects with neurological impairments (e.g., encephalosclerosis, epilepsy, or traumatic brain injury) or with claustrophobia, substance abuse disorders, and/or with cardiac pacemakers that could affect the results of the MRI scan, were excluded from both NC and SCI groups in this study. Twenty-seven participants presenting with SCI and 20 NC participants underwent MRI testing. All participants answered demographic questionnaires and underwent a battery of neuropsychological tests. This study was approved by the Institutional Review Board at Korea University Guro Hospital (KUGH13028). All study subjects provided written informed consent prior to participation. All procedures were performed in accordance with the Helsinki Declaration of 1975, as revised in 2013.

MRI Acquisition

All participants underwent a structural MRI examination at the Brain Imaging Center of Korea University. The

scan parameters were: b = 1,000 s/mm^2, echo time (TE) / repetition time (TR) = 84 ms/6.3 s; matrix = 128 × 128 on a 230 × 230 mm field-of-view; 3-mm slices without a gap, resulting in voxels of 1.8 × 1.8 × 3.0 mm. Sufficient signal-to-noise ratios were provided by four magnitude averages. Volumetric T1-weighted anatomic images were acquired using a magnetization-prepared rapid gradient-echo sequence (TE/TR/inversion time [TI] = 2.60 ms/1.9 s/900 ms; 256 × 256 × 176 matrix for 0.86 × 0.86 × 1 mm voxels).

Image Processing and Cortical Measurements

We computed cortical thickness and LGI from T1-weighted MR images using FreeSurfer version 5.1.0 (Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu). This software extracts various surfaces, including the pial surface (the outer boundary of the gray matter), and white surfaces (the boundary between the gray and white matter) [24,25]. We processed T1-weighted MR images of each subject using the software following the recommended reconstruction procedure including visual validation and correction of the intermediate results by neurophysiologists. The extracted surfaces consist of vertices and are isomorphic; they have the identical number of vertices with identical relations between vertices. The cortical thickness was estimated by the closest distance between two surfaces at each vertex of the white surface [17].

The LGI is defined as a metric that quantifies the amount of cortex buried within the sulcal folds, as compared to the amount of visible cortex. In this study, we used FreeSurfer's built-in function to determine this value [26,27]. A larger LGI indicates a more folded area, while a smaller LGI represents a smoother area. In order to compute LGI, first, a smooth outer surface that wraps the pial surface is created. Then, a circular ROI is created, centered on a particular vertex and the pial surface. The LGI value was computed as the ratio between the areas of those two ROIs, considering the distance between the two surfaces. Repeating this procedure over the vertices of the pial surface generated an LGI map.

Inter-subject correspondence of data-points is critical in surface analysis. Due to inter-subject variability in brain shape, the number of vertices on the brain surfaces often varies across subjects, and this may seriously hamper analysis. FreeSurfer provides spatial registration of the surfaces between subjects, using the major folding patterns, ensuring isomorphic surfaces with an identical number of vertices in all subjects [28]. We registered each subject's surfaces on the FreeSurfer's average subject, and resampled cortical thickness and LGI. Then, we smoothed the resampled values with a full-width at half-maximum filter with a radius of 10 mm.

Demographic and Cognitive Measures

For all participants, information about age, sex, and education level were collected. Additionally, the apolipoprotein E (APOE) genotype was also determined, given that APOE alleles are accepted genetic determinants of AD risk [29].

The cognitive functions of participants were measured using the Consortium to Establish a Registry for AD (CERAD) neuropsychological battery of clinical testing [30]. In this study, we used the Korean version of CERAD and the Korean specific age-, sex-, and education-adjusted norms [31]. All participants scored within 1.5 SD below the mean. The Mini-Mental State Examination (MMSE) is an easy to use a measure of cognitive function that has been widely implemented in the screening and clinical evaluation of patients with dementia [32]. We conducted the MMSE in the Korean version of the CERAD assessment package and adopted the Korean specific age-, sex-, and education-adjusted norms base on z-score [33]. In addition, we included the Korean version of the Geriatric Depression Scale (GDS) to assess the degree of distress in our subjects [34].

Statistical Analysis

Differences between the SCI and the NC groups in demographic and cognitive measures were analyzed using Predictive Analytics Software 18.0 for Windows (IBM Co., Armonk, NY, USA; i.e., Mann−Whitney test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables).

