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Research article

Domain-specific longitudinal associations between brain volume, white matter lesions, and cognitive function changes

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ABSTRACT

Objectives: We investigated the domain-specific patterns of the association of segmental brain volume and white matter signal abnormality (WMSA) volume with longitudinal changes in cognitive function.

Methods: Participants from an institutional health check-up program who were aged >50 years, did not have a confirmed central nervous system disorder and underwent baseline and follow-up evaluations for cognitive function and brain MRI with an interval of at least 1 year were included. Cognitive function was assessed using the Consortium to Establish a Registry for Alzheimer's Disease-Korean version (CERAD-K) assessment battery. Performance changes in each cognitive domain were analyzed for associations with serial data of segmental brain volume and WMSA volume.

Results: A total of 190 subjects were included (115 [60.1 %] females, mean age 68.2 ± 8.2 years [range 50–82 years]). Declines in global cognition were associated with lower baseline (P=0.001) and decreasing volumes (P=0.001) of the hippocampus and amygdala and with increasing total WMSA volumes (P=0.008). Declines in the executive function domain were associated with lower baseline volumes of the hippocampus and amygdala (P = 0.018) and with increasing total WMSA volumes (P=0.015). Declines in the language function and the verbal learning domains were associated with lower baseline (P=0.009 and P=0.002, respectively) and decreasing volumes (P=0.008 and P=0.001, respectively) of the hippocampus and amygdala. Decline in the memory recall was associated with higher total WMSA volumes at baseline (P=0.014). Declines in the recognition memory domains were associated with lower baseline hippocampus and amygdala volume (P = 0.020) and with increases in total WMSA volumes (P=0.012).

Conclusions: The segmental brain volume and the WMSA volume parameters have domain-specific associations with longitudinal cognitive changes, which might reflect the different dependence on the brain reserve according to the cognitive domains.

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1. Introduction

While the main mechanism of aging-related cognitive decline is the long-term pathological process of neuronal degeneration in the brain [1–3], the connections among the functional brain areas also plays an important role in compensating for the degeneration and maintaining cognitive resilence, a phenomenon known as 'brain reserve' [4–6]. Given that each cognitive domain might vary in its functional dependence on the integrity of specific anatomical regions or their connections to other brain areas [4,6], the impact of neuronal degeneration or the disruption of brain functional reserve on the long-term cognitive decline might differ across domains.

Segmental brain volume and white matter signal abnormalities (WMSA) are among the most widely investigated structural MRI parameters for understanding the pathomechanisms of aging-related cognitive changes, across normal aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD) [3,7–20]. Healthy aging is known to involve hippocampal and prefrontal atrophy and increased periventricular WMSA [14,19]. Amnestic MCI shows significant hippocampal and medial temporal volume decrement, while non-amnestic MCI involves atrophy in prefrontal and parietal regions. WMSA burden also differs, with posterior WMH in amnestic MCI and diffuse WMSA in non-amnestic MCI [16,18,20]. In AD, hippocampal and temporal atrophy accelerates and WMSA increases, correlating with memory decline [18].

Brain volume parameters, WMSA, and their rates of change may differentially impact cognitive outcomes depending on baseline cognitive status and specific domains. While both baseline profiles and longitudinal changes in these parameters are linked to long-term cognitive outcomes [2,3,9–13,21], limited studies have comprehensively examined how segmental brain volumes and WMSA contribute to changes in specific cognitive domains [22–24]. Such an approach could clarify the pathophysiological mechanisms underlying domain-specific cognitive decline and enhance MRI-based models for predicting cognitive impairment and neurodegenerative diseases.

We hypothesized that specific segmental brain volume and WMSA parameters would show domain-specific associations with longitudinal changes in cognitive function, reflecting distinct patterns of vulnerability across cognitive domains. Based on this hypothesis, the study aimed to identify the brain volume and WMSA parameters that influence long-term changes in global cognitive function and major cognitive domains in cognitively intact older adults.

