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ORIGINAL COMMUNICATION

Volume reduction in subcortical regions according to severity of Alzheimer's disease

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Abstract We investigated whether there exists a hierarchical vulnerability of subcortical structures with respect to the severity of Alzheimer's disease (AD). A total of 236 subjects (179 with AD and 57 with normal cognition) underwent 1.5-T magnetic resonance (MR) imaging. The volumes of the five subcortical structures (amygdala, thalamus, putamen, globus pallidus, and caudate nucleus) and hippocampus were analyzed using a large deformation diffeomorphic metric mapping algorithm. The volume changes were evaluated according to the Clinical Dementia Rating (CDR). Correlation between the volumes of the subcortical structures and scores of the cognitive domain-specific neuropsychological tests were evaluated. Volume loss of the amygdala occurred even in the very mild stage of AD (CDR 0.5), as did volume loss in the hippocampus. Similar reductions in volume occurred in the thalamus and putamen, however during the mild (CDR 1) and moderate (CDR 2) stages of AD, respectively. The globus pallidus and caudate nucleus remained devoid of changes until the moderate stage of AD ($p < 0.01$). Volume loss in those subcortical structures correlated with the neuropsychological test scores ($p < 0.01$). Our results suggest that there is a hierarchical vulnerability in subcortical structures according to the clinical severity of AD and that subcortical volume reductions correlate with cognitive impairment.

Keywords Alzheimer's disease · Subcortical structures · MRI · Volume

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Introduction

Although many magnetic resonance imaging (MRI)-based studies have shown volume loss of whole brain or cortical structures including the hippocampus in Alzheimer's disease (AD) [9, 32], little is known about the volume loss of subcortical structures, including the amygdala, thalamus, putamen, globus pallidus, and caudate nucleus. Since extrapyramidal symptoms [10, 29] and behavioral changes [7, 21] in patients with AD tend to develop later in the disease course, it can be speculated that the degeneration in relevant subcortical structures associated with frontal–subcortical circuits may occur later than the degeneration in the hippocampus and neocortex [6, 17]. Results from pathologic studies, however, suggested that neurofibrillary tangles begin to deposit in some subcortical structures as early as in the hippocampus [3, 4]. As such, if the primary pathological changes in the subcortical structures develop earlier than previously believed and if such pathologic burden progresses with the severity of the disease, volume analyses of subcortical structures at each disease stage of AD may be informative as potential biomarkers for predicting disease status.

To date, only a few MRI studies have evaluated the atrophy of subcortical structures among patients with AD [8, 11, 12]. Two previous studies compared healthy elderly controls, patients with mild cognitive impairment (MCI) and patients with AD (median Clinical Dementia Rating, CDR, 0.75 and 1.0, respectively) [11, 12]. However, changes in the volumes of subcortical structures were not the focus of these studies. Another study compared healthy elderly with patients with AD and described decreases in the volumes of the thalamus and putamen among the patients with AD [8]. However, the small number of patients with AD enrolled in that study limited classification of patients into subgroups according to the severity of the disease.

In this study, we analyzed the volumes of five subcortical structures (amygdala, thalamus, putamen, globus pallidus, and caudate nucleus) and the volume of the hippocampus as a reference. First, potential differences in volume loss across the subcortical structures were examined according to disease severity varying from normal cognition (NC; CDR 0) to the different stages of AD (CDR from 0.5 to 2). Second, correlations between the volumes of the subcortical structures and the scores of the cognitive domain-specific neuropsychological tests and the Mini-Mental Status Examination (MMSE) were examined to further understand the volume loss in subcortical structures.

