

Brain Volume Metric Analysis Is Correlated with Aging Changes and Sex Differences in Thai Older Adults

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Keywords

Aging brain · Brain volume · Brain imaging · Aging and cognition · Cognitive aging · Aging · Dementia · Older adults

Abstract

Introduction: Normative data on structural brain volume changes with age and sex differences are required as a reference standard for future research and clinical use. **Methods:** We studied a two-center, metropolitan-based, prospective cohort of adults aged 55 years and older who were recruited from community-dwelling settings and outpatient clinics without cognitive impairment at baseline and who were followed up for 2 years. The clinical data, neuropsychological tests, and brain MRI obtained with FreeSurfer software were utilized for quantitative volumetric measurements. **Results:** A total of 296 participants were

recruited at the beginning, with 17 participants (5.8%, excluding 2 subjects with claustrophobia) excluded due to abnormal MRI findings and 27 participants (9.1%) excluded due to MCI/dementia. Among the 250 remaining, 14 patients dropped out or were lost to follow-up, and 35 had MCI or AD converters (14.8%). The remaining 201 subjects with normal cognitive function aged 55–85 years were analyzed for structural brain volume. There were significant correlations between age and brain parameters, including the hippocampus, corpus callosum, thalamus, and ventricular volume changes (p value <0.05). There were significant differences between males and females in total intracranial volume, caudate, temporal lobe, and ventricle volumes in subjects aged 65–74 years, and in total intracranial volume and ventricle volumes in subjects aged 55–64 years (p value <0.05). **Conclusion:** Age and sex contributed to differences in brain structure and ventricular volume. These data could be used as a normative reference for clinical

interpretation in people up to 85 years old and for understanding the physiological aging-related changes in the brain.

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Introduction

Thailand is a country that is classified as an aged society and is expected to become a superaged society in the near future [1]. Alongside the rapid growth of the aging population, there has been an increase in the incidence of mild cognitive impairment (MCI) and dementia [2]. These conditions appear to be a burden on society not only for patients but also for their families.

MRI studies have shown that brain atrophy is associated with normal aging [3–8] and is reportedly associated with brain function [9, 10]. While studies on brain atrophy and its association with aging exist, there is limited research focusing on the Thai population, which is rapidly transitioning to a superaged society. Cultural, genetic, and lifestyle factors may influence brain aging, but these are not well documented for Thai individuals. Moreover, as sex has been consistently reported to correlate with brain volume [11–14], the effects of age and sex on brain volume should be considered.

The development of neuroimaging technologies allows researchers and clinicians to study and make a reference to normal aging changes in the brain and cognition. These technologies for understanding normal brain aging in Thai older adults are underutilized. There is a need for region-specific reference data to improve the accuracy of diagnosing deviations associated with conditions like MCI or dementia. Quantitative analysis using automated software for measuring brain volume has been evaluated in various studies of aging people [15, 16].

Magnetic resonance imaging (MRI) has been established as a gold standard for noninvasive, high-resolution imaging of brain structures. It enables accurate tracking of volumetric changes over time, which is critical in understanding both normal aging and pathological conditions like Alzheimer's disease (AD). FreeSurfer performs automated segmentation of brain structures, providing highly detailed and consistent labeling of cortical and subcortical regions. This reduces manual effort and observer bias, ensuring reproducibility. FreeSurfer (the software) eliminates interobserver variability, enhancing reproducibility and reliability. This is crucial for large-scale studies and longitudinal data. It provides precise measurements of brain volumes, including cortical thickness, subcortical structure volumes, and re-

gional brain metrics, which are critical for studying aging, dementia, and other neurological conditions. FreeSurfer also has specific tools designed for longitudinal studies, enabling accurate tracking of structural changes in the brain over time. This is particularly useful for understanding the progression of neurodegenerative diseases like AD.