2. Materials and methods

2.1. Study subjects and clinical data

This retrospective cohort study included 190 consecutive subjects who were ≥50 years of age, voluntarily participated in a routine health check-up program provided by Seoul National University Healthcare System, Gangnam Center, between January 2010 and December 2020, performed baseline cognitive function and brain MRI evaluations with intervals of 3 months or less between each evaluation, and performed follow-up cognitive function and brain MRI evaluations with an interval of at least 1 year from baseline. The included subjects did not have a confirmed diagnosis of a central nervous system disorder such as dementia, stroke, tumor, or other structural or neurodegenerative diseases. In every subject, the indication for MRI and MR angiography evaluation was for a regular health check-up. Every subject voluntarily decided to perform brain MRI and MR angiography, and pay the full cost of evaluation, which is not uncommon in Korea in which the cost of brain MRI evaluation is relatively cheaper than that in other developed countries. The Institutional Review Board of the Seoul National University Hospital approved this study protocol (IRB no. H-2004-23201119), and informed consent for the use of medical records for research was waived by the board. All methods were performed in accordance with the relevant guidelines and regulations. This study is reported in accordance with STROBE guidelines.

Clinical profiles included information on age, sex, years of education, and the presence of hypertension, diabetes mellitus, hyperlipidemia, taking of antidepressants, regular alcohol consumption, and a history of smoking within the past 5 years. Laboratory data at baseline, such as systolic and diastolic blood pressure (millimeter of mercury, mmHg), pulse pressure (mmHg), and the levels of fasting glucose (mg/dL), total cholesterol (mg/dL), low-density lipoprotein (LDL, mg/dL), high-density lipoprotein (HDL, mg/dL), triglycerides (mg/dL), blood urea nitrogen (mg/dL), creatinine (mg/dL), and high-sensitivity C-reactive protein (mg/dL), were obtained.

2.2. Cognitive function analysis

The Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological assessment battery (CERAD-K) was used for the assessment of cognitive function [25]. The total CERAD-K score was calculated by summing the scores of six subtests (verbal fluency for the executive function domain, Boston naming for the language function domain, word list memory for the verbal learning domain, constructional praxis for the visuospatial function domain, word list recall for the memory recall domain, and word list recognition for the recognition memory function domain), except those of the Mini-Mental State Examination (MMSE) and the constructional praxis recall subtests [26]. For the total and subset scores, z-scores normalized for age, sex, and years of education were used. These z-scores were derived from a separate, previously conducted population-level study [25] Based on a prior study involving a large elderly population in Korea, including individuals with mild cognitive impairment (MCI) and dementia, MCI was determined using a cutoff score of 59.5, and dementia was identified using a cutoff score of 49.5 [27].

2.3. Magnetic resonance imaging analysis

For every participant, a 3.0-T MRI scanner with a 32-channel head coil was used. For T1-weighted images, a multiecho MPRAGE pulse sequence was utilized, and for T2-weighted images, a turbo-spin–echo sequence with variable flip-angle was used. Images were obtained using the following parameters: 0.8 mm isotropic voxels; sagittal field of view = 256 × 240 × 166 mm; matrix = 320 × 300 × 208; for the T1-weighted images, repetition time/inversion time = 2500/1000 ms, echo time = 1.8/3.6/5.4/7.2 ms, and flip angle = 8°, water excitation employed for fat suppression, up to 30 repetition times allowed for motion-induced reacquisition; and for the T2-weighted images, repetition time/echo time = 3200/564 ms and turbo factor = 314 [28].

The FreeSurfer image analysis suite (www.surfer.nmr.mgh.harvard.edu/, version 6.0.0) was used for image preprocessing [28–31]. Brain segmentation and volume measurement were performed according to the fully automated process using the T1-based MP-RAGE sequence [28–31]. Total brain, cortex, subcortical gray matter, WM, basal ganglia, thalamus, hippocampus, amygdala, cerebellum, and ventricle volumes were obtained from the reconstruction and segmentation data. Each volume was expressed as a percentage of the intracranial volume.

WMSAs were automatically segmented based on T1-weighted images according to the signal intensity and spatial information [30,32]. Compared to T2-or Fluid Attenuated Inversion Recovery (FLAIR)-based evaluation of white matter hyperintensity, the lesion volume of WMSA might be smaller, due to that this approach selects only the most hypointense component of the lesions visible on T2/FLAIR [33]. However, this measurement is highly correlated with the T2/FLAIR-based white matter hyperintensity volumes [32]. WMSAs were classified based on the relative distance from the lateral ventricle into periventricular (within 13 mm from the ventricular surface) and deep (13 mm or further) lesions based on each mask created using FreeSurfer procedures of segmentation for the lateral ventricle, periventricular WM, and deep WM regions [28,30].