We compared the cortical thickness and LGI at the level of vertices between subjects in the SCI and NC group, using the general linear model (GLM) with the Query, Design, Estimate, Contrast interface of FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki/Qdec). Specifically, we tested the group differences in cortical measures between SCI and NC subjects, controlling for the effects of age, sex, and education levels by using the

Table 1. Basic characteristics and cognitive measures of normal control and subjective cognitive impairment groups

Variable	NC (n = 20)	SCI (n = 27)	p value[a]
Age (yr)	70.20 ± 7.46	69.07 ± 8.14	0.511
Sex			0.188
Male	8 (40.0)	6 (22.2)	
Female	12 (60.0)	21 (77.8)	
Education (yr)	10.58 ± 5.39	5.93 ± 5.25	0.005**
APOE4 allele carriers	5 (25.0)	8 (29.6)	0.831
MMSE	27.05 ± 2.88	23.67 ± 4.29	0.002**
GDS	8.44 ± 5.54	16.96 ± 6.20	< 0.001**
CERAD			
Constructional praxis	9.94 ± 1.95	8.96 ± 1.59	0.011*
Word list memory	17.06 ± 5.05	15.54 ± 4.22	0.131
Word list recall	6.63 ± 1.26	5.31 ± 2.02	0.026*
Word list recognition	9.47 ± 0.70	8.96 ± 1.11	0.140
Constructional recall	8.00 ± 2.20	5.38 ± 2.98	0.004**
Verbal fluency	15.79 ± 3.85	13.42 ± 3.29	0.052
Boston Naming Test	12.84 ± 2.04	10.42 ± 2.64	0.001**
Trail Making Test A (sec)	58.57 ± 14.99	91.08 ± 49.43	0.046*

Values are presented as mean ± standard deviation or number (%).
NC, normal control; SCI, subjective cognitive impairment; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease.
[a]p value were calculated using the chi-squared test or Fisher's exact test and the Mann−Whitney test.
*$p < 0.05$. **$p < 0.01$.

following GLM equation. We assumed different offsets and the same slope across groups at each vertex i:

$$y_i = b_0 + b_1 \cdot group + b_2 \cdot age + b_3 \cdot sex + b_4 \cdot education\ level$$

where y_i is the cortical measure of the i-th vertex (cortical thickness or LGI), and b_0, b_1, b_2, b_3 and b_4 correspond to the regression coefficients for each term: bias, group, age, sex, and education level. The resulting significance map yielded a $-log_{10}$ (p value) and was thresholded with 2.3 for cortical thickness and 2.0 for LGI (2.3 and 2.0 corresponds to $p = 0.005$ and $p = 0.01$, respectively) for visualization. We reported clusters with an area larger than 50 mm^2 and with a group difference of mean cortical thickness (uncorrected $p < 0.01$). The adjusted cortical measures in figures were computed by deducting the confounder terms from both sides of the GLM equation.

We evaluated the correlation between the measurements and scores obtained from the CERAD battery of tests in the SCI group for regions where the between-group differences were significant. We first computed the average values of cortical thickness and the LGI for the identified cluster. We employed a partial correlation coefficient between the average values and CERAD scores, controlling for age, sex, and education levels. We used our in-house MATLAB codes (MathWorks, Natick, MA, USA) for all additional analyses and parameter visualization.

RESULTS

Table 1 shows the basic characteristics and cognitive measures for both groups. The mean ages in the NC and SCI groups were 70.20 years (SD = 7.46 years) and 69.07 years (SD = 8.14 years), respectively. More females than males participated in both groups (NC, 60.0%; SCI, 77.8%). The SCI participants were less educated than the NC participants. Naturally, the two groups differed from each other in cognitive measure scores, including MMSE and CERAD subtests. GDS scores were also different between groups.

Group Comparisons between the SCI and NC Groups

Our analyses showed significant between-group differences in both cortical thickness and LGI scores (Table 2). The SCI subjects showed significantly reduced mean cortical thickness in the left entorhinal, superior temporal, insula, rostral middle frontal, precentral, superior frontal, and supramarginal regions, and the right supramarginal, precentral, insula, postcentral (uncorrected p equals to or

Table 2. Cluster regions with significant group differences in cortical thickness and local gyrification index

