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ORIGINAL ARTICLE

Changes in the volumes and asymmetry of subcortical structures in healthy individuals according to gender

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Abstract

In recent years, with the development of technology, three-dimensional software has entered our lives. Volumetric measurements made with Magnetic Resonance Imaging (MRI) are essential in the morphometry of the brain and subcortical structures. In this study, we aim to share the volume and asymmetry of the hippocampus, its sub-branches, and other subcortical structures and their interaction with age/sex using volBrain, a web-based automated software.

1.5 T T1-weighted volumetric MRI, of 90 healthy individuals (51 females, 39 males) of both genders were included in our study. Pallidum, hippocampus, Cornu Ammonis1 (CA1), Cornu Ammonis2-3 (CA2-CA3), and Cornu Ammonis4-Dentate Gyrus (CA4-DG) measurements in females and males had a statistically higher mean in the right region ($p < 0.05$). In addition, females' hippocampus, CA1, CA2-CA3, and CA4-DG averages decreased more rapidly in the right region than in the left region. Subiculum measurement had a higher mean in the left region in both males and females ($p < 0.05$).

The mean subiculum of males decreased more rapidly in the right region than in the left region. When the total values of the subcortical region in males and females were compared according to age categories, amygdala, pallidum, putamen, hippocampus, CA2-CA3, and subiculum values did not differ to gender in individuals aged 50 and over ($p > 0.05$). In individuals under 50 years old, the mean of females was statistically lower than the mean of males ($p < 0.05$).

The Stratum radiatum (SR), Stratum lacunosum (SL), and Stratum molecuare (SM) asymmetry values of males in the examined subcortical regions had a higher mean than females ($p = 0.039$). In other regions, there was no statistically asymmetrical difference ($p > 0.05$). Studies evaluating the volumetric analysis and asymmetry of hippocampus subbranches and other subcortical structures in adults are very limited. As a result, the morphometry of the hippocampus subbranches and other subcortical structures was examined in detail. It was determined that the structures differed according to age, gender and body side.

Keywords Asymmetry · Hippocampus · Sex · Subcortical · Volume

Introduction

Magnetic Resonance Imaging (MRI) has been an essential visual analysis tool in the non-invasive examination of the cortical and subcortical structures of the brain (Kang et al. 2017; Abdelgawad et al. 2021). Imaging the brain with MRI is essential not only for the diagnosis of the disease but also for the visual analysis and knowledge of the pathogenesis of many neuropsychiatric disorders (DeMyer et al. 1988; Shenton et al. 2001; Carper et al. 2016; Kang et al. 2017; Lai et al. 2017). MRI-based cortical or subcortical volumetric studies provide information about biomarkers of diseases such as Alzheimer's, Parkinson's, and Schizophrenia (Guttman et al. 1998; Corson et al. 1999; Good et al. 2001; Okada et al. 2016; Van Erp et al. 2016; Akudjedu et al. 2018; Pietracupa et al. 2018).

Cortical or subcortical morphometry age (Madan and Kensinger 2017), neuro-psychiatric diseases (Bourque et al. 2009; Okada et al. 2016; Van Erp et al. 2016; Zuo et al. 2019), and dominant hand use (Jang et al. 2017) may differ depending on the circumstances. Age-related changes in

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brain volume have been reported in both postmortem and in vivo studies (Ho et al. 1980; Raz et al. 2000). In in vivo volumetric MRI studies, it has been observed that there are age-related differences in basal ganglia structures such as putamen, pallidum, thalamus, and accumbens (Madan and Kensinger 2017).

It has been reported that the differences in the brain structure of males and females may be related to biological and environmental factors (McCarthy and Arnold 2011). While previous studies found that caudate volume was higher in females (Filipek et al. 1994), another study reported the interaction of putamen between age and gender (Murphy et al. 1996). Goto et al. (2011) reported a decrease in hippocampus volume in males over 60 and postmenopausal females. In another study, it has been reported that different motor skills, such as dominant hand use preference and language function, create asymmetric differences in brain structures (Haaland and Harrington 1996; Mellet et al. 2014). Finally, studies report gender-specific differences in subcortical volumes in neuropsychiatric diseases (Wang et al. 2018; Bourque et al. 2009).

In recent years, many new software tools have replaced conventional measurement methods with the development of neuroimaging techniques. With these new software tools, automatic volume and segmentation measurements can be made using medical image data. One of this software is volBrain. VolBrain analyses the brain Magnetic Resonance structure online, reliable, practical and in a short time (Manjón and Coupé 2016).

Our study aims to use volBrain to share the volume and asymmetry of the hippocampus, its sub-branches, and other subcortical structures and their interaction with age/sex with MRI study.

Material method

Participants

MRI of 90 healthy individuals (51 females, 39 males) between the ages of 18–81 were included in the study. MR data consist of healthy individuals of both genders who applied to the clinic with headaches between 2017 and 2022, had no neurological/psychiatric disease and did not undergo neurosurgery.

The permission of Kırşehir Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee (Date: 10.05.2022, Approval Decision No: 2022–09/95) was obtained.

MR protocol and segmentation method

MRI was examined using a standard head coil on a 1.5 Tesla (GE SIGNA Explorer, 2020, United States) device. The high-resolution, sagittal plane, T1-weighted 3D BRAVO sequence was taken to show the anatomical detail better. TR (Repetition Time):7, TE (Echo Time):2.99 ms, FOV (Field of View):250X250 mm2, matrix: 256 × 256, section thickness was taken as 1 mm. A total of 272 sections were obtained with the specified parameters in an average of 3 min and 20 s.