Most studies have focused on cross-sectional data, whereas longitudinal studies that track brain volume changes over time in cognitively normal individuals are scarce, particularly in non-Western populations. Understanding normal brain aging in the Thai population is critical to identifying early markers of pathological aging and developing tailored interventions. The objective of this study was to examine structural brain volume changes and correlations with aging changes and sex differences in preaging and aging Thai people who had normal cognitive function and followed up for 2 years to measure these changes.

Materials and Methods

The Thai Aging Brain (TAB) study is a two-center, metropolitan-based, prospective cohort study. This study aimed to recruit adults aged 55 years and older without cognitive impairment to participate and establish normative data. This is Thailand's first cohort for which extensive biological and radiological studies with established neurocognitive tests were performed in a prospective manner. This study recruited participants from public media through both posters and social media. The participants came from both community-dwelling settings and outpatient clinics in Siriraj Hospital and Bangkok Hospital, such as the geriatric clinic, screening clinic, and health checkup clinic. After they expressed their interest in the study, the research assistants explained the study objectives and protocol. If they were interested in participating in the study, the research assistants scheduled the appointment with both clinicians (geriatricians and neurologists) and clinical psychologists, the inclusion and exclusion criteria were checked, and informed consent was obtained. On the day of the study, both the participants and their family members were asked to visit the outpatient clinic at Siriraj Hospital or Bangkok Hospital.

The inclusion criteria were participants who met the following checklists:

1. Age 55–90 years, both genders
2. No symptoms or signs of cognitive impairment according to medical history or physical examination

3. A normal score on the Thai version of the Mini Mental State Examination according to age and educational level
4. The Clinical Dementia Rating (CDR) Scale score of 0
5. No depression
6. Intact activities of daily living (ADLs) (no functional impairment from cognitive problems)
7. No history of neurological or psychiatric illnesses such as stroke, Parkinson's disease, head injury, or known active psychiatric illness
8. No history of current drug use that could interfere with cognitive performance.
9. Ability to attend the 1- to 1.5-h session of data collection, clinical interview, cognitive assessment, and 20 min of the brain MRI scan
10. Expected ability to follow up for 2 years

The exclusion criteria were as follows:

1. Ability to become pregnant
2. Unstable medical conditions, known HIV or AIDS status, history of alcohol dependence or use of illicit drugs, and brain tumors (both primary tumors and metastases)
3. Patients with significant brain lesions, such as traumatic brain injury, previous brain surgery, previous cranial radiotherapy, and abnormal intracranial vasculature
4. Conditions potentially affecting the study results, such as depression, delirium, amnesic syndrome, or cognitive impairment
5. Previously or currently receiving medications modulating amyloid deposition, antidementia medications, or other medications that included those pharmacological actions
6. Contraindication for brain MRI, claustrophobia, or inability to stay still for 20 min in the scan

The withdrawal or termination criteria were as follows:

1. Participants who asked to withdraw from the study.
2. Participants who could not complete the study protocol.
3. Participants who died before the study ended.

Data Collection Process

A trained research coordinator collected the baseline characteristics of the patients prior to assessment by the clinical psychologists and clinicians. Participants who showed no signs of cognitive impairment were called for result disclosure and were recruited for the study if they were interested. The data were collected 2 times (at baseline and in the second year of the follow-up). There was no preregistration or deviations from the protocol in this study. The clinical and neuropsychological assess-

ments were performed at both visits and were evaluated by geriatricians and neurologists who specialize in neurocognitive disorders.