SCI < NC Cluster	Peak location[a]				Overall		
	P_{peak}[b]	Talairach coordinate			Area[c]	$N_{vertices}$[d]	F-statistics[e]
		X	Y	Z			
Cortical thickness							
L entorhinal	< 0.001	−24.8	−7.2	−28.5	281.18	635	24.251*
L superior temporal	0.001	−62.6	−17.3	0.4	151.09	395	18.792*
L superior temporal	0.001	−52.5	−1.8	−6.1	119.63	228	15.193*
L insula	< 0.001	−31.7	8.3	11.4	94.63	305	13.802**
L rostral middle frontal	< 0.001	−22.5	44.0	16.3	70.23	109	12.159**
L precentral	0.001	−56.7	−1.0	10.1	68.03	167	12.654**
L superior frontal	0.001	−22.4	4.0	43.6	58.21	142	14.415*
L supramarginal	0.001	−49.5	−30.3	34.8	56.09	136	12.198**
L superior frontal	0.001	−10.7	21.9	34	55.4	127	12.668**
R supramarginal	< 0.001	57.8	−38.1	30.1	238.91	464	20.106*
R precentral	< 0.001	36.0	−10.7	59.8	208.54	475	20.618*
R supramarginal	< 0.001	58.9	−34.3	18.1	153.12	339	16.537*
R supramarginal	0.001	55.3	−24.3	26.7	96.39	235	17.409*
R insula	< 0.001	34.1	−22.1	20.1	79.76	269	15.174*
R postcentral	0.001	33.8	−30.3	61.2	71.84	182	14.320*
R precentral	< 0.001	40.2	−0.4	15.9	71.53	221	11.871**
R posterior cingulate	0.002	6.4	−23.4	38.1	52.36	120	11.522***
LGI							
L lingual	0.009	−17.9	−78.9	−3.4	12.70	14	7.452****

SCI, subjective cognitive impairment; NC, normal control; LGI, local gyrification index.
[a]Peak location: the location of the minimum p value in a cluster. [b]P_{peak}: the minimum p value in a cluster. [c]Area: surface area (in mm^2) of a cluster. [d]$N_{vertices}$: the number of vertices in a cluster. [e]F-statistics: F statistics for group comparison of mean cortical thickness between the NC and SCI groups, controlling for the effects of age, sex, and education level, and the relevant p value.
*$p < 0.001$. **$p = 0.001$. ***$p = 0.002$. ****$p = 0.009$.

below 0.001 for the results until here), and posterior cingulate regions (uncorrected $p = 0.002$), as compared to the NC group (Figs. 1A, 1B, 2). The left lingual gyrus had a reduced LGI in SCI subjects (uncorrected $p = 0.009$), although the area of its identified cluster did not exceed 50 mm^2 (Figs. 1C, 2).

Correlation of Cortical Thickness and LGI Values with Cognitive Scores

Cortical thickness of regions that differed significantly between groups showed positive correlations with SCI group scores of constructional praxis, word list memory, word list recall, constructional recall, and verbal fluency under the CERAD battery of cognitive testing. Negative correlations were found for the time taken for the trail making test A (shown in seconds, Table 3). The LGI of the left lingual gyrus was positively associated with scores from the constructional praxis subtest (Table 3, Fig. 3; Supplementary Figs. 1−4, available online).

DISCUSSION

In the present study, we investigated the differences between MRI brain scans of subjects with SCI and NC participants, focusing on cortical thickness and LGI values. Cortical thickness was reduced in SCI subjects as compared to that in the NC group, specifically in the left entorhinal, superior temporal, insula, rostral middle frontal, precentral, superior frontal, and supramarginal regions, and the right supramarginal, precentral, insula, postcentral, and posterior cingulate regions. Analysis of the LGI revealed significantly decreased gyrification in the left lingual gyrus in SCI subjects. In addition, we demonstrated the association of scores in the subtests in the CERAD battery in the SCI group with LGI and cortical thickness.

Changes in the brain's cortical folding geometry have been associated with cognitive decline [35], but there have been few studies that have analyzed cortical gyrification in individuals with SCI. Liu *et al.* [36] estimated