The volumes were calculated with respect to the number of voxels, where one voxel corresponded to 1 cubic millimeter. All the parameters were measured individually for each hemisphere. To reduce the number of segmental volume parameters and minimize the redundancy and co-linearity among them, volume parameters were plotted based on Pearson's r coefficient and classified using the hierarchical clustering of the correlation matrix, which returned 8 classes of brain segments as follows: cortex, white matter, corpus callosum, striatum, thalamus, hippocampus and amygdala, diencephalon and brainstem, and cerebellum segments. Given that all parameters had the most substantial correlation between the two hemispheres, we combined the parameters from both hemispheres. (Supplemental Figs. 1 and 2).

2.4. Statistical analysis

All statistical analyses were performed using R software (version 4.0.3; R team, Vienna, Austria). Data are presented as the mean ± standard deviation, median [interquartile range, IQR], or numbers (percentages). WMSA volume parameters were log-transformed to obtain a normal distribution. The normality of the distribution of WMSA volume parameters was evaluated using boxplots with jitter elements and Shapiro-Wilk tests (Supplemental Fig. 3). The changes in the brain segmental volume, WMSA volume, and cognitive function scores were divided by the follow-up interval to obtain the annual rate of change of the parameters. Paired-samples T-test was used to compare the baseline and follow-up cognitive function and MRI profiles. Pearson's r coefficient was used to evaluate the correlations between the brain MRI parameters and the change in the cognitive function scores. Variables with P values < 0.10 from the correlation analyses were in the linear regression analyses to identify MRI parameters associated with the annual rate of cognitive function score changes, using the backward elimination method. Baseline MRI parameters and longitudinal change rates of MRI parameters were separately included in the linear regression models, which were conducted for the total CERAD-K score and its six subset scores, resulting in 14 regression models.

The annual rate of cognitive function score changes was designated as the outcome parameter to account for heterogeneous follow-up intervals among individuals [34,35]. The lines-and-dots plot visualizing participant-level changes in the CERAD-K total score (Supplemental Fig. 4) and the boxplots with jitter elements comparing absolute changes in the CERAD-K score and the rate of CERAD-K score change (Supplemental Fig. 5) across quartiles of follow-up intervals indicated that the annual rates of change in the CERAD-K total score and CERAD-K z-score were comparable across the quartiles of follow-up intervals.

All regression models were adjusted for demographic variables (age, sex, and years of education), clinical factors (presence of hypertension, hyperlipidemia, diabetes mellitus, antidepressant use, regular alcohol consumption, and smoking history within the past 5 years), and baseline laboratory parameters (systolic blood pressure, pulse pressure, hemoglobin A1c, serum creatinine, total cholesterol, and low-density lipoprotein). To explore potential interaction effects between age and MRI parameters, the regression analyses were re-performed by incorporating an interaction variable between age and MRI parameters found to be significant in the original models. The R^2 values of the original and new models were compared, and the statistical significance of the interaction variable in the new model was assessed. The variance inflation factor (VIF) was used to check for multicollinearity among variables in the regression analyses, and a scatterplot of the standardized predicted values and the standardized residuals was checked to assess the linearity of the regression model. Generalized Estimating Equations (GEE) analyses were conducted to validate the MRI parameters that showed significant associations in each linear regression model, including all demographic, clinical, and laboratory parameters described above. For all analyses, P values were adjusted for multiple comparisons using the Benjamini-Hochberg method, and statistical significance was determined based on a false discovery rate threshold of 0.05.

2.5. Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon request.

3. Results

A total of 190 subjects were included in this study (115 [60.1 %] females, mean age 68.2 ± 8.2 years [range 50–82 years]). The mean years of education were 14.2 ± 3.7 years. At baseline, the mean total CERAD-K score was 74.3 ± 15.0 (z score 0.5 ± 1.3). Twenty subjects (10.5 %) were classified as having MCI based on the total CERAD-K score. The clinical, laboratory, and total CERAD-K score profiles are shown in Table 1. After a median of 3.9 [2.3–5.4] years, the mean total CERAD-K score at follow-up was 70.7 ± 16.6 (z score 0.3 ± 1.5), and the rate of change of the total CERAD-K z score was 0.1 ± 0.4 per year. Among the 170 subjects without MCI at baseline, 14 (8.2 %) progressed to MCI, and 8 (4.7 %) progressed directly to dementia. Among the 20 subjects with MCI at baseline, 10 (50.0 %) progressed to dementia, 8 (40.0 %) remained stable, and 2 (10.0 %) improved to a non-MCI status. Compared to the baseline, the scores for the total CERAD-K and each of the cognitive function domains exhibited a significant decline (all, $P < 0.05$), except for the scores of the executive function and the visuospatial function ($P = 0.658$ and $P = 0.096$, respectively) (Table 2).