1. The data collected included baseline characteristics such as age, sex, education, height, weight, underlying disease status, location of residence, smoking habit, alcohol intake, lifestyle factors, medications and supplements used, previous hospitalization, falls, previous acute illness, and new diagnosis of the underlying disease.
2. Neuropsychological tests were conducted by certified clinical psychologists:
 - The Thai Mental Status Exam (TMSE) [17] was used to assess global cognitive function, with a total score of 30 and a cutoff value for cognitive impairment of 23 or less. It includes assessments of orientation, registration (3-word registration), attention, calculation, language ability, picture copying, and abstract thinking (similarity) and 3-word recall. The distribution of normative scores was dependent on age and educational level.
 - The Thai version of the Montreal Cognitive Assessment (MoCA) [18] can distinguish normal cognitive function from MCI. It contains visuospatial, executive function, language ability, attention, memory, and orientation tests. The total score was 30, and the cutoff value for cognitive impairment was 24 or less. The cutoff values also depend on age and educational level.
 - The Clinical Dementia Rating (CDR) Scale was used for both participants and their family caregivers [19]. The CDR was used to assess global and cognitive function and severity in 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The global CDR ranges from 0 (normal) to 3 (severe dementia) possibly.
 - The Patient Health Questionnaire-9 (PHQ9) [20] was used to assess depression in the primary care setting.
 - The Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2) [21] was used to evaluate short- and long-term memory. There were normative data with scores ranging between 5 and 90 years.
 - The Trail Making Tests A and B were used to test for visual attention and mental shift.

ADLs were assessed to evaluate any functional impairment of both basic ADLs and instrumental ADLs related to cognitive function.

3. MRI data collection: The MRI brain protocol for each subject was created considering patient comfort and sufficient information for excluding silent lesions in asymptomatic patients. Subjects underwent MRI scanning using a 1.5T MRI scanner (GE Signa) with a 19-channel head coil and T1-weighted image and fluid-attenuated inversion recovery (FLAIR) were acquired. The imaging parameters were as follows: three-dimensional T1-weighted image using TR/TE/TI = 9.2, 3.7, 1,000 ms, flip angle = 9 degrees, field of view = 240 × 240 mm, matrix size = 256 × 256, and 2D-FLAIR using TE/TR = 116/8,500 ms, flip angle = 1,400 degrees, field of view = 240 × 244 mm, and matrix size = 256 × 192. The quality of the scanner was tested according to the quality control guidelines of the American College of Radiology (ACR). Brain segmentation was performed by a radiological technologist who was blinded to the participants' clinical data and neuropsychological test results:
- Axial FLAIR was used by an experienced neuro-radiologist (with more than 30 years of experience) to exclude subjects with silent infarction, masses, or any parenchymal lesions except for nonspecific white matter changes.
 - FreeSurfer software was utilized for quantitative volumetric measurements using three-dimensional T1-weighted image [22, 23]. In brief, DCM2NII software version 2016 was used to convert DICOM files to Nifti files running on a CentOS6 Linux workstation. FreeSurfer (version 6.0) using the recon-all command with standard pipeline from the software was performed for fully automating the processing steps in this study [24], and the result images were visually checked for image quality control using Freeview software. The low-quality images (i.e., distorted or incomplete skull stripping, etc.) were excluded from the image repository. The software provided the final segmentation based on both a subject-independent probabilistic atlas and subject-specific measured values. The first step in the software is an affine registration with MNI305 space [25]. Then, initial volumetric labeling of the brain was performed. The variation in intensity due to the B1 bias field was corrected. Finally, high-dimensional nonlinear volumetric alignment to the MNI305 atlas was performed. After preprocessing, the volume was labeled. The intracranial volume, hippocampal volume, regional lobe volume, and posterior cingulate volume of each subject were recorded and analyzed, and the data are presented as age range and sex. The volumetric parts seg-

mented by the recon-all results were reported in the asegstats folder and were obtained and normalized by the total intracranial brain volume for each subject.

Statistical Analysis

Demographic data are presented as the mean ± standard deviation (SD) for continuous data and *n* (%) for categorical data. The mean, SD, and 5th, 25th, 50th, 75th, and 95th percentiles for brain parameters were calculated for males and females separately and for the age subgroups. Pearson's correlation coefficient was used to determine the correlation between age and brain parameters. The effects of age and gender on brain parameters were analyzed using multivariate analysis of variance (MANOVA), with adjustments for multiple comparisons made using the Bonferroni correction. Quantile regression analysis was used to construct smoothed percentile curves of brain parameters. The 5th, 25th, 50th, 75th, and 95th percentiles for brain parameters were calculated and plotted as smoothed reference curves. All analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp, Armonk, NY, USA). A *p* value <0.05 indicated statistical significance.