Methods

Subjects

We identified a total of 456 individuals who visited our memory disorder clinic from October 1999 to March 2008, completed both clinical assessment for dementia and high-resolution T1-weighted volumetric MRI scans using the same scanner, and were diagnosed as NC, MCI, or AD. Of these, after excluding subjects with advanced AD (CDR 3 and 4), MCI, and NC with CDR 0.5, we included 66 individuals with NC and 187 patients with AD (CDR 0.5–2). All subjects underwent neurological examinations and neuropsychological tests. Laboratory tests, including complete blood count (CBC), chemistry, vitamin B12/folate, syphilis serology, and thyroid function tests, were normal for all subjects involved in the study. Patients who had infarction, hemorrhage, tumor, trauma, or severe white matter hyperintensity (deep white matter $\geq$25 mm and caps or band $\geq$10 mm) were excluded from the study. The diagnosis of probable AD was made by two experienced neurologists (DL Na and SW Seo) according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [16]. Subjects with NC fulfilled the following criteria: (1) no history of neurological or psychiatric disorders except for memory complaint, (2) intact cognition measured by neuropsychological tests (described later), and (3) normal activities of daily living (ADL) measured by Seoul-Instrumental Activities of Daily Living (S-IADL) as a score of <8 out of 20 [14].

Out of the initial 253 individuals recruited for the study, 17 (8 with AD and 9 NC) were excluded because of failure to analyze subcortical volume due to abnormal tracing of structures. As such, 236 participants (179 with AD and 57 NC) were analyzed. Patients with AD were divided into three groups according to CDR score (0.5, 1, and 2). We did not include the normal elderly with CDR 0.5 and the patients with MCI, due to their heterogeneous clinical and pathological findings [22]. The four groups of subjects did not differ with respect to sex ratio or intracranial volume (ICV). Age, duration of education, and cognitive status, as measured by MMSE, differed among the groups (Table 1). Informed, written consent for participation was obtained from each individual, and the Institutional Review Board of the Samsung Medical Center approved the protocol of this study.

Neuropsychological tests

The Seoul Neuropsychological Screening Battery (SNSB), a standardized neuropsychological battery, was used to assess each subject. The SNSB consists of tests for verbal and visual memory, attention, language, praxis, four elements of Gerstmann syndrome, visuoconstructive function, frontal executive function, and the MMSE. The Seoul Neuropsychological Screening Battery-Dementia version (SNSB-D) is composed of five subscores: attention, language-related function, visuospatial function, memory, and frontal executive function. Each cognitive domain of the SNSB-D consists of the scorable items of the SNSB (Table 2), and details have been described elsewhere [1]. Each of the scores on the SNSB-D subscales falling below the 16th percentile of normally distributed scores was regarded as abnormal.

MR imaging for volumetric analysis

Image acquisition

Brain MRI was performed using a 1.5-T MRI scanner (Sigma; GE Healthcare). Fast fluid-attenuated inversion recovery images, T1-weighted images, and T2-weighted images were obtained. All images were acquired during the same session using the same orientation and slice positions. Three-dimensional, T1-weighted spoiled gradient (SPGR) echo images were obtained with the following imaging

Table 1 Demographic and clinical characteristics of individuals with normal cognition and AD

	NC ($N = 57$)	AD			AD, total ($N = 179$)	p value
		CDR 0.5 ($N = 66$)	CDR 1 ($N = 79$)	CDR 2 ($N = 34$)		
Mean age, years (±SD)[a]	66.1 ± 8.3	75.2 ± 7.0*	73.4 ± 8.6*	71.3 ± 9.6*	73.7 ± 8.4	<0.001
Sex ratio (men:women)[b]	21:36	24:42	26:53	10:24	60:119	0.634
Education, years (±SD)[a]	11.5 ± 5.0	8.6 ± 5.1*	8.0 ± 5.9*	8.6 ± 5.6	8.4 ± 5.6	<0.001
K-MMSE score (IQR)[c]	29 (28–30)	23 (20–25)*	19 (16–22)*, **	12.5 (11–18)*, **, §	20 (15–25)	<0.001
ICV, cm^3 (±SD)[a]	1,309.4 ± 103.2	1,322.3 ± 125.0	1,291.8 ± 118.7	1,262.8 ± 118.0	1,298.5 ± 124.3	0.211