At the baseline brain MRI, the total brain volume was 1044.3 ± 96.9 mL, and the total WMSA volume was 5.0 ± 5.9 mL. At follow-up MRI evaluations with a median interval of 3.9 [2.3–5.5] years from the baseline MRI, the total brain volume was 1031.8 ± 101.9 mL, and the total WMSA volume was 6.2 ± 7.1 mL. Compared to the baseline, volume parameters for each brain segment significantly decreased (all, $P < 0.05$), except for the thalamus volume ($P = 0.096$), while WMSA parameters significantly increased (all, $P < 0.001$), except for the log-transformed deep WMSA volume ($P = 0.352$) (Table 3) (the volume profiles of the original brain segments are shown in Supplemental Table 1). The annual change rate of the segmental brain volume and WMSA volume parameters were comparable between female and male participants and between participants with short (≤ 48 months) or long (>48 months) MRI follow-up intervals. (Supplemental Table 2. Supplementa Fig. 6 for comparison of MRI parameter change rates by sex).

In the regression analyses for the baseline MRI parameters, the volumes of the hippocampus and amygdala were associated with the rates of change in the global cognitive score (B coefficient 0.975; 95 % confidence interval [CI] 0.365–1.585; $P = 0.001$) and the scores of the executive function (B 0.812; 95 % CI 0.130–1.568; $P = 0.018$), language function (B 0.647; 95 % CI 0.165–1.130; $P = 0.009$), verbal learning (B 1.001; 95 % CI 0.377–1.625; $P = 0.002$), and recognition memory domains (B 1.594; 95 % CI 0.259–2.929; $P = 0.020$). Additionally, the log-transformed total WMSA volume was associated with the rates of change in the memory recall (B −0.694; 95 % CI -1.489–0.301; $P = 0.014$) (Table 4, Supplemental Table 3 for the univariate correlation analyses). In the regression models re-performed to include the interaction variable between age and MRI parameters with clinical significance, none of the interaction variables remained statistically significant. However, these models demonstrated higher R^2 values compared to the original models (Supplemental Table 4).

In the regression analyses for the longitudinal change rate of the MRI parameters, the rate of change in the hippocampus and

Table 1
Clinical score profiles of the study population.

Clinical profiles	N = 190
Age (years)	68.2 ± 8.2
Male Sex (%)	75 (39.5 %)
Education (years)	14.2 ± 3.7
Hypertension (%)	31 (16.3 %)
Diabetes mellitus (%)	24 (12.6 %)
Hyperlipidemia (%)	25 (13.2 %)
Use of antidepressants (%)	17(8.9 %)
Regular alcohol consumption (%)	31(16.3 %)
Smoking within the past 5 years (%)	17(8.9 %)
Laboratory profiles	
HbA1c (%)	5.8 ± 0.6
Total cholesterol (mg/dL)	196.1 ± 36.1
Low-density lipoprotein (mg/dL)	117.5 ± 32.8
Creatinine (mg/dL)	0.9 ± 0.2
Systolic blood pressure (mmHg)	123.6 ± 14.5
Pulse pressure (mmHg)	49.1 ± 11.5
Cognitive scores	
Total CERAD-K raw score at baseline	74.3 ± 15.0
Total CERAD-K z-score at baseline	0.5 ± 1.3
Follow-up interval (years)	3.8 [2.3–5.4]
Total CERAD-K raw score at follow-up	70.7 ± 16.6
Total CERAD-K z-score at follow-up	0.3 ± 1.5
Total CERAD-K z-score change rate (/year)	0.1 ± 0.4

Data are reported as a number (percentage), mean ± standard deviation, or median [interquartile range, IQR]. Z-scores were derived by normalizing for age, sex, and years-of -education. HbA1c, hemoglobin A1c and CERAD-K, consortium to Establish a Registry for Alzheimer's Disease-Korean version.