3D T1-weighted brain MRI data of all subjects ($n = 90$) included in the study were exported with Picture Archiving and Communication Systems (PACS). These exported data were uploaded to the personal computer. This data in DICOM format was converted to Neuroimaging Informaties Technology Initiative (NIFTI) format with free software MRIcron (https://www.nitrc.org/projects/mricron). T1-weighted MRI data, anonymised in NIFTI format, was uploaded to volBrain's segmentation tools, HIPS pipeline and vol2Brain pipeline. VolBrain is a free, online, web-based data processing system that enables automatic analysis of MRI data. The results are presented as a PDF file when the data processing process is finished.

The vol2Brain and HIPS pipeline (v.1.0, http://volbrain.upv.es) used for volumetric analysis of the hippocampus and its sub-branches and other subcortical structures have been integrated into the volBrain web service (Manjón and Coupé 2016).

The vol2Brain pipeline automatically segments the brain volume into 135 structures. In our study, the volumes of subcortical structures (accumbens, amygdala, caudate, pallidum, putamen, thalamus) and Intracranial Cavity (ICC) tissues, namely white matter (WM), gray matter (GM), Cerebro Spinal Fluid (CSF), will be examined using this program (Manjon et al. 2022).

The Hips pipeline provides automatic segmentation of the hippocampus and its subdivisions. The Winterburn identification protocol, a new and high-resolution atlas, is used in this program. This described protocol covers hippocampus Cornu Ammonis1 (CA1), Cornu Ammonis2-3 (CA2-CA3), Cornu Ammonis4-Dentate Gyrus (CA4-DG), Stratum radiatum (SR), Stratum lacunosum (SL), Stratum molecuare (SM) and subiculum, by dividing it into 5 subsections (Winterburn et al. 2013; Romero et al. 2017). In our study, the volumes of the hippocampus and its subsections will be examined using this program. The volBrain data was converted to a 3D image with ITK-SNAP (http://www.itksnap.org) and MRIcroGL (https://www.nitrc.org/projects/mricrogl) (Figs. 1 and 2).

The program automatically measures all volumes obtained with vol2Brain and the Hips pipeline. With these software tools, tissue volumes are measured in absolute value (cm3) and given as a ratio to ICC volume (covering 100%) (Manjón and Coupé 2016).

The asymmetry index gives information about the differences in the right and left parts of the subcortical structures.

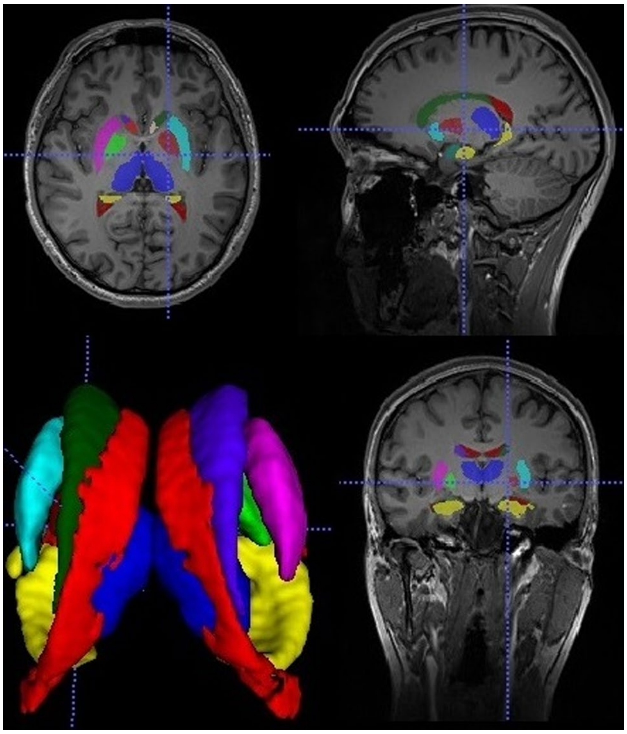

Fig. 1 Coloring and 3D modeling of volBrain data with ITK-SNAP

In our study, the asymmetry index was calculated in the age and gender categories of subcortical structures. The asymmetry index was calculated by dividing the difference between the right and left volumes by their mean (as a percentage) (Manjón and Coupé 2016; Kurth et al. 2018). Asymmetry index = (right volume–left volume)/mean (right volume, left volume) × 100. The positive values of the calculated asymmetry index results represent a right (right > left) asymmetry. Negative values indicate an asymmetry to the left (left > right). As the asymmetry index calculated by the volume values of the right and left regions of the subcortical structures moved away from zero, that region was thought to show lateralization.

Statistical method

Data were evaluated in the statistical package programs of IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics were given as mean ± standard deviation (mean ± sd), median (M), minimum (min) and maximum (max) values. The normal distribution of the data of numerical variables was evaluated with the Shapiro–Wilk normality test. Independent Samples *t* Test for normally distributed variables in the comparison of gender (female, male) and age ($<50, \geq 50$) groups; Mann–Whitney-U test was used for the variables that did not show normal distribution.