Results

A total of 296 participants were recruited from two sites (Siriraj Hospital and Bangkok Hospital). After excluding 2 subjects with claustrophobia, 17 (5.8%) had abnormal MRI findings (old lacunar infarction = 11, intracranial mass = 3, severe white matter change = 2, brain atrophy = 1). There were 27 subjects (9.1%) whose cognition was not clinically normal. MR images and cognitive tests were collected for the remaining 250 patients. There were 14 subjects dropped out/were lost to follow-up and 35 patients converted to AD or MCI (14.8%). The remaining 201 subjects had available data for all neuropsychological tests and ADLs, which were normal at the 2-year follow-up. Table 1 shows the demographic data of all normal cognitive subjects at 2 years for MRI analysis.

There were significant correlations between age and brain parameters, including changes in the hippocampus, corpus callosum, thalamus, and ventricular volume (*p* value <0.05) (Table 2). There was a marginally significant correlation between age and the amygdala (*p* value 0.067). The mean and SD of brain parameters for the subjects (90 males and 111 females) in each age group are presented in Table 3. For comparisons between sexes, significant differences were found between males and females in total

Table 1. Demographic data of participants

Variables	Total (n = 201)	Male (n = 90)	Female (n = 111)
Age (mean±SD), years	66.6±7.0 (55–85)	66.0±6.9 (55, 85)	67.0±7.0 (55, 85)
Age			
55–64 years	82 (40.8%)	40 (44.4%)	42 (37.8%)
65–74 years	87 (43.3%)	38 (42.3%)	49 (44.2%)
≥75 years	32 (15.9%)	12 (13.3%)	20 (18.0%)
Education			
Elementary school	21 (10.4%)	8 (8.9%)	13 (11.7%)
Junior high school	11 (5.5%)	2 (2.2%)	9 (8.1%)
Senior high school	17 (8.5%)	10 (11.1%)	7 (6.3%)
Diploma	12 (6.0%)	8 (8.9%)	4 (3.6%)
Bachelor degree or higher	138 (68.7%)	62 (68.9%)	76 (68.4%)
Other education	2 (1.0%)	0	2 (1.8%)
TMSE (mean±SD), range	28.7±1.5 (24–30)	28.6±1.4 (25–30)	28.8±1.5 (24–30)
CDR Scale = 0	201 (100%)	90 (100%)	111 (100%)

TMSE, Thai Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR Scale, Clinical Dementia Rating Scale; SD, standard deviation.

intracranial volume, caudate, temporal lobe, and ventricle volumes in subjects aged 65–74 years, and in total intracranial volume and ventricle volumes in subjects aged 55–64 years (p value <0.05) (Table 4). The 5th, 25th, 50th, 75th, and 95th percentiles for the brain parameters of each brain region are shown in the online supplementary data (for all online suppl. material, see <https://doi.org/10.1159/000543774>).

Discussion

Age-related brain changes detected via quantitative MRI analysis have been demonstrated in previous studies [3, 4, 7, 11, 26]. However, quantitative analysis using MRI has not been well studied systematically in Thailand. We found age-related changes in the hippocampus, corpus callosum, thalamus, and ventricle. There were sex differences in the total intracranial brain volume, temporal lobe, caudate, whole ventricle, and CSF region.