Data are presented as mean (±SD) for normally distributed variables and median (25th–75th percentile, IQR) for non-normally distributed variables

CDR Clinical Dementia Rating, *SD* standard deviation, *IQR* interquartile range, *K-MMSE* Korean version of the Mini-Mental State Examination

* Significant difference ($p < 0.01$) between subjects with CDR 0 and the other groups

** Significant difference ($p < 0.01$) between subjects with CDR 0.5 and the other groups

§ Significant difference ($p < 0.01$) between subjects with CDR 1.0 and the other groups

[a] Analysis of variance (ANOVA) followed by Bonferroni's post hoc test

[b] χ^2 test

[c] Kruskal–Wallis test followed by Bonferroni's post hoc test

Table 2 The cognitive domain-specific scoring system of the Seoul Neuropsychological Screening Battery-Dementia version (SNSB-D)

SNSB-D total score (300)	
Memory (150)	*Frontal executive function (70)*
Orientation (6)	Motor impersistence (3)
SVLT free/delayed recall (48)	Contrasting program (3)
SVLT recognition (12)	Go-no-go (3)
Rey figure immediate/delayed recall (72)	Fist-edge-palm (3)
Rey figure copy recognition (12)	Luria loop (3)
Language and related function (27)	Word fluency, semantic (20)
K-BNT (15)	Word fluency, phonemic (15)
Calculation (12)	Stroop test (20)
Visuospatial function (36)	*Attention (17)*
Rey figure copy (36)	Digit span forward (9)
	Digit span backward (8)

SVLT Seoul Verbal Learning Test, *K-BNT* Korean version of the Boston Naming Test

parameters: coronal slice thickness, 1.5 mm; echo time, 7 ms; repetition time, 30 ms; number of excitations, 1; flip angle, 45°; field of view, 22 cm × 22 cm; and matrix size, 256 × 256 pixels.

Subcortical volume analysis

We automatically delineated the subcortical structures from intensity inhomogeneity-corrected T1-weighted MR images [31] using a Markov random field model which incorporates the subcortical anatomical definition as prior. The Markov random field model was first applied to label each voxel in the image volume as either gray matter, white matter, cerebrospinal fluid (CSF), or subcortical structure [12]. Due to the lack of constraints on structural shapes, this process resulted in unsmoothness and a number of topological errors (e.g., holes) at the boundaries of the structures. This lack of constraint on the structural shapes may have led to increased variation in the volume measurements, thus reducing the statistical power to detect differences among the groups. To avoid this issue, subcortical volumes were generated for each individual subject with the appropriate properties of smoothness and topology by injecting a template shape with a smooth boundary into them and using a large deformation diffeomorphic metric mapping (LDDMM) algorithm [24]. The template shape was created from 41 manually labeled subcortical volumes via a large deformation diffeomorphic template generation algorithm [23]. Each volume was approximated using the transformed template through the LDDMM diffeomorphic map. The mathematical derivation of this template injection procedure and its evaluation with a variety of subcortical structures have been detailed in other works [26]. This delineation approach has been used successfully to investigate subcortical structure shapes in AD [25], hippocampal shapes in geriatric depression [27], basal ganglia shapes in attention deficit hyperactivity disorder (ADHD) [24], and thalamic abnormalities in schizophrenia [28].

Statistical analysis

One-way analysis of variance (ANOVA) and the Kruskal–Wallis test were used to compare the demographic data of the four diagnostic groups. Components that fulfilled the preconditions of ANOVA, normal distribution of variables and homogeneity of variance, were used in the ANOVA followed by a Bonferroni's post hoc test for multiple pairwise comparisons. The demographic components that