For repeated tests, the sphericity assumption was checked with the Mauchly test. When the sphericity assumption was met, the Sphericity Assumed test was applied. The epsilon value was checked for the case where it was not provided. Huynh–Feldt test results were evaluated for cases where it was greater than 0.75, and the Greenhouse Geisser test for cases where it was smaller. In our analysis, mixed-design analysis of variance and Bonferroni-Dunn test, one of the multiple comparison tests, and Bonferroni-Dunn test over time were used to make an overall assessment between repeated measures (Clinical Parameters) and categorical variables (age, gender). In addition, a two-way analysis of variance and the Bonferroni-Dunn test, one of the multiple comparison tests, were used to evaluate two independent categorical variables. The $p < 0.05$ level was considered statistically significant.

Results

The average age of the participants is 45.17 (range 18–75) for females and 42.82 (range 18–81) for males, respectively. The mean age of both sexes did not differ statistically ($p > 0.525$).

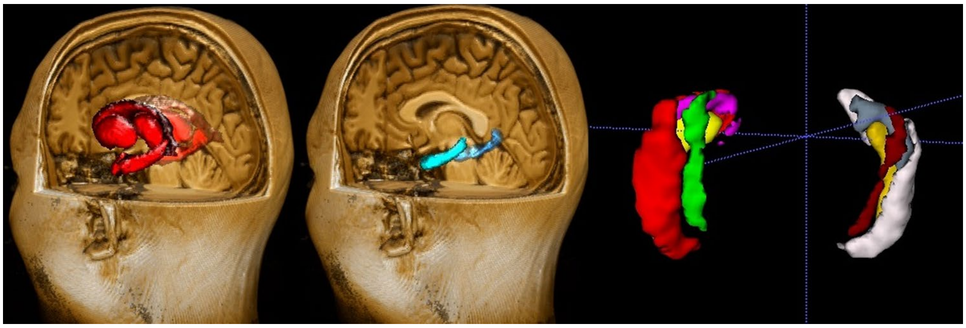

Fig. 2 3D visualization of volBrain data with MRIcroGL (left-middle) and ITK-SNAP (right)

Total brain

The mean of WM, GM, CSF and ICC were statistically lower in females than in males ($p < 0.05$) (Table 1). In age categories, the mean of WM, GM and intracranial cavity were statistically higher in individuals younger than 50 ($p < 0.05$). Conversely, the mean of CSF was lower in individuals under 50 years of age ($p < 0.001$) (Table 2). Toplam beyin ölçümlerine ilişkin tanıtıcı istatistikler detaylı olarak verilmiştir (Supplementary Table 1).

WM, GM and ICC values were lower for females under 50 years of age than for males ($p < 0.05$). The mean CSF values of females aged 50 and over were statistically lower than the mean of males ($p < 0.001$). WM and ICC values were statistically higher in males under 50 years of age (for all, $p = 0.001$). The GM values of females and males had a statistically higher mean in individuals under 50 years of age (respectively; $p = 0.001$, $p < 0.001$). The CSF values of females and males were statistically higher in individuals aged 50 and over (respectively, $p = 0.002$, $p < 0.001$) (Supplementary Table 2).

Subcortical volume

Introductory statistics regarding the right, the left and total volume measurements of subcortical structures in the individuals included in the study are shown in Table 3.

Gender

According to the comparisons between groups in Table 4, amygdala, pallidum, and subiculum values in the right and left regions were statistically lower in females than males ($p < 0.05$). According to in-group comparisons, pallidum, hippocampus, CA1, CA2-CA3, and CA4-DG measurements in males and females had statistically higher mean values in the right region ($p < 0.05$). In addition, the female's hippocampus, CA1, CA2, CA3, and CA4-DG averages decreased more rapidly in the right region than in the left region. According to in-group comparisons, the mean of the subiculum was higher in the left region in males and females ($p = 0.008$ and $p = 0.002$). The mean subiculum of males decreased more rapidly in the right region than in the left region.

In Table 5, the total averages of the amygdala, pallidum, putamen, and subiculum right and left regions were statistically lower in females than in males ($p < 0.05$).

Age

According to the comparisons between the groups, the values of the accumbens, caudate, pallidum, putamen, thalamus, hippocampus, CA1, CA4-DG, SR-SL-SM, and subiculum were statistically higher in the right and left regions in individuals under 50 years of age

Table 1 Comparison of total values in total brain region in male and female (cm^3)

	Female $n = 51$	Male $n = 39$	Test statistics ‡	
	Mean ± SD	Mean ± SD	Test value	p
White matter	463,11 ± 56,56	493,08 ± 73,55	− 2,187	0.031*
Gray matter	654,9 ± 61,89	710,13 ± 85,76	− 3,549	0.001*
Cerebro spinal fluid	157,91 ± 34,55	180,49 ± 41,05	− 2,831	0.006*
Intracranial cavity	1294,6 ± 111,35	1403,64 ± 146,72	− 4,010	< 0.001*

*$p < 0{,}05$; ‡Independent samples t test (t); Summary statistics are given as mean ± standard deviation

Table 2 Comparison of total values in total brain region in age categories (cm^3)

	< 50 ($n = 49$)	≥ 50 ($n = 41$)	Test statistics ‡	
	Mean ± SD	Mean ± SD	Test value	p
White matter	496,49 ± 72,56	451,73 ± 46,87	3,399	0.001*
Gray matter	719,71 ± 75,2	629,98 ± 46,71	6,640	< 0.001*
Cerebro spinal fluid	151,97 ± 30,16	186,49 ± 40,22	− 4,648	< 0.001*
Intracranial cavity	1387,66 ± 154,2	1287,11 ± 91,33	3,669	< 0.001*