Table 2
CERAD-K score profiles of the study population.

	Baseline		Follow-up			
	raw score	**z-score**	**raw score**	**z-score**	**z-score change rate (per year)**	***P*‡**
Total score	74.3 ± 15.0	0.5 ± 1.3	70.7 ± 16.6	0.3 ± 1.5	0.1 ± 0.4	<0.001*
Executive function (J1, Verbal fluency)	13.5 ± 4.1	−0.4 ± 1.1	13.4 ± 4.6	−0.3 ± 1.2	0.0 ± 0.4	0.658
Language function (J2, Boston Naming)	11.6 ± 2.4	0.2 ± 1.0	11.1 ± 2.6	0.1 ± 1.2	0.1 ± 0.3	<0.001*
MMSE (J3)	25.8 ± 3.2	−1.0 ± 1.6	24.3 ± 4.4	−1.7 ± 2.3	0.2 ± 0.8	<0.001*
Verbal learning (J4, Word list encoding)	17.8 ± 4.4	0.2 ± 1.2	16.4 ± 4.6	−0.1 ± 1.3	0.1 ± 0.4	<0.001*
Visuospatial function (J5, Constructional praxis)	10.3 ± 1.4	0.1 ± 1.1	10.2 ± 1.4	0.1 ± 1.1	0.0 ± 0.5	0.096
Memory recall (J6, Word list recall + J8, Construction praxis recall)	12.7 ± 3.3	−0.1 ± 2.0	11.3 ± 3.5	−0.6 ± 2.2	0.1 ± 0.9	<0.001*
Recognition memory (J7, Word list recognition)	8.6 ± 2.0	−0.2 ± 1.2	8.3 ± 2.2	−0.3 ± 1.4	0.1 ± 0.7	0.021*

Data are reported as mean ± standard deviation. Z-scores were derived by normalizing for age, sex, and years-of -education. CERAD-K, consortium to establish a registry for Alzheimer's disease-Korean version and MMSE, mini-mental status examination. **P*-values with a false discovery rate (FDR) below 0.05, adjusted for multiple comparisons using the Benjamini-Hochberg method. ‡*P*-values were derived from paired-sample t-tests comparing baseline and follow-up values and were not adjusted for the varying time intervals between baseline and follow-up assessments.

Table 3
Brain magnetic resonance image profiles of the study population.

	Baseline	Follow-up	Change rate (per year)	*P*‡
Volume parameters (normalized to total intracranial volume)				
Cortex (%)	37.6 ± 2.4	36.9 ± 2.8	−0.164 ± 0.713	<0.001*
Subcortical white matter (%)	28.1 ± 2.3	27.2 ± 2.9	−0.008 ± 0.025	<0.001*
Corpus callosum (%)	0.2 ± 0.0	0.2 ± 0.0	−0.001 ± 0.005	<0.001*
Striatum (%)	1.4 ± 0.2	1.3 ± 0.2	−0.019 ± 0.052	<0.001*
Thalamus (%)	0.9 ± 0.1	0.9 ± 0.1	0.001 ± 0.032	0.096
Hippocampus and amygdala (%)	0.7 ± 0.1	0.6 ± 0.1	−0.008 ± 0.025	<0.001*
Diencephalon and brainstem (%)	1.9 ± 0.2	1.8 ± 0.2	−0.014 ± 0.042	<0.001*
Cerebellum (%)	8.2 ± 1.0	8.0 ± 1.0	−0.010 ± 0.278	0.016*
White matter signal abnormality parameters				
Total WMSA volume (mL)	5.0 ± 5.9	6.2 ± 7.1	0.308 ± 0.724	<0.001*
Total WMSA volume, $\log_{10}$	3.6 ± 0.3	3.6 ± 0.3	0.020 ± 0.052	<0.001*
Periventricular WMSA volume, $\log_{10}$	3.5 ± 0.3	3.6 ± 0.3	0.020 ± 0.050	<0.001*
Deep WMSA volume, $\log_{10}$	1.7 ± 0.8	1.7 ± 0.9	−0.026 ± 0.217	0.352

Data are reported as mean ± standard deviation. WMSA, white-matter signal abnormality. **P*-values with a false discovery rate (FDR) below 0.05, adjusted for multiple comparisons using the Benjamini-Hochberg method. ‡*P*-values were derived from paired-sample t-tests comparing baseline and follow-up values and were not adjusted for the varying time intervals between baseline and follow-up assessments.