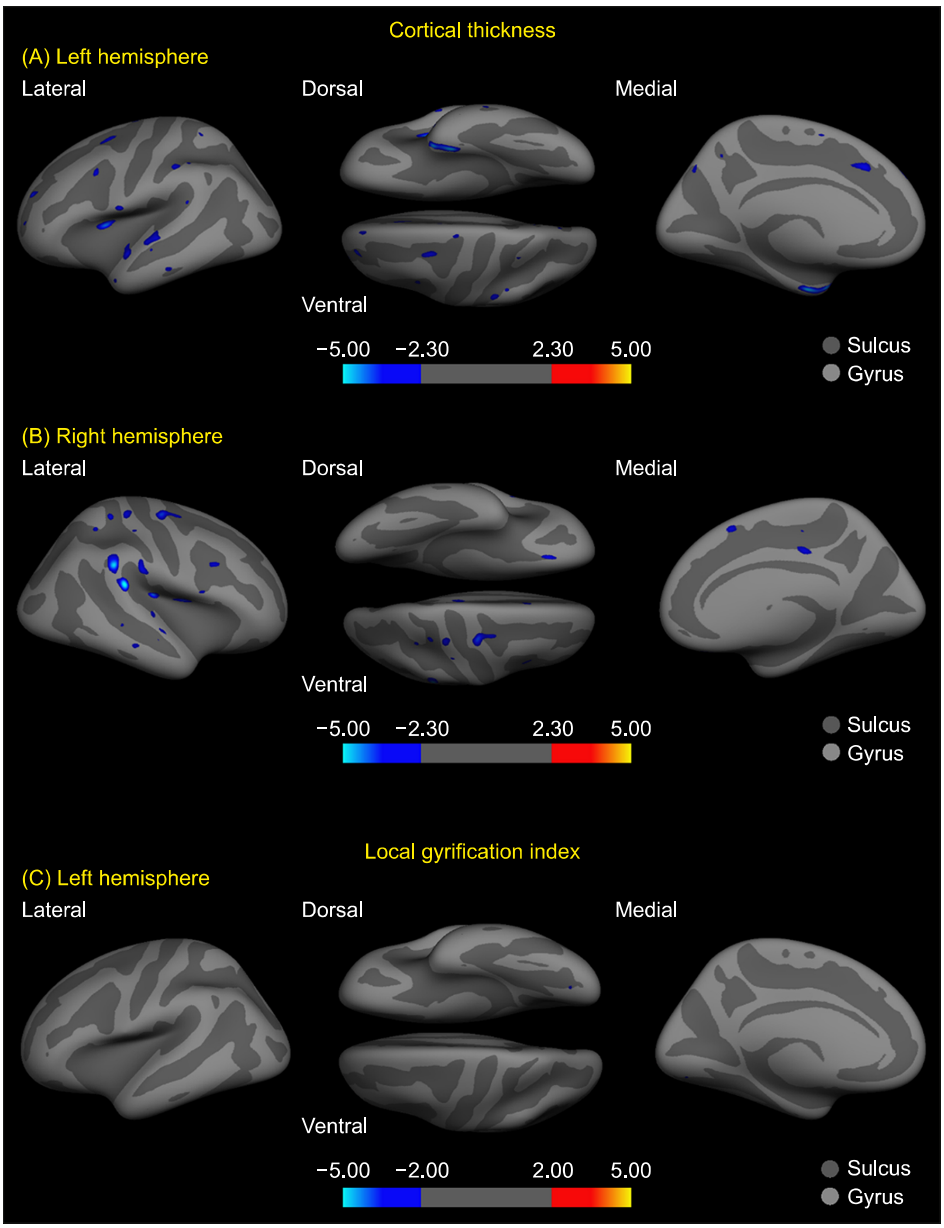

Fig. 1. Whole-brain significance map of cortical thickness and local gyrification index (LGI) differences between the subjective cognitive impairment (SCI) and normal control (NC) group. Each inflated cortical surface shows clusters of regions with cortical thickness differences between the groups in the (A) left hemisphere, in the (B) right hemisphere, and (C) between-group LGI differences in the left hemisphere. The maps consist of $-log_{10}$ (p value) where 2.3 corresponds to $p = 0.005$ for cortical thickness, and 2.0 corresponds to $p = 0.01$ for the LGI. The cooler (bluer) color indicates decreased values in the SCI group compared to the NC group, while the warmer (redder) color indicates increased values (not found). The only clusters with areas exceeding 50 mm^2 are shown in (A, B).

the global gyrification index values in early-stage AD and revealed negative associations with the severity of AD. They also reported positive associations between the global gyrification index values and MMSE scores. Lebed *et al.* [23] used LGI scores on individuals with a CDR score of 0, 0.5, and 1, and revealed various regions that showed decreased gyrification as CDR scores increased. These studies demonstrated the value of cortical gyrification analysis in the early stages of AD [23,36].