*$p < 0{,}05$ ‡ Independent samples t test (t); Summary statistics are given as mean ± standard deviation

Table 3 Descriptive statistics on measurements in the subcortical region

	Total		Right		Left		Asymmetry	
	Mean ± SD	M (Min.-Max)	Mean ± SD	M (Min.–Max)	Mean ± SD	M (Min.–Max)	Mean ± SD	M (Min.–Max)
Accumbens	0,67 ± 0,13	0,66 (0,36–1,09)	0,32 ± 0,07	0,31 (0,15–0,56)	0,35 ± 0,06	0,35 (0,21–0,53)	− 9,83 ± 11,29	− 10,71 (−36,9–35,02)
Amygdala	1,90 ± 0,24	1,87 (1,26–2,53)	0,95 ± 0,13	0,93 (0,63–1,3)	0,94 ± 0,14	0,95 (0,55–1,28)	1,19 ± 11,90	1,68 (− 53,83–47,46)
Caudate	7,26 ± 1,00	7,12 (5,33–10,28)	3,65 ± 0,50	3,6 (2,65–5,17)	3,61 ± 0,51	3,51 (2,44–5,11)	1,13 ± 5,08	0,26 (− 7,87–35,51)
Pallidum	2,66 ± 0,32	2,65 (2,01–3,34)	1,35 ± 0,17	1,34 (1,01–1,66)	1,32 ± 0,17	1,32 (0,96–1,69)	2,29 ± 7,10	1,89 (− 14,51–22,47)
Putamen	8,52 ± 1,20	8,35 (5,74–12,32)	4,23 ± 0,59	4,16 (2,74–6,13)	4,29 ± 0,65	4,23 (1,66–6,19)	− 1,04 ± 10,22	− 2,31 (− 19,07–86,86)
Thalamus	11,67 ± 1,64	11,49 (7,75–16,92)	5,77 ± 0,79	5,66 (3,84–8,21)	5,91 ± 0,87	5,83 (3,91–8,71)	− 2,25 ± 4,95	− 2,42 (− 17,49–29,52)
Hippocampus	4,58 ± 0,73	4,6 (1,73–6,31)	2,34 ± 0,35	2,35 (1,01–3,23)	2,24 ± 0,40	2,22 (0,71–3,09)	5,14 ± 10,08	4,03 (− 27,34–34,97)
CA1	1,69 ± 0,28	1,69 (0,57–2,4)	0,87 ± 0,14	0,87 (0,31–1,22)	0,82 ± 0,15	0,82 (0,26–1,18)	5,41 ± 11,31	5,32 (− 23,41–30,58)
CA2-CA3	0,33 ± 0,06	0,32 (0,15–0,53)	0,18 ± 0,04	0,17 (0,1–0,29)	0,15 ± 0,04	0,15 (0,03–0,24)	19,31 ± 24,29	17,93 (− 37,71–115,37)
CA4-DG	1,14 ± 0,23	1,15 (0,38–1,65)	0,60 ± 0,11	0,59 (0,27–0,88)	0,54 ± 0,12	0,55 (0,11–0,77)	10,13 ± 16,91	8,88 (− 29,65–86,9)
SR-SL-SM	0,85 ± 0,17	0,87 (0,21–1,26)	0,43 ± 0,09	0,43 (0,14–0,62)	0,43 ± 0,09	0,44 (0,07–0,64)	0,11 ± 16,20	− 1,95 (− 39,08–69,89)
Subiculum	0,57 ± 0,10	0,57 (0,35–0,86)	0,28 ± 0,05	0,28 (0,17–0,42)	0,30 ± 0,06	0,29 (0,15–0,44)	− 5,66 ± 13,92	− 6,63, (− 35,64–27,01)

Summary statistics are given as Mean ± Standard Deviation and Median (Minimum–Maximum) value

($p < 0.05$). CA2-CA3 values were statistically higher in the left region in individuals under 50 years of age ($p = 0.014$). Compared to within-group comparisons, the hippocampus, CA1, CA2-CA3 and CA4-DG values were statistically higher in the right region ($p < 0.05$). The hippocampus and CA1 mean of individuals aged 50 and over increased more rapidly in the right region than in the left region (Table 6).

In all subcortical structures examined in Table 7, the total mean of the right and left regions was statistically higher in individuals under 50 years of age ($p < 0.05$).

Gender x age

The total values of the subcortical region in males and females were compared according to age categories. According to the comparisons between the groups, amygdala, pallidum, putamen, hippocampus, CA2-CA3 and subiculum values did not differ according to gender in individuals aged 50 and over ($p > 0.05$). However, in individuals under 50 years of age, the mean of females was statistically lower than that of males ($p < 0.05$). According to in-group comparisons, accumbens, caudate, thalamus, pallidum, putamen, CA4-DG and subiculum values in both genders were statistically higher in individuals under 50 years of age ($p < 0.05$). Males hippocampus, CA1, CA2-CA3 and subiculum values were statistically higher in individuals under 50 years of age ($p < 0.05$) (Table 8).

The comparison of the values in the subcortical region in male and female, in the right and left regions, according to age categories is given in detail (Supplementary Table 3, Supplementary Table 4).

Asymmetry

The asymmetry index was calculated for subcortical structures. The calculated asymmetry values of the right and left volume measurements of the subcortical structures in the individuals included in the study ($n = 90$) are shown in Table 3.