did not fulfill the preconditions of ANOVA were analyzed using the Kruskal–Wallis test followed by a Bonferroni's post hoc test for multiple comparisons of mean ranks. Sex ratios were evaluated using a χ^2 test. Normally distributed variables are presented as mean ± standard deviation (SD), and non-normally distributed variables are presented as median and interquartile range (IQR; 25th−75th percentile). General linear model was used to examine the volume differences in each subcortical structure among the groups after controlling for age, gender, and ICV. Bonferroni's post hoc analysis was performed for the pairwise comparisons between each group of subjects ($p < 0.01$). A Spearman's bivariate correlation analysis was performed to evaluate the correlations among the neuropsychological test scores and the volumes of each of the subcortical structures ($p < 0.01$). Linear regression analysis was performed using each of the SNSB-D subscores as the dependent factor and the volumes of the subcortical structures as the independent factors. Gender served as a fixed factor, and age, duration of education, and ICV were included as covariates. For the regression analysis, p-values of <0.05 were considered to be statistically significant. All statistical tests were two tailed.

Results

Volumes of subcortical structures according to CDR stage

Hippocampal volume decreased as the severity of the disease increased from the NC group to the CDR 2 group. Post hoc analysis revealed that hippocampal volume differed between the NC group and CDR 0.5 group and among the CDR 0.5 group and each of the remaining groups ($p < 0.01$). The amygdala showed a similar pattern of volume reduction; however, unlike the hippocampus, there were no differences between the CDR 0.5 group and the other groups ($p < 0.01$). The volume of the thalamus was also reduced as a function of disease severity; however, a statistically significant volume reduction was only noted when the severity reached CDR 1 ($p < 0.01$). The volume in the putamen was only different between the NC group and the CDR 2 group ($p < 0.01$). In contrast, there were no differences in the volumes of the globus pallidus or the caudate nucleus among the NC and any of the different CDR groups ($p > 0.05$; Fig. 1).

Correlation between subcortical volumes and the scores of the neuropsychological tests

The results from each of the cognitive domain-specific scores and the total score of the SNSB-D differed between the NC participants and the patients with AD. These scores also differed among each of the groups of the AD subjects according to disease severity (Table 3). The volumes of the hippocampus and amygdala correlated with language, memory, frontal executive function scores, and total scores on the SNSB-D and the MMSE score. The volumes of the thalamus and putamen demonstrated lower-degree correlation with each of the SNSB-D scores and the MMSE score. Volumes of the globus pallidus also correlated with language, memory, frontal executive function scores, and total SNSB-D scores to a very weak degree. Neither positive nor negative correlations were observed between any of the neuropsychological test scores and the volume of the caudate nucleus (Table 4).

In the regression models, after controlling for age, sex, duration of education, and ICV, the volume of the hippocampus correlated with memory ($B = 13.282$, $p < 0.001$), visuospatial function ($B = 3.523$, $p = 0.003$), frontal executive function ($B = 4.576$, $p = 0.007$), and total SNSB-D scores ($B = 23.011$, $p < 0.001$). Out of the five subcortical structures, only the volume of the putamen showed correlation with the frontal executive function score ($B = 4.534$, $p < 0.001$) and the language ($B = 1.162$, $p = 0.031$) and total scores of the SNSB-D ($B = 9.675$, $p = 0.024$).

Discussion

The first goal of this cross-sectional study is to demonstrate the different vulnerabilities of five subcortical structures according to the clinical severity of AD, using an automated MR volumetric analysis. The stage at which the volume was significantly reduced from normal cognition differed among subcortical structures. Volume loss in the amygdala was observed even in the very mild stage of AD (CDR 0.5), as it was in the hippocampus. Compared with the amygdala and hippocampus, the volumes of the thalamus and putamen demonstrated a similar but "shifted to the right" pattern of volume reduction; that is, the volume of the thalamus was reduced only when disease severity reached the mild stage (CDR 1), and the putamen showed changes only when the severity reached the moderate stage of AD (CDR 2). In contrast, volume changes in the globus pallidus and caudate nucleus were not noted even in the moderate stage of AD.