Our study used LGI analysis to investigate cortical gyrification in individuals with SCI and identified a gyrification decrease in the lingual gyrus of the brain, although the cluster regions found were relatively small. Previous studies have reported that the lingual gyrus plays

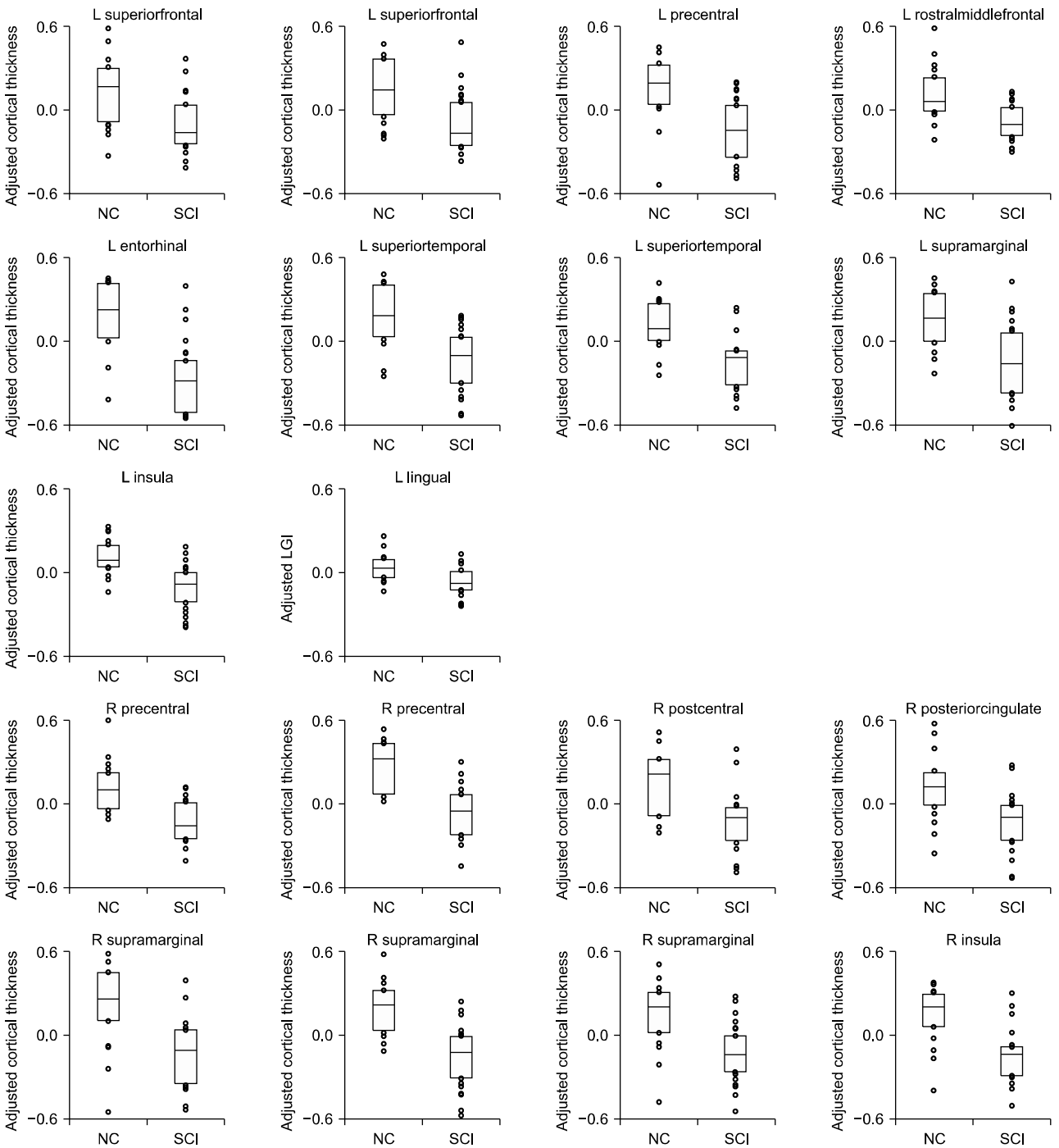

Fig. 2. Group comparison of adjusted mean cortical thickness and local gyrification index between subjective cognitive impairment (SCI) and normal control (NC) groups. Each subplot corresponds to its respective cluster, shown in Table 2. The adjusted values contained only the group effect; we first averaged the cortical measurement over an identified cluster, and controlled for the effects of age, sex, and education level. The boxes represent the first and third quartiles of the data with the median (solid line), whereas the circles outside the boxes represent data-points outside the central quartiles.

a critical role in mediating cognitive deficits in visual processing and memory [37,38], which have been associated with AD [39]. Our results are noteworthy because SCI is known to be associated with an increased risk of developing AD dementia [1-6]. The positive correlation between the lingual gyrus and constructional praxis tasks

Table 3. Correlation between cortical thickness/local gyrification index and cognitive measures in the subjective cognitive impairment group