Gender

There was no statistically asymmetric difference between males ($n = 39$) and females ($n = 51$) in the examined subcortical regions ($p > 0.05$). Only males had a higher mean

Table 4 Comparison of the values in the subcortical region of female and male according to the right and left regions

Right–Left	Female $n=51$	Male $n=39$	Test statistics †	
	Mean ± SD	Mean ± SD	F	P
Accumbens				
Right	0,31 ± 0,05	0,33 ± 0,08	2,002	0.161
Left	0,33 ± 0,08	0,37 ± 0,08	4,580	**0.035**
Test statistics$^{¥}$	$F=29{,}477$; **$p=0{,}001$**	$F=37{,}654$; **$p=0{,}001$**		
Sex: $F=3{,}346$; $p=0{,}071$; Time: $F=67{,}128$; $p=0{,}001$; Time*Sex: $F=1{,}092$; $p=0{,}299$				
Amygdala				
Right	0,92 ± 0,11	0,99 ± 0,14	7,381	**0,008**
Left	0,90 ± 0,13	1,00 ± 0,12	13,421	**< 0.001**
Test statistics$^{¥}$	$F=2{,}308$; $p=0{,}132$	$F=0{,}195$; $p=0{,}66$		
Sex: $F=12{,}385$; $p=0{,}001$; Time: $F=0{,}446$; $p=0{,}506$; Time*Sex: $F=1{,}775$; $p=0{,}186$				
Caudate				
Right	3,60 ± 0,49	3,71 ± 0,51	1,175	0.281
Left	3,59 ± 0,49	3,64 ± 0,54	0,260	0.612
Test statistics$^{¥}$	$F=0{,}317$; $p=0{,}575$	$F=7{,}498$; **$p=0{,}007$**		
Sex: $F=0{,}644$; $p=0{,}425$; Time: $F=5{,}913$; $p=0{,}017$; Time*Sex: $F=2{,}859$; $p=0{,}094$				
Pallidum				
Right	1,31 ± 0,14	1,39 ± 0,18	5,791	**0,018**
Left	1,29 ± 0,14	1,36 ± 0,19	4,185	**0,044**
Test Statistics$^{¥}$	$F=3{,}968$; **$p=0{,}049$**	$F=5{,}958$; **$p=0{,}017$**		
Sex: $F=5{,}353$; $p=0{,}023$; Time: $F=9{,}914$; $p=0{,}002$; Time*Sex: $F=0{,}277$; $p=0{,}600$				
Putamen				
Right	4,09 ± 0,44	4,41 ± 0,70	6,976	**0.010**
Left	4,20 ± 0,47	4,40 ± 0,83	1,959	0.165
Test statistics$^{¥}$	$F=6{,}158$; **$p=0{,}015$**	$F=0{,}076$; $p=0{,}783$		
Sex: $F=4{,}181$; $p=0{,}044$; Time: $F=2{,}032$; $p=0{,}158$; Time*Sex: $F=3{,}391$; $p=0{,}069$				
Thalamus				
Right	5,66 ± 0,65	5,90 ± 0,94	2,096	0,151
Left	5,84 ± 0,71	5,99 ± 1,05	0,672	0,414
Test Statistics$^{¥}$	$F=21{,}313$; **$p=0{,}001$**	$F=3{,}932$; $p=0{,}051$		
Sex: $F=1{,}284$; $p=0{,}260$; Time: $F=20{,}536$; $p=0{,}001$; Time*Sex: $F=2{,}391$; $p=0{,}126$				
Hipokampus				
Right	2,30 ± 0,31	2,39 ± 0,39	1,268	0.263
Left	2,18 ± 0,38	2,31 ± 0,42	2,515	0.116
Test statistics$^{¥}$	$F=19{,}404$; **$p=0{,}001$**	$F=5{,}672$; **$p=0{,}019$**		
Sex: $F=2{,}014$; p = 0,150; Time: $F=22{,}201$; $p=0{,}001$; Time*Sex: $F=1{,}349$; p = 0,249				
CA1				
Right	0,86 ± 0,13	0,88 ± 0,15	0,402	0.528
Left	0,81 ± 0,15	0,84 ± 0,15	0,718	0.399
Test Statistics$^{¥}$	$F=12{,}786$; **$p=0{,}001$**	$F=6{,}994$; **$p=0{,}010$**		
Sex: $F=0{,}613$; $p=0{,}436$; Time: $F=18{,}967$; $p=0{,}001$; Time*Sex: $F=0{,}170$; p = 0,681				
CA2-CA3				
Right	0,17 ± 0,03	0,18 ± 0,04	1,022	.
Left	0,14 ± 0,03	0,16 ± 0,04	5,281	**0.024**
Test statistics$^{¥}$	$F=48{,}546$; **$p=0{,}001$**	$F=20{,}071$; **$p=0{,}001$**		
Sex: $F=3{,}537$; $p=0{,}063$; Time: $F=63{,}747$; $p=0{,}001$; Time*Sex: $F=1{,}705$; $p=0{,}195$				
CA4-DG				
Right	0,58 ± 0,11	0,61 ± 0,11	1,140	0.289
Left	0,53 ± 0,12	0,56 ± 0,13	1,526	0.220
Test statistics$^{¥}$	$F=24{,}082$; **$p=0{,}001$**	$F=14{,}681$; **$p=0{,}001$**		