Our findings regarding the hierarchical volume loss in subcortical structures are in accordance with previous autopsy studies [4, 15]. According to the Braak and Braak staging, neurofibrillary tangles accumulate in the anterodorsal nuclei of the thalamus and amygdala at the transentorhinal stage along with those in the hippocampus (stage II out of VI) and then accumulate in the other nuclei

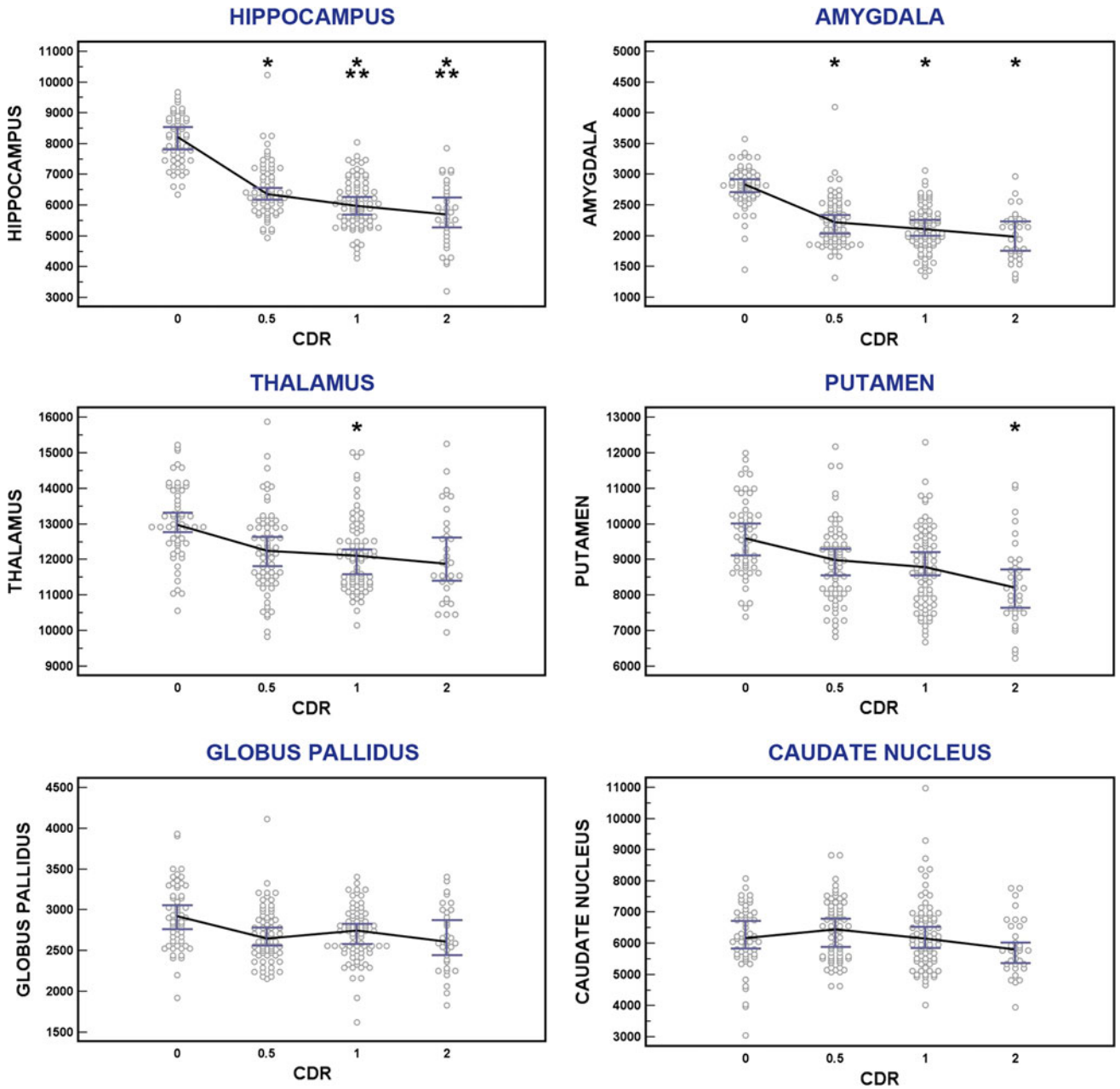

Fig. 1 Patterns of change in the volumes of the five subcortical structures and hippocampus. The volume change of the five subcortical structures and hippocampus are presented from normal cognition (Clinical Dementia Rating scale, CDR 0) to each of the AD severity states (CDR 0.5, 1, and 2). *Error bars* indicate 95% confidence intervals. *Solid lines* connecting the scatter plots of each group represent the median values of the subcortical structure volume (in microliters). *Asterisks* indicate statistical difference between the CDR 0 group and the other groups, and *double asterisks* indicate statistical difference between the CDR 0.5 group and the other groups, with a p value <0.01

of the thalamus and putamen at the limbic stage (stage IV out of VI) [4]. The lack of change in the volume of the globus pallidus in our study is consistent with previous pathological studies that reported that amyloid plaques and neurofibrillary tangles deposit less frequently in this area [5, 15, 19].

Lack of volume loss in the caudate nucleus is inconsistent with autopsy findings of amyloid plaques and neurofibrillary tangles accumulation in this area [4, 5, 15, 30, 33]. There may be two possible reasons for the discrepancy in the caudate nucleus. First, there may be a time lag between the initial pathological burden of the plaques and tangles and the subsequent volume change. Alternatively, the discrepancy may be related to the method we used to measure the whole caudate volume. Since the head of the caudate nucleus is known to be most relevant to