Cognitive measures	Cluster	R^a	p value[b]
Cortical thickness			
Constructional praxis	Left superior temporal	0.456	0.019
	Left insula	0.547	0.004*
	Left superior frontal	0.535	0.005*
	Left supramarginal	0.681	< 0.001*
	Right supramarginal	0.409	0.038
	Right insula	0.533	0.005*
	Right precentral	0.443	0.024
Word list memory	Left superior temporal	0.648	< 0.001*
	Left superior temporal	0.490	0.011
	Left superior frontal	0.560	0.003*
	Right insula	0.407	0.039
	Right precentral	0.496	0.010
	Right posterior cingulate	0.499	0.010
Word list recall	Left superior temporal	0.455	0.020
	Left precentral	0.390	0.049
	Left superior frontal	0.660	< 0.001*
	Right supramarginal	0.515	0.007
	Right insula	0.401	0.042
	Right precentral	0.523	0.006*
	Right posterior cingulate	0.721	< 0.001*
Constructional recall	Left rostral middle frontal	−0.402	0.042
	Left supramarginal	−0.519	0.007
	Right supramarginal	0.476	0.014
Verbal fluency	Right supramarginal	0.459	0.018
	Right postcentral	0.398	0.044
Trail making test A (sec)	Left superior temporal	−0.738	< 0.001*
	Left insula	−0.657	< 0.001*
	Left supramarginal	−0.605	0.001*
	Right supramarginal	−0.445	0.026
	Right supramarginal	−0.428	0.033
	Right insula	−0.413	0.040
	Right posterior cingulate	−0.540	0.005*
LGI			
Constructional praxis	Left lingual	0.549	0.004*

LGI, local gyrification index.
[a]Partial correlation coefficient, controlling for the effects of age, sex, and education level. [b]Uncorrected.
*Bonferroni corrected $p < 0.05$.

was also consistent with the role of the lingual gyrus in cognitive processing [37,38]. In addition, Jeong *et al.* [40] have found reduced cerebral glucose metabolism in the lingual gyrus of older women with subjective memory impairment. Other studies have found that individuals with MCI presented gray matter volume reduction in the lingual gyrus [41,42]. Yetkin *et al.* [43] also detected deactivation of the lingual gyrus in an MCI group, based on functional MRI analysis. Our study reproduced similar findings in the context of gyrification changes in subjects with SCI.

Cortical thinning of the entorhinal and posterior cingulate regions was found in individuals presenting SCI. These results were plausible, given that these regions have been associated with memory dysfunction, which is at the core of functional disability in AD [44,45]. Previous studies have also reported the association between the entorhinal/posterior cingulate regions and cognitive impairment. Some studies of SCI individuals have shown cortical thickness reduction in these regions [9,20,21]. Ryu *et al.* [16] showed lower entorhinal cortical volumes in individuals with subjective memory impairment, and Jeong *et al.* [40] found reduced glucose metabolism in the posterior cingulate of elderly women with subjective memory