Table 4 (continued)

Right–Left	Female $n=51$	Male $n=39$	Test statistics †	
	Mean ± SD	Mean ± SD	*F*	*P*
Sex: $F=1,487$; $p=0,226$; Time: $F=37,546$; $p=0,001$; Time*Sex: $F=0,173$; $p=0,679$				
SR-SL-SM				
Right	0,42 ± 0,08	0,43 ± 0,09	0,130	0.719
Left	0,42 ± 0,09	0,44 ± 0,09	2,043	0.156
Test Statistics$^{¥}$	$F=0,722$; $p=0,398$	$F=2,29$; $p=0,134$		
Sex: $F=0,920$; $p=0,340$; Time: $F=0,315$; $p=0,576$; Time*Sex: $F=2,872$; $p=0,094$				
Subiculum				
Right	0,27 ± 0,04	0,29 ± 0,06	5,559	**0.021**
Left	0,28 ± 0,05	0,31 ± 0,06	5,827	**0.018**
Test Statistics$^{¥}$	$F=7,348$; $\mathbf{p=0,008}$	$F=9,819$; $\mathbf{p=0,002}$		
Sex: $F=6,575$; $p=0,012$; Time: $F=17,162$; $p=0,001$; Time * Sex: $F=0,279$; $p=0,599$				

F Mixed Order analysis of variance † Between-group comparison, ¥ Intra-group comparison, summary statistics are given as mean ± standard deviation. The parts determined in bold are statistically significant ($p<0.05$)

Table 5 Comparison of total values in the subcortical region in male and female

Total	Female $n=51$	Male $n=39$	Test statistics ‡	
	Mean ± SD	Mean ± SD	Test Value	*p*
Accumbens	0,65 ± 0,10	0,70 ± 0,15	– 1,829	0.,071
Amygdala	1,82 ± 0,23	1,99 ± 0,22	– 3,519	**0.001** *
Caudate	7,18 ± 0,98	7,35 ± 1,03	– 0,802	0.425
Pallidum	2,60 ± 0,27	2,75 ± 0,36	– 2,314	**0.023** *
Putamen	8,30 ± 0,90	8,81 ± 1,47	– 2,045	**0.044** *
Thalamus	11,50 ± 1,34	11,90 ± 1,96	– 1,133	0.260
Hippocampus	4,48 ± 0,66	4,70 ± 0,79	– 1,419	0.159
CA1	1,67 ± 0,26	1,71 ± 0,30	– 0,783	0.436
CA2-CA3	0,31 ± 0,06	0,34 ± 0,07	– 1,881	0.063
CA4-DG	1,11 ± 0,22	1,17 ± 0,23	– 1,220	0.226
SR-SL-SM	0,84 ± 0,16	0,87 ± 0,18	– 0,959	0.340
Subiculum	0,55 ± 0,09	0,60 ± 0,12	– 2,564	**0.012** *

*$p<0,05$; ‡ Independent samples *t* test (*t*); Summary statistics are given as mean ± standard deviation

The parts determined in bold are statistically significant ($p<0.05$)

SR-SL-SM asymmetry value than females ($p=0.039$) (Supplementary Table 5).

Age

In age categories under 50 ($n=49$) and 50 years and over ($n=41$), asymmetry values did not differ statistically ($p>0.05$) (Supplementary Table 6).

Gender x age

Asymmetry values in the subcortical region of females and males were compared according to age categories. According to the comparisons between the groups, the accumbens and putamen values of males were found to be more asymmetric than females in individuals aged 50 and over ($p=0.042$, $p=0.005$, respectively). Thalamus values were asymmetrical in females aged 50 and over compared to males ($p=0.016$). CA2-CA3 values were more asymmetric in female individuals under 50 years of age than in males ($p=0.041$). According to in-group comparisons, the putamen values of males aged 50 and over were asymmetrical compared to those under 50 years of age ($p<0.021$). Thalamus values were asymmetrical in males under 50 years of age ($p=0.013$) (Supplementary Table 7).

Discussion

In the current literature, there are studies on the volumetric analysis of subcortical structures. However, there are very few studies in which volume and asymmetric measurements of subcortical structures and hippocampus subdivisions are evaluated together. Our study examined healthy individuals between the ages of 18–81. In previous studies, volumetric analyses were made by creating certain age groups. Wang et al. (2019) commented that there is no appropriate age range for volume loss that may occur in the 18–42 age range.

In the literature, it was seen that volumetric analyses were made by grouping them as under 50 years old and over 50 years old (Takahashi et al. 2011). In this direction,

Table 6 Comparison of values in the subcortical region according to the right and left regions in age categories