amygdala volume was associated with the rate of change in the global cognitive scores (B 4.235; 95 % CI 1.682–6.789; $P = 0.001$) and the scores of the language function (B 2.772; 95 % CI 0.736–4.808; $P = 0.008$) and the verbal learning domains (B 4.477; 95 % CI 1.868–7.085; $P = 0.001$). The rate of change in the log-transformed total WMSA volume was associated with the rate of change in the global cognitive (B −1.174; 95 % CI -2.216–0.087; $P = 0.008$), executive function scores (B −1.584; 95 % CI -2.377–0.609; $P = 0.015$), and the recognition memory domains (B −1.370; 95 % CI –2.263–0.404; $P = 0.012$). (Table 5, Supplemental Table 5 for the univariate correlation analyses). In the re-performed regression models, none of the interaction variables between age and MRI parameters were statistically significant. (Supplemental Table 6). The VIF values were <1.70 for all the factors that were included in the linear regression analyses.

In the GEE analyses conducted to validate the MRI parameters that showed significant associations in each linear regression model, all MRI parameters remained significantly associated with the annual change rates in the normalized total CERAD-K score or its subset scores (all, $P < 0.05$). Additionally, the use of antidepressants was associated with a more preserved total cognitive CERAD-K score over time, whereas higher pulse pressure was linked to a greater decline in both the total cognitive CERAD-K score and verbal learning. No other significant associations were observed for specific cognitive domains. Detailed results are presented in Supplemental Table 7 (validation of regression models with baseline MRI parameters) and Supplemental Table 8 (validation of regression models with longitudinal MRI change parameters).

4. Discussion

This study demonstrated the domain-specific patterns of association of segmental brain volume and WMSA volume parameters with longitudinal changes in cognitive function. First, the change in the global cognition score was associated with the volume of the hippocampus and amygdala segments at baseline, as well as the rate of longitudinal change in the hippocampus and amygdala segment volumes and the total WMSA volume during follow-up. Second, the change in the executive function domain score was associated with

Table 4
Baseline MRI parameters associated with the annual change rates in the normalized total CERAD-K score and its six subset scores from linear regression models.

Total CERAD z-score[a]	**B (95 % CI)**	***P***
Hippocampus and amygdala	0.975 (0.365–1.585)	0.001*
Executive function z-score[b]	**B (95 % CI)**	***P***
Hippocampus and amygdala	0.812 (0.130–1.568)	0.018*
Language function z-score[c]	**B (95 % CI)**	***P***
Hippocampus and amygdala	0.647 (0.165–1.130)	0.009**
Verbal learning z-score[d]	**B (95 % CI)**	***P***
Hippocampus and amygdala	1.001 (0.377–1.625)	0.002*
Visuospatial function z-score[e]	**B (95 % CI)**	***P***
No significantly associated factor		
Memory recall[f]	**B (95 % CI)**	***P***
Total WMSA volume, $\log_{10}$	−0.694 (−1.489–0.301)	0.014*
Recognition memory[g]	**B (95 % CI)**	***P***
Hippocampus and amygdala	−1.594 (−2.929–0.259)	0.020*

R = [a]0.151, [b]0.102, [c]0.144, [d]0.118, [e]0.072, [f]0.054, [g]0.083, and all $P < 0.01$, for the linear regression equations. All models were adjusted for age, sex, years of education, the presence of hypertension, hyperlipidemia, diabetes mellitus, taking of antidepressants, regular alcohol consumption, and a history of smoking within the past 5 years, as well as laboratory parameters such as, systolic blood pressure, pulse pressure, hemoglobin A1c, serum creatinine, total cholesterol, and low-density lipoprotein.
B, unstandardized coefficient, CERAD-K, consortium to establish a registry for Alzheimer's disease-Korean version, and WMSA, white-matter signal abnormality. **P*-values with a false discovery rate (FDR) below 0.05, adjusted for multiple comparisons using the Benjamini-Hochberg method.

Table 5
Longitudinal changes in the MRI parameters that are associated with the change rates in the normalized total CERAD-K score and its six subset scores from linear regression models.