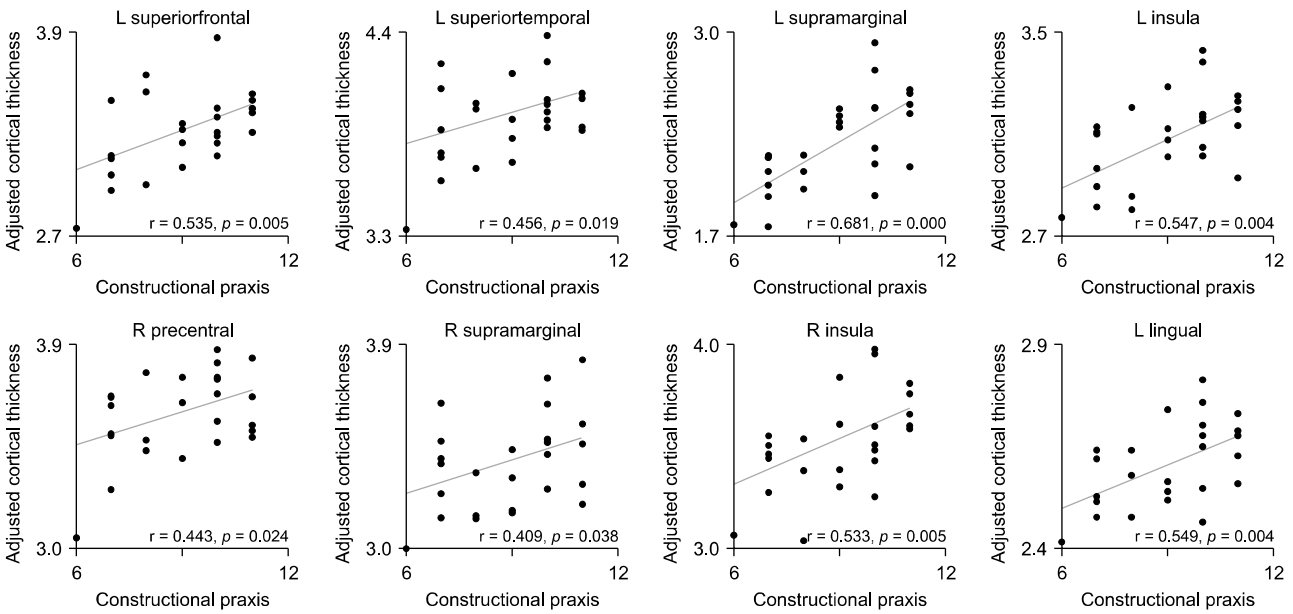

Fig. 3. Correlation of constructional praxis, in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) assessment, with the adjusted mean cortical thickness and local gyrification index (LGI). Each subplot corresponds to a cluster in Table 3. We used partial correlation coefficients between the CERAD score and the average values of cortical measurements, controlling for age, sex, and education level using a general linear model, where the average value was obtained over each cluster.

impairment. In addition, Liu *et al.* [46] reported cortical thinning of both these regions in progressive MCI individuals, as compared with control groups. Our correlation analysis showed the association between the posterior cingulate region and word list memory/recall tasks performed by individuals in the SCI group. This is also consistent with the functional role of the posterior cingulate region.

The superior frontal and rostral middle frontal regions also showed a decrease in cortical thickness in individuals in the SCI group. These regions are known to play a critical role in executive and higher cognitive functions such as working memory [47,48]. Consistent with these roles, thinning in the superior frontal region was found to be associated with word list memory tasks in our correlation analysis. Our findings on the superior frontal and rostral middle frontal regions were consistent with those of previous studies. Meiberth *et al.* [21] reported cortical thinning of the superior frontal region in individuals with SCI. Structural abnormalities in the superior frontal region were also found in familial studies on AD mutation carriers and prodromal AD [49,50]. In addition, Liu *et al.* [46] reported cortical thinning of the superior frontal and rostral middle frontal regions in an AD group.

Additionally, a reduction in the cortical thickness in individuals in the SCI group was also observed in the supramarginal and superior temporal regions. These regions were positively correlated with various cognitive domains in the CERAD battery of tests performed by subjects with SCI. The supramarginal and superior temporal regions are related to dysfunction of visual and auditory word recognition, respectively, which is also associated with AD [39,51]. Cerebral glucose hypometabolism in the superior temporal region was observed in studies on elderly women with subjective memory impairment [40]. Blanc *et al.* [50] previously reported gray matter atrophy of the superior temporal region in individuals with prodromal AD. Other studies have found cortical thinning of the supramarginal region in patients with early-stage AD and familial AD mutation carriers [49,52]. In addition, Lau *et al.* [53] conducted a meta-analysis based on resting-state functional MRI, and reported abnormalities in the supramarginal region of subjects with MCI as compared to healthy controls. Additionally, Redolfi *et al.* [54] demonstrated changes in the supramarginal and superior temporal regions in individuals with AD, based on structural MRI scans. Our results were consistent with these previous findings.

The insula plays a major role in speech and language processing [55]. Patients with AD frequently show lan-

guage difficulties [39]; therefore, thinning of the insular cortex in individuals with SCI was plausible. The results of previous studies were also consistent with those of our study. Davatzikos *et al.* [56] previously reported a decrease in the volume of the insular region in MCI individuals who later developed AD. Eskildsen *et al.* [57] analyzed the cortical thickness of subjects with progressive MCI, and found cortical thinning in the insular region.

In addition to the abovementioned regions, cortical thinning was also found in precentral and postcentral regions of the brain. These regions are associated with motor and somatosensory functions, respectively [58,59]. Song *et al.* [15] showed precentral glucose hypometabolism in these regions in an MCI group, and Liu *et al.* [46] reported cortical thinning of these regions in a group of AD patients, as compared to NCs. Nonetheless, there have been few studies explaining the association between these regions and AD pathology. Further studies are needed to clarify the details of these associations.