Right-Left	< 50 $n=49$	≥ 50 $n=41$	Test statistics †	
	Mean ± SD	Mean ± SD	Test value	p
Accumbens				
Right	0,34 ± 0,07	0,29 ± 0,06	13,991	**< 0.001**
Left	0,37 ± 0,06	0,32 ± 0,05	18,854	**< 0.001**
Test statistics$^{¥}$	F = 38,533; **p = 0,001**	F = 26,922; **p = 0,001**		
Age: F = 17,694; p = 0,001; Time: F = 64,293; p = 0,001; Time*Age: F = 0,131; p = 0,719				
Amygdala				
Right	0,97 ± 0,13	0,93 ± 0,11	2,998	0.087
Left	0,97 ± 0,12	0,91 ± 0,14	3,886	0.052
Test statistics$^{¥}$	F = 0,094; p = 0,760	F = 0,844; p = 0,361		
Age: F = 4,109; p = 0,046; Time: F = 0,782; p = 0,379; Time*Age: F = 0,222; p = 0,638				
Caudate				
Right	3,85 ± 0,51	3,40 ± 0,36	23,025	**< 0.001**
Left	3,83 ± 0,50	3,35 ± 0,39	24,729	**< 0.001**
Test Statistics$^{¥}$	F = 1,240; p = 0,269	F = 4,157; **p = 0,044**		
Age: F = 24,714; p = 0,001; Time: F = 5,090; p = 0,027; Time*Age: F = 0,567; p = 0,453				
Pallidum				
Right	1,42 ± 0,15	1,27 ± 0,14	23,038	**< 0.001**
Left	1,40 ± 0,16	1,22 ± 0,13	32,447	**< 0.001**
Test statistics$^{¥}$	F = 2,044; p = 0,156	F = 9,465; **p = 0,003**		
Age: F = 30,352; p = 0,001; Time: F = 10,465; p = 0,002; Time*Age: F = 1,703; p = 0,195				
Putamen				
Right	4,50 ± 0,59	3,91 ± 0,39	30,082	**< 0.001**
Left	4,58 ± 0,59	3,94 ± 0,55	28,161	**< 0.001**
Test Statistics$^{¥}$	F = 3,019; p = 0,086	F = 0,313; p = 0,577		
Age: F = 31,812; p = 0,001; Time: F = 2,515; p = 0,116; Time*Age: F = 0,577; p = 0,449				
Thalamus				
Right	6,13 ± 0,79	5,33 ± 0,53	30,900	**< 0.001**
Left	6,34 ± 0,84	5,39 ± 0,57	36,888	**< 0.001**
Test Statistics$^{¥}$	F = 26,608; **p = 0,001**	F = 2,438; p = 0,122		
Age: F = 35,187; p = 0,001; Time: F = 21,472; p = 0,001; Time*Age: F = 5,426; p = 0,022				
Hippocampus				
Right	2,45 ± 0,35	2,21 ± 0,31	12,666	**0.001**
Left	2,38 ± 0,35	2,07 ± 0,39	15,389	**< 0.001**
Test statistics$^{¥}$	F = 7,128; **p = 0,009**	F = 18,674; **p = 0,001**		
Age: F = 15,259; p = 0,001; Time: F = 24,906; p = 0,001; Time*Age: F = 1,923; p = 0,169				
CA1				
Right	0,90 ± 0,15	0,83 ± 0,13	5,095	**0.026**
Left	0,86 ± 0,14	0,78 ± 0,15	7,591	**0.007**
Test Statistics$^{¥}$	F = 6,919; **p = 0,010**	F = 13,791; **p = 0,001**		
Age: F = 7,036; p = 0,009; Time: F = 20,39; p = 0,001; Time*Age: F = 0,931; p = 0,337				
CA2-CA3				
Right	0,18 ± 0,04	0,17 ± 0,03	2,511	0,117
Left	0,16 ± 0,04	0,14 ± 0,03	6,349	**0,014**
Test Statistics$^{¥}$	F = 28,958; **p = 0,001**	F = 38,183; **p = 0,001**		
Age: F = 5,500; p = 0,021; Time: F = 67,101; p = 0,001; Time*Age: F = 0,860; p = 0,356				
CA4-DG				
Right	0,64 ± 0,11	0,55 ± 0,10	16,160	**< 0.001**
Left	0,59 ± 0,11	0,50 ± 0,12	13,376	**< 0.001**
Test statistics $^{¥}$	F = 20,647; **p = 0,001**	F = 17,872; **p = 0,001**		

Table 6 (continued)

Right-Left	<50 $n=49$ Mean ± SD	≥ 50 $n=41$ Mean ± SD	Test statistics † Test value	 p
Age: $F=16,626$; $p=0,001$; Time: $F=38,27$; $p=0,001$; Time*Age: $F=0,003$; $p=0,958$				
SR-SL-SM				
Right	0,44 ± 0,08	0,40 ± 0,09	5,226	**0.025**
Left	0,46 ± 0,08	0,39 ± 0,09	11,112	**0.001**
Test statistics$^{¥}$	$F=1,913$; $p=0,170$	$F=0,914$; $p=0,342$		
Age: $F=8,965$; $p=0,004$; Time: $F=0,052$; $p=0,820$; Time*Age: $F=2,686$; $p=0,105$				
Subiculum				
Right	0,30 ± 0,05	0,25 ± 0,05	17,936	**< 0.001**
Left	0,32 ± 0,05	0,27 ± 0,05	24,056	**< 0.001**
Test statistics$^{¥}$	$F=16,659$; $\mathbf{p=0,001}$	$F=2,871$; $p=0,094$		
Age: $F=24,884$; $p=0,001$; Time: $F=16,041$; $p=0,001$; Time*Age: $F=2,264$; $p=0,136$				

F Mixed Order analysis of variance † Between-group comparison, ¥ Intra-group comparison, summary statistics are given as mean ± standard deviation. The parts determined in bold are statistically significant ($p < 0.05$)