Total CERAD z-score[a]	**B (95 % CI)**	***P***
Hippocampus and amygdala	4.235 (1.682–6.789)	0.001*
Total WMSA volume, $\log_{10}$	−0.174 (−2.216–0.087)	0.008*
Executive function z-score[b]	**B (95 % CI)**	***P***
Total WMSA volume, $\log_{10}$	−1.584 (−2.377–0.609)	0.015*
Language function z-score[c]	**B (95 % CI)**	***P***
Hippocampus and amygdala	2.772 (0.736–4.808)	0.008*
Verbal learning z-score[d]	**B (95 % CI)**	***P***
Hippocampus and amygdala	4.477 (1.868–7.085)	0.001*
Visuospatial function z-score[e]	**B (95 % CI)**	***P***
No significantly associated factor	–	–
Memory recall[f]	**B (95 % CI)**	***P***
No significantly associated factor	–	–
Recognition memory[g]	**B (95 % CI)**	***P***
Total WMSA volume, $\log_{10}$	−1.370 (−2.263–0.404)	0.012*

R = [a]0.153, [b]0.100, [c]0.132, [d]0.123, [e]0.069, [f]0.045, [g]0.083, and all $P < 0.01$, for the linear regression equations. All models were adjusted for age, sex, years of education, the presence of hypertension, hyperlipidemia, diabetes mellitus, taking of antidepressants, regular alcohol consumption, and a history of smoking within the past 5 years, as well as laboratory parameters such as, systolic blood pressure, pulse pressure, hemoglobin A1c, serum creatinine, total cholesterol, and low-density lipoprotein. B, unstandardized coefficient, CERAD-K, consortium to establish a registry for Alzheimer's disease-Korean version, and WMSA, white-matter signal abnormality. **P*-values with a false discovery rate (FDR) below 0.05, adjusted for multiple comparisons using the Benjamini-Hochberg method.

the hippocampus and amygdala segment volumes at baseline and the rate of longitudinal change in the total WMSA volume during follow-up. Third, the changes in the language function and the verbal learning domain scores were associated with the volume of the hippocampus and amygdala segments at baseline and with its rate of change during follow-up. Fourth, changes in memory recall scores were associated with baseline total WMSA volumes. Additionally, changes in recognition memory scores were linked to lower baseline hippocampal and amygdalar volumes, as well as the rate of increase in total WMSA volumes during follow-up. Although previous studies have explored the associations between segmental brain volumes, WMSAs, and changes in cognitive function, this is the first study to demonstrate the comprehensive impact of both baseline values and longitudinal changes in brain volume and WMSA parameters on cognitive function across different domains [7,9,11–14].

Several hypotheses could explain the domain-specific patterns of association between the brain volume or WMSA parameters and the changes in cognitive function. First, reductions in brain volume might reflect the anatomical changes resulting from the long-term process of neurodegeneration. Second, connectivity among the different brain regions might compensate for neurodegeneration preserving cognitive resilience through a mechanism known as brain reserve [4–6]. Third, WMSA volume, of which change is more dynamic than that of the brain volume, might reflect the decreased capacity of the brain reserve due to the disrupted integrity of the

association fibers in the white matter [3,7–9,11–13,36–38]. Fourth, the capacity for functional resilience through brain connectivity might vary significantly across different cognitive domains [4,6,36–40].

In this context, the domain-specific pattern of association between the brain volume or WMSA and the cognitive changes might reflect the varying dependence of the cognitive function on their corresponding brain region or the connectivity to other regions, depending on the cognitive domain. Memory functions, particularly recognition memory and memory recall, rely heavily on interactions across widespread functional domains, including attention, visuospatial function, language, and emotion. This makes these functions particularly dependent on brain connectivity and longitudinal changes in WMSA [38,41]. However, among the cognitive domains, language function and verbal learning were less dependent on WMSA changes but more dependent on hippocampus and amygdala volume and its change [42]. The functional network responsible for these domains might be more confined to the language system in the dominant hemisphere; thus, these systems might be less dependent on general white matter disruption [43]. For cognitive domains with intermediate dependence on specific brain regions or their connectivity to other areas, such as global cognitive function and executive function, both baseline hippocampal and amygdalar volumes and longitudinal changes in WMSA may be associated with functional changes [36,37,40].