Previous studies have shown that age is significantly related to changes in cerebral structure and ventricular volume and is associated with decreases in cerebral hemisphere volume [3, 4, 14]. Although cortical gray matter, limbic structures, white matter, and ventricular and sulcus volume have been shown to be related to aging changes, more prominent age-dependent changes have been found in frontal/temporal lobes, anterior/inferior white matter, and ventricular and sulcus volume [4, 7, 27,

28]. For all subjects, we found correlations between age and brain parameters, including the hippocampus, corpus callosum, thalamus, and ventricular volume changes, which was in line with prior studies [4, 7, 27, 28]. A previous study found that age significantly affects all brain volume measurements, with stronger correlations in the ventricles and hippocampus for older adults (60–85 years) compared to middle-aged adults [26]. This aligns with our findings in older Thai adults. For the hippocampus, there were prior studies, showing early changes in MCI or AD subjects [27, 29] and volume reductions with age in normal older adults [30–36]. Our findings in Thai subjects align with previous studies and provide a valuable reference for future research in Asian countries.

Our CSF space analysis findings are consistent with those of prior studies [7, 28, 32, 37]. Increased age appears to increase ventricular volume due to adjacent cerebral white matter or deep gray matter volume loss. In demented older adults with hydrocephalus, sometimes we cannot differentiate ventricular enlargement between atrophic change and normal pressure hydrocephalus causing cognitive decline. Our results for normative data of ventricular volume in each age group might help as an additional parameter for evaluating these patients.

The thalamus is an important structure connecting several cortical structures. The greatest changes were observed in the anterior thalamus and thalamofrontal projection [38]. Our findings on age-related thalamic volume are consistent with those of prior studies in older

Table 2. Correlations between age and brain parameters using Pearson correlation

	All (n = 201)		Male (n = 90)		Female (n = 111)	
	Pearson correlation (r)	p value	Pearson correlation (r)	p value	Pearson correlation (r)	p value
Brain segment not ventricle	−0.069	0.329	0.002	0.982	−0.142	0.136
Estimated total intracranial volume	0.034	0.635	0.043	0.690	0.068	0.480
Caudate	0.051	0.468	0.023	0.826	0.105	0.272
Putamen	−0.079	0.265	−0.027	0.803	−0.127	0.184
Pallidum	−0.002	0.973	−0.013	0.905	0.026	0.786
Hippocampus	−0.188	0.008*	−0.207	0.049*	−0.171	0.074
Amygdala	−0.129	0.067	−0.079	0.459	−0.170	0.074
Corpus callosum	−0.207	0.003*	−0.218	0.039*	−0.193	0.042*
Thalamus proper	−0.218	0.002*	−0.201	0.057	−0.218	0.021*
Ventricle	0.314	<0.001*	0.240	0.023*	0.466	<0.001*
Frontal	−0.117	0.099	−0.160	0.132	−0.070	0.464
Cingulate	−0.057	0.418	−0.124	0.244	0.008	0.933
Occipital	−0.015	0.837	−0.062	0.560	0.045	0.639
Temporal	−0.096	0.175	−0.110	0.301	−0.063	0.508
Parietal	−0.081	0.251	−0.101	0.345	−0.049	0.608
Insula	−0.102	0.149	−0.121	0.257	−0.072	0.456
Lateral ventricle	0.008	0.914	−0.032	0.767	0.069	0.474
The whole ventricle	0.030	0.676	−0.011	0.918	0.096	0.318
The whole ventricles and CSF	0.040	0.577	−0.002	0.986	0.108	0.259

CSF, cerebrospinal fluid. *p value <0.05.

adults [39–41]. However, sex differences in thalamic volume have been inconsistently reported. Some studies have shown sex differences, whereas other studies have reported no effect of sex on thalamic volume [13, 40].

There were significant differences in total intracranial volume, the caudate, the thalamus, the ventricle, and the temporal and occipital lobes between males and females. Previous studies [8, 14] showed that age-related increases in ventricular volume were greater in men than in women, consistent with our findings. Similarly, studies on sex differences in temporal lobe volume [8, 14] align with our results, which showed significant differences only in the 65–74 age group, not in younger or older groups. This might help radiologists evaluate sex differences in the hippocampus in older patients. Differences in occipital lobe volume between sexes have rarely been reported, but it was found that the occipital lobe volume was greater in aging males [11]. In the 55–64 age group, we found sex

differences only in total intracranial volume and ventricle volumes. However, in the 65–74 age group, significant differences were observed in total intracranial volume, caudate, temporal lobe, and ventricle volumes. No differences were found in those over 75 years.