Previous studies have reported cortical thinning in the entorhinal, fusiform, posterior cingulate, parahippocampal, and inferior parietal cortices [9,20,21]. Our findings on cortical thickness overlapped with these previous results in part, perhaps due to the differences in spatial resolution used in analysis between those studies and our own. In previous studies, ROI analyses were conducted, rather than the sub-regional whole-brain analyses that we used in our study. In this respect, our analyses on cortical thickness deserve attention. In addition, as far as we know, no previous study had included an LGI analysis of brain MRI scans of individuals with SCI. Furthermore, our results on the LGI values were compatible with previous reports on AD pathology. Our findings on both cortical thickness and LGI scores may support those of previous studies that found association between SCI and future cognitive impairment [1-6]. Further longitudinal studies, examining earlier to later phases of AD, are needed to clarify and validate these findings.

Nonetheless, there are some limitations to this study. First, the sample size of our study was relatively small. This may reduce the generalizability of the present results. Second, we only compared participants with SCI and NC subjects. Considering that SCI is associated with an increased risk of future cognitive decline and AD dementia [1-6], a study that includes both patients with MCI and those with AD would be more appropriate and useful. In addition, a longitudinal design that can observe changes in cognitive function and brain MRI may be more informative than a cross-sectional design as used in this study. Third, we did not check the cognitive domain of main complaints in our SCI participants. Classifying and analyzing the groups according to their main cognitive complaints will help to advance the findings of this study. Fourth, this study did not control confounding factors—especially depressive symptom (GDS score)—that can be associated with SCI. However, given that many older adults who have cognitive complaints and visit the psychiatric clinic tend to have depressive symptoms—whether major or minor degree—, relatively higher GDS scores may reflect this real-life situation in the clinical setting [60]. Further studies controlling various confounding factors may be necessary to verify and advance our findings. Fifth, the score of constructional recall was negatively associated with the left rostral middle frontal and left supramarginal regions in our study. These results were unexpected and cannot be explained in the context of the major functions of these regions and the results of previous studies. Sixth, the size of the identified regions in our analysis was relatively small. Thus, the results should be interpreted with caution; they might contain false positives, especially given the small patient sample size. Despite these caveats, our results are indeed compatible with those of previous studies and the major functional roles of the ROIs. Our identified brain regions were confirmed to demonstrate significant differences between the two groups based on the average value of cortical measurement over the identified brain regions (Figs. 2, 3). Moreover, we found a significant association between cognitive decline in SCI and the average value of cortical measurements over the identified brain regions (Fig. 3; Supplementary Figs. 1—4, available online). In addition, unlike previous studies, this study used LGI analysis in individuals with SCI. Though the very local difference in LGI of the lingual gyrus, it was first reported, and was strongly correlated with the specific cognitive function. Further studies are needed to clarify the regions that represent reduced gyrification in individuals with SCI. Finally, the absence of additional biomarkers indicating AD pathology, such as CSF biomarkers, FDG, or amyloid PET-imaging, is another limitation of this study. The addition of AD biomarkers may increase reliability and can help to max-

imize the findings of this study.

This study compared structural MRI of SCI individuals with those of a NC group by analyzing brain cortical thickness and local gyrification. In the SCI group, we found cortical thinning in the left entorhinal, superior temporal, insula, rostral middle frontal, precentral, superior frontal, and supramarginal regions, and the right supramarginal, precentral, insula, postcentral, and posterior cingulate regions, as compared to the NC group. In addition, decreased gyrification was found in the left lingual gyrus of SCI individuals.

In conclusion, our results may provide a further basis for the concept that SCI may be associated with future cognitive impairment. This study may help clinicians assess individuals with SCI who may progress to MCI and AD, and eventually, may contribute to early diagnosis of AD. In addition, our LGI analyses in individuals with SCI may form a basis for future studies.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Data Curation: Hyun-Ghang Jeong, Suji Lee, HyunChul Youn. Formal Analysis: Myungwon Choi, Daegyeom Kim, Cheol E. Han, HyunChul Youn, Sangil Suh. Funding Acquisition: Hyun-Ghang Jeong, Cheol E. Han. Investigation: Sangil Suh, Hyun-Ghang Jeong, Suji Lee. Methodology: Myungwon Choi, Cheol E. Han. Project Administration: Hyun-Ghang Jeong. Resources: Hyun-Ghang Jeong, Sangil Suh. Software: Myungwon Choi, Daegyeom Kim, Cheol E. Han. Supervision: Hyun-Ghang Jeong. Visualization: Myungwon Choi, Daegyeom Kim, Cheol E. Han. Writing−Original Draft Preparation: HyunChul Youn, Myungwon Choi. Writing−Review & Editing: HyunChul Youn, Myungwon Choi, Cheol E. Han, Hyun-Ghang Jeong.

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