Another key finding of this study is that the volume of the hippocampal and amygdala segments at baseline was widely associated with the longitudinal declines in the global cognition score, as well as the executive function, language function, verbal learning, and recognition memory domains. This result was derived from linear regression with backward elimination method, which sequentially removes brain MRI parameters with the least association from the model. This suggest that the amygdala, hippocampus and WMSA are the brain regions most strongly associated with changes in cognitive function across various domains, even though the regression analyses may have overlooked some relevant parameters with modest statistical significance. Beyond its primary role in learning and memory, the hippocampus also supports flexible cognition and recognition by constructing relational memory representations [44]. The amygdala interacts synergistically with the hippocampus and has a critical role in emotion-based attention, valuation, and decision-making [1,45]. The hippocampus and amygdala also maintain extensive functional connections with the neocortical areas, making them the segments most significantly associated with changes in global cognition scores and its major domains [42,46].

Additionally, GEE analyses revealed that antidepressant use was associated with a better rate of change in the total cognitive CERAD-K score. This finding aligns with previous studies suggesting potential cognitive benefits of antidepressants, particularly serotonin reuptake inhibitors [47], which are the most frequently prescribed antidepressants in Korea [48]. However, this result should be interpreted with caution, as responses to antidepressants may vary according to the status of underlying depressive symptoms. Higher pulse pressure was associated with a worse rate of change in both the total cognitive CERAD-K score and verbal learning over time. This result is consistent with previous findings demonstrating a prospective decline in verbal learning, nonverbal memory, working memory, and global cognition in individuals with increasing levels of pulse pressure [49]. Arterial stiffness and the resulting cerebral small vessel disease might be the pathomechanistic link [49].

This study has several limitations to be addressed. First, as a retrospective cohort design, the intervals between baseline and follow-up brain MRI and cognitive function evaluations were not standardized among participants. Although linear regression analyses along with GEE were employed with the annual rate of cognitive function score changes designated as the outcome parameter to compensate for these heterogeneous follow-up intervals, it might have been more appropriate to use residual change scores in mixed models. Such an approach could better account for potential non-linearity in the relationship and the influence of baseline MRI parameters and cognitive states on the rate of change [40,50,51]. Although analyses for progression to MCI or AD, such as Cox regression, were not within the primary scope of this study, they could provide valuable insights and serve as an important focus for future research. Second, evaluations for the apolipoprotein E genotype, which is a major risk factor for dementia, and might significantly alter the changes in the structural brain MRI parameters across the lifespan, were not included in this study [52]. Third, the association of the clinical risk factors for cognitive decline, such as the level of income, use of anxiolytics or hypnotics, and body mass index, was not evaluated in this study [53]. Fourth, by using the backward elimination method in the regression models, this study might have missed some relevant brain MRI parameters with marginal or modest statistical significance. Fifth, by combining the parameters from both hemispheres, this study might have missed some association between the MRI parameter and the laterality-specific functional domains, such as language function. The difference between the T1-based WMSA and the T2/FLAIR-based white matter hyperintensity volume measurements might be considered as a factor limiting the generalization of the study result. Further prospective studies with long-term standardized follow-up evaluations, along with the comprehensive acquisition of biomarkers, should be performed.

5. Conclusion

Segmental brain volume and WMSA volume exhibit domain-specific associations with longitudinal cognitive changes. These domain-specific patterns of association between WMSA and cognitive changes likely reflect varying levels of functional dependence on brain reserve across different cognitive domains.

CRediT authorship contribution statement

Woo-Jin Lee: Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Keun-Hwa Jung:** Writing – review & editing, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Kyung-Il Park:** Writing – review & editing, Supervision, Resources, Investigation, Conceptualization. **Kon Chu:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Sang Kun Lee:** Writing – review & editing, Investigation, Formal analysis, Data curation.

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Declaration of competing interest

None of the original material contained in the manuscript has been submitted for consideration nor will any of it be published elsewhere. All methods were performed in accordance with the relevant guidelines and regulations. This study is reported in accordance with STROBE guidelines. We have no conflicts of interest to report. All authors have read and approved the manuscript for submission to Helyion; have made a substantial contribution to the conception, design, gathering, analysis and/or interpretation of data and a contribution to the writing and intellectual content of the article; and acknowledge that they have exercised due care in ensuring the integrity of the work. If this manuscript is accepted by the Helyion, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e42536.

Abbreviations

CERAD-K Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological assessment battery
MMSE Mini-Mental State Examination, and WMSA: White matter signal abnormality

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