The findings of abnormal brain MR images (5.8%) with apparent clinical manifestations and no history of disease affecting cognitive function or abnormal neurological findings could be used as incidental findings. This prevalence is much lower than that in a previous report in China in individuals aged 55–65 years [42]. The prevalence of lacunes, white matter hyperintensity, cerebral microbleeds, and the perivascular space was 26.69%, 10.68%, 18.51%, and 27.76%, respectively. This might be because our study included extensive clinical interviews, neuropsychological tests, and physical examinations by geriatricians and neurologists to establish clinically normal cognitive function. A German study reported

Table 3. Mean and SD of brain parameters of the subjects (90 males and 111 females) in each age group

Male (<i>n</i> = 90)	Age 55–64 years (<i>n</i> = 40)		Age 65–74 years (<i>n</i> = 38)		Age ≥75 years (<i>n</i> = 12)	
	Mean	SD	Mean	SD	Mean	SD
Brain segment not ventricle	1,025,000.3	197,403.7	1,052,225.0	98,358.3	1,004,341.8	112,565.7
Estimated total intracranial volume	1,522,582.4	161,226.9	1,559,448.5	161,692.1	1,521,820.8	186,425.4
Caudate	7,434.3	1,006.1	7,603.4	1,085.7	7,783.9	2,103.1
Putamen	7,907.5	1,151.0	8,106.6	999.0	8,113.3	2,630.3
Pallidum	3,707.3	611.7	3,746.9	641.2	3,760.1	743.2
Hippocampus	7,452.2	985.0	7,406.7	933.2	6,953.7	828.3
Amygdala	2,799.8	421.0	2,874.2	506.2	2,706.0	379.0
Corpus callosum	3,340.5	561.2	3,222.7	592.8	2,936.7	548.3
Thalamus proper	15,249.0	1,842.2	14,574.6	1,873.6	14,391.6	1,352.2
Ventricle	24,206.4	15,719.8	28,149.1	17,057.2	33,006.0	19,298.8
Frontal	142,566.7	16,045.9	142,248.4	15,384.1	132,697.3	12,687.9
Cingulate	16,445.4	2,470.2	16,737.9	2,413.8	15,190.0	1,560.1
Occipital	40,545.4	4,796.6	40,468.1	5,136.5	38,867.3	3,755.4
Temporal	93,766.2	10,629.5	94,934.0	10,788.1	88,394.8	9,278.7
Parietal	95,936.9	11,881.9	96,104.1	11,399.0	90,490.8	9,385.6
Insula	12,932.1	1,713.6	12,854.9	1,687.9	12,280.8	1,464.3
Lateral ventricle	211,251.0	23,194.5	214,655.1	22,871.4	203,779.4	19,193.9
The whole ventricle	215,473.7	23,765.7	219,442.2	23,593.2	209,220.7	20,286.4
The whole ventricles and CSF	218,167.9	24,006.7	222,338.5	23,986.1	212,239.4	20,693.3
Female (<i>n</i> = 111)	Age 55–64 years (<i>n</i> = 42)		Age 65–74 years (<i>n</i> = 49)		Age ≥75 years (<i>n</i> = 20)	
	Mean	SD	Mean	SD	Mean	SD
Brain segment not ventricle	1,023,318.5	105,760.1	990,010.7	97,414.2	990,590.8	79,055.9
Estimated total intracranial volume	1,446,900.6	164,264.2	1,421,365.0	156,066.1	1,478,634.6	172,794.5
Caudate	7,273.0	780.0	7,087.2	921.7	7,580.6	1,121.9
Putamen	8,178.8	1,106.5	7,623.1	982.2	7,918.3	964.1
Pallidum	3,609.3	457.3	3,554.8	500.9	3,674.8	510.3
Hippocampus	7,483.5	873.0	7,338.8	849.4	7,063.1	773.0
Amygdala	2,864.2	370.3	2,732.1	440.8	2,750.4	377.7
Corpus callosum	3,334.9	682.6	3,130.3	390.8	3,021.1	532.1
Thalamus proper	14,589.6	2,289.1	13,789.4	2,874.6	12,881.5	3,424.6
Ventricle	16,305.4	5,675.2	20,528.2	9,740.9	30,778.8	18,158.0
Frontal	140,017.4	16,698.7	135,945.7	15,025.4	137,236.6	14,643.2
Cingulate	16,015.3	2,821.6	15,885.5	2,002.1	16,176.5	1,840.0
Occipital	38,675.7	4,993.2	38,580.7	4,626.4	39,625.4	3,943.1
Temporal	90,589.6	11,306.2	89,812.0	9,015.2	88,765.7	8,500.7
Parietal	92,823.6	10,754.7	92,771.2	10,462.2	91,169.0	10,444.7