Table 3 Neuropsychological test results of individuals with normal cognition (NC) and Alzheimer's disease (AD)

	NC ($N = 57$)	AD			AD ($N = 179$)
		CDR 0.5 ($N = 66$)	CDR 1 ($N = 79$)	CDR 2 ($N = 34$)	
Attention (IQR)[a]	10.0 (9.0–11.0)	8.0 (7.0–9.0)*	8.0 (6.0–9.0)*	6.0 (4.0–7.0)*, **, §	7.0 (6.0–9.0)*
Language (IQR)[a]	25.0 (23.0–26.0)	17.0 (13.4–21.0)*	15.0 (11.0–19.0)*	9.9 (6.8–13.5)*, **, §	15.0 (10.0–19.0)*
Visuospatial function (IQR)[a]	34.0 (32.0–36.0)	29.0 (16.5–33.0)*	21.0 (12.0–31.0)*	7.0 (1.4–23.2)*, **, §	22.5 (9.5–31.0)*
Memory (IQR)[a]	87.5 (71.8–97.0)	27.3 (24.4–34.6)*	24.5 (17.0–33.0)*	13.0 (7.9–22.0)*, **, §	24.5 (17.0–31.5)*
Executive function (±SD)[b]	56.9 ± 12.2	31.8 ± 12.2*	28.2 ± 11.0*	17.8 ± 11.7*, **, §	27.5 ± 12.5*
SNSB-D sum score (IQR)[a]	216.0 (190.9–231.7)	112.0 (89.9–127.9)*	98.5 (70.7–117.3)*	52.5 (33.6–85.3)*, **, §	99.9 (66.5–119.0)*

Data are presented as mean ± SD for normally distributed variables and median (25th–75th percentile, IQR) for non-normally distributed variables

CDR Clinical Dementia Rating, *SD* standard deviation, *IQR* interquartile range, *SNSB-D* Seoul Neuropsychological Screening Battery-Dementia version

* Significant difference ($p < 0.01$) between subjects with CDR 0 and the other groups

** Significant difference ($p < 0.01$) between subjects with CDR 0.5 and the other groups

§ Significant difference ($p < 0.01$) between subjects with CDR 1.0 and the other groups

[a] Kruskal–Wallis test followed by Bonferroni's post hoc test

[b] ANOVA followed by Bonferroni's post hoc test

Table 4 Correlations between the subcortical structure volume and the scores of the SNSB-D and MMSE