Table 3 (continued)

Female (<i>n</i> = 111)	Age 55–64 years (<i>n</i> = 42)		Age 65–74 years (<i>n</i> = 49)		Age ≥75 years (<i>n</i> = 20)	
	Mean	SD	Mean	SD	Mean	SD
Insula	12,501.1	1,458.1	12,361.4	1,718.4	12,341.1	1,320.6
Lateral ventricle	202,478.4	23,116.8	201,763.9	20,374.0	206,570.2	18,499.1
The whole ventricle	205,883.6	23,254.8	205,328.7	20,518.0	211,750.9	19,298.7
The whole ventricles and CSF	208,017.3	23,491.2	207,673.3	20,685.7	214,642.3	19,278.4

CSF, cerebrospinal fluid.

Table 4. Multiple comparison analysis for assessing the differences between groups

	<i>p</i> value between sexes within each age group			<i>p</i> value between age groups in male			<i>p</i> value between age groups in female		
	Age 55–64 (1)	Age 65–74 (2)	Age ≥75 (3)	(1) vs. (2)	(1) vs. (3)	(2) vs. (3)	(1) vs. (2)	(1) vs. (3)	(2) vs. (3)
Brain segment not ventricle	0.952	0.022*	0.764	1.000	1.000	0.747	0.620	1.000	1.000
Estimated total intracranial volume	0.037*	<0.001*	0.470	0.961	1.000	1.000	1.000	1.000	0.564
Caudate	0.494	0.026*	0.602	1.000	0.960	1.000	1.000	0.868	0.248
Putamen	0.306	0.063	0.656	1.000	1.000	1.000	0.085	1.000	1.000
Pallidum	0.430	0.115	0.678	1.000	1.000	1.000	1.000	1.000	1.000
Hippocampus	0.874	0.725	0.737	1.000	0.272	0.379	1.000	0.252	0.735
Amygdala	0.496	0.126	0.777	1.000	1.000	0.709	0.429	0.984	1.000
Corpus callosum	0.964	0.444	0.678	1.000	0.086	0.367	0.246	0.118	1.000
Thalamus proper	0.214	0.131	0.086	0.645	0.833	1.000	0.340	0.028	0.463
Ventricle	0.010*	0.011*	0.657	0.617	0.158	0.858	0.434	<0.001*	0.016*
Frontal	0.458	0.062	0.424	1.000	0.164	0.193	0.640	1.000	1.000
Cingulate	0.406	0.093	0.249	1.000	0.312	0.140	1.000	1.000	1.000
Occipital	0.075	0.067	0.662	1.000	0.849	0.926	1.000	1.000	1.000
Temporal	0.159	0.021*	0.921	1.000	0.331	0.161	1.000	1.000	1.000
Parietal	0.199	0.160	0.865	1.000	0.396	0.369	1.000	1.000	1.000
Insula	0.227	0.158	0.918	1.000	0.662	0.849	1.000	1.000	1.000
Lateral ventricle	0.070	0.007*	0.726	1.000	0.898	0.401	1.000	1.000	1.000
The whole ventricle	0.053	0.004*	0.756	1.000	1.000	0.501	1.000	0.999	0.835
The whole ventricles and CSF	0.042*	0.003*	0.770	1.000	1.000	0.530	1.000	0.839	0.733

CSF, cerebrospinal fluid. **p* value <0.05.

incidental brain imaging findings in 17% of participants, but it included three cohorts: those with depression, cardiovascular disease, and community dwellers, with the

latter making up less than half of the participants [43]. This could have led to a greater proportion of WM hyperintensities in that study.

The strengths of this study include the extensive clinical evaluation needed to identify normal cognitive participants and the relatively large sample size (typical studies with fewer than 100 participants) needed to perform regional brain volume metric analysis. There were participants up to 85 years old (participants in most studies were less than 75 years old). The results could be used as a reference for future practice. However, several limitations should be taken into account. First, we performed the scans on 1.5T MRI, which has a lower performance than 3T MRI. We used 1.5T MRI to ensure that our results could be widely applied in Thailand and other countries where 1.5T machines are more common, enhancing their clinical relevance. Additionally, we used 2D FLAIR images instead of 3D images to reduce scan time, which supports reproducibility across similar machines, though it may have slightly reduced image quality compared to 3D scans. Second, all participants were asymptomatic with normal cognitive function and ADLs at the 2-year follow-up, so no MCI or early dementia cases were included. However, the study did not use molecular imaging or biomarkers, and the 2-year follow-up was too short to fully assess dementia risk, meaning that preclinical AD may not have been entirely excluded. Third, the participants had higher education levels than did participants in the same age group nationwide. This could lead to better cognitive performance and might limit the generalizability of the findings. However, the population we recruited from two hospitals was able to represent normal Thai older adults, which decreased selection bias. Fourth, we performed the MRI scan only once, so new asymptomatic brain lesions could not be fully identified, and changes in brain volume over time could not be assessed. Finally, there were a limited number of participants aged 75 years and over (32 subjects). This might lead to nonsignificant sex differences in this age group.

Conclusions

Using automated software, we demonstrated that structural brain volume changes were correlated with aging changes and sex differences in Thai older adults. The study establishes normative brain volume data for Thai older adults, which can be used as a reference for diagnosing aging-related brain changes and neurodegenerative diseases like dementia. This is especially critical for Thailand, which is transitioning into a superaged society. Future research in other Asian pop-

ulations with similar demographics can leverage these findings to establish broader region-specific databases, improving diagnostic accuracy.

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Statement of Ethics

This study protocol was reviewed and approved by the Siriraj Institutional Review Board, Mahidol University, Bangkok, Thailand (Approval No. COA No. Si 666/2016), BMC-IRB (Approval No. 2016-12-025), and BDMS Hospital (Approval No. COA No. 2021/04). All participants provided written informed consent according to the Declaration of Helsinki. Written informed consent was obtained from patient's legal guardians/healthcare proxies for all vulnerable participants.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Conceptualization and methodology: Muangpaisan W., Chawalparit O., and Vichianin Y. Software, validation, and formal analysis: Pooliam J., Pongnapang N., Chawalparit O., Vichianin Y., Pongmoragot J., Dumrikarnlert C., Seeboonruang A., Charnchaowanish P., Kanjanapong S., Phannarus H., and Muangpaisan W. Investigation, resources, and data curation: all coauthors. Writing of original draft and visualization: Ngamsombat C. and Muangpaisan W. Writing of final paper: all coauthors. Project administration and supervision: Muangpaisan W. and Chawalparit O.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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