		Attention	Language	Visuospatial function	Memory	Frontal executive function	SNSB-D total score	K-MMSE
Hippocampus	Spearman's rho	0.321**	0.441**	0.398**	0.573**	0.482**	0.527**	0.600**
	Sig. (two-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Amygdala	Spearman's rho	0.317**	0.457**	0.387**	0.525**	0.473**	0.505**	0.540**
	Sig. (two-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Thalamus	Spearman's rho	0.228*	0.365**	0.268*	0.240**	0.265**	0.300**	0.300**
	Sig. (two-tailed)	0.002	<0.001	0.001	<0.001	<0.001	<0.001	<0.001
Putamen	Spearman's rho	0.202*	0.323**	0.231*	0.293**	0.327**	0.315**	0.293**
	Sig. (two-tailed)	0.002	<0.001	0.001	<0.001	<0.001	<0.001	<0.001
Globus pallidus	Spearman's rho	0.070	0.204*	0.167	0.192*	0.199*	0.202*	0.185*
	Sig. (two-tailed)	0.285	0.002	0.010	0.003	0.002	0.002	0.003
Caudate nucleus	Spearman's rho	0.068	0.090	0.101	0.063	0.066	0.079	0.111
	Sig. (two-tailed)	0.301	0.167	0.123	0.332	0.313	0.227	0.088

SNSB-D Seoul Neuropsychological Screening Battery-Dementia version, *K-MMSE* Korean version of the Mini-Mental State Examination

* Significant correlation ($p < 0.01$)

** Significant correlation ($p < 0.001$)

cognitive functioning [20], the volume measurement of the body and tail of the caudate nucleus might have served to offset the volume reductions in the head of the caudate nucleus.

The second goal of this study is to examine the correlations of the volumes of the subcortical structures with the scores of the neuropsychological tests. The results also support the hierarchical volume loss in subcortical structures. That is, the volume reductions in the hippocampus and amygdala correlated with decreased MMSE and SNSB-D scores. The volume reductions in the thalamus and putamen, which occurred at greater disease severity, also correlated with decreased MMSE and SNSB-D scores but to a lower degree. Lastly, the globus pallidus and caudate nucleus with no significant volume loss showed no or very weak correlation with the neuropsychological test scores. The correlations between the volumes of the subcortical structures and the results of the neuropsychological tests were also examined using a linear regression model after controlling for age, sex, duration of education, and ICV. The volume of the putamen correlated with the scores of the frontal executive and language functions. This finding is consistent with prior functional and structural imaging studies that reported that the putamen plays

important roles in language and executive function [2, 13]. However, except for the putamen, no other subcortical structures showed correlations with the neuropsychological test scores in the linear regression model. The reason for this remains to be elucidated, but it may be related to the method we used to measure the whole volume of each subcortical structure rather than to analyze shape of each subcortical structure. Previous autopsy series have revealed that there are regions which are more vulnerable to AD pathology among substructures of the subcortical structures; for example, amyloid plaques or neurofibrillary tangles deposit earlier in the antero–ventral or central medial nuclei of the thalamus [3, 4], which are associated with cognitive functioning such as attention and memory [18, 34]. Therefore, this subregional specificity might not have been detected by our correlation analyses between the whole volume measurement and neuropsychological test scores.

Our study was based on cross-sectional data, which may not represent the actual progression of the disease. Thus, future studies investigating degenerative changes in the subcortical structures of patients with AD based on longitudinal follow-up are needed.

Conclusions

We found a hierarchical volume reduction in subcortical structures in patients with AD, first in the hippocampus and amygdala, and then in the thalamus and putamen. The globus pallidus and caudate nucleus remained devoid of volume reductions until the moderate stage of AD. The volume losses of these subcortical structures correlated with the neuropsychological test results. This hierarchical vulnerability of subcortical structures may help to predict the onset of AD and to monitor the progression of AD along with other multimodal techniques for diagnosing and predicting the prognosis of AD.

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Conflicts of interest None.

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