Table 7 Comparison of total values in subcortical region in age categories

Total	<50 $n=49$ Mean ± SD	≥ 50 $n=41$ Mean ± SD	Test statistics ‡ Test value	 p
Accumbens	0,72 ± 0,13	0,61 ± 0,11	4,206	**< 0.001***
Amygdala	1,94 ± 0,24	1,84 ± 0,23	2,027	**0.046***
Caudate	7,68 ± 1,00	6,75 ± 0,73	4,971	**< 0.001***
Pallidum	2,81 ± 0,30	2,49 ± 0,25	5,510	**< 0.001***
Putamen	9,08 ± 1,18	7,85 ± 0,83	5,640	**< 0.001***
Thalamus	12,47 ± 1,62	10,72 ± 1,06	5,932	**< 0.001***
Hippocampus	4,83 ± 0,68	4,28 ± 0,67	3,906	**< 0.001***
CA1	1,76 ± 0,27	1,61 ± 0,26	2,652	**0.009***
CA2-CA3	0,34 ± 0,07	0,31 ± 0,05	2,345	**0.021***
CA4-DG	1,22 ± 0,21	1,04 ± 0,21	4,078	**< 0.001***
SR-SL-SM	0,90 ± 0,15	0,80 ± 0,17	2,994	**0.004***
Subiculum	0,62 ± 0,10	0,52 ± 0,09	4,988	**< 0.001***

*$p<0,05$; ‡ Independent samples *t* test (*t*); Summary statistics are given as mean ± standard deviation

The parts determined in bold are statistically significant ($p<0.05$)

we created two groups in our study, under 50 years old and 50 years old and over. Volume and asymmetry values of the lower branches of the hippocampus and other subcortical structures; We aimed to explain with current statistical analyses according to gender/age variables.

With automatic software development, volumetric analyses of neuroanatomical structures can be made according to age and gender (Wang et al. 2019). In previous studies, when the total volume of the brain was controlled, it was observed that there was no difference in volume measurements of subcortical structures according to gender (Tang et al. 2013). In another study, it was stated that there is a decrease in the volumes of subcortical structures with increasing age, which may be related to the reduction of sensorimotor functions (Serbruyns et al. 2015). Our study determined that the volume measurements of subcortical structures were higher in individuals under 50 years of age. In addition, the amygdala, pallidum, putamen and subiculum total volume averages were higher in males.

The literature has conflicting findings about WM. Many studies have reported that the WM volume decreases with age (Lemaître et al. 2005; Guttman et al. 1998). Taki et al. (2004) stated that the WM volume of both sexes increased until the age of 50 and then decreased. In addition, unlike these findings, studies say that total WM volume is not associated with age (Good et al. 2001; Taki et al. 2004). GM volume has also been reported to decrease with age (Lemaître et al. 2005; Pell et al. 2008). Soysal et al. (2022) reported that WM and GM were higher in males aged 50 and younger. In our study, BM and GM volume was higher in males under 50 years of age than in females.

In another study, GM volume (9%) and WM volume (13%) were found to be higher in males (Ruigrok et al. 2014). Similarly, WM and GM volumes were higher in males in our study. We think the reason for the differences in the findings may be related to the number of samples, gender and mean age. In addition, there is information in the literature that factors such as alcohol use and systolic blood pressure locally affect GM volume (Taki et al. 2004). Since our study was retrospective, correlations could not be made for these parameters.

Grant et al. (1987) reported that CSF volume in a group of healthy participants aged 18–64 increased with age in both sexes. Soysal et al. (2022) reported that males had higher CSF volume. Similarly, in our study, CSF volume

Table 8 Comparison of total values in the subcortical region of female and males by age categories

Total	Female $n=51$	Male $n=39$	Test statistics †	
	Mean ± SD	Mean ± SD	Test value	p
Accumbens				
< 50	0,69 ± 0,1	0,75 ± 0,15	3,487	0.065
≥ 50	0,61 ± 0,09	0,61 ± 0,13	0,010	0.920
Test Statistics¥	$F=5,359$; **$p=0,023$**	$F=12,196$; **$p=0,001$**		
Sex: $F=1,716$; $p=0,194$; Age: $F=17,304$; $p=0,001$; Sex*Age: $F=1,344$; $p=0,250$				
Amygdala				
< 50	1,85 ± 0,23	2,04 ± 0,20	8,751	**0.004**
≥ 50	1,80 ± 0,23	1,92 ± 0,24	2,710	0.103
Test statistics¥	$F=0,691$; $p=0,408$	$F=2,735$; $p=0,102$		
Sex: $F=10,182$; $p=0,002$; Age: $F=3,233$; $p=0,076$; Sex*Age: $F=0,520$; $p=0,473$				
Caudate				
< 50	7,51 ± 1,07	7,86 ± 0,92	1,856	0.177
≥ 50	6,86 ± 0,77	6,55 ± 0,61	1,227	0.271
Test statistics¥	$F=6,915$; **$p=0,010$**	$F=20,358$; **$p<0,001$**		
Sex: $F=0,005$; $p=0,945$; Age: $F=26,423$; $p=0,001$; Sex*Age: $F=2,999$; $p=0,087$				
Pallidum				
< 50	2,73 ± 0,25	2,90 ± 0,33	4,958	**0.029**
≥ 50	2,47 ± 0,23	2,51 ± 0,28	0,203	0.653
Test statistics ¥	$F=10,992$; **$p=0,001$**	$F=18,584$; **$p=0,001$**		
Sex: $F=3,278$; $p=0,074$; Age: $F=29,503$; $p=0,001$; Sex*Age: $F=1,286$; $p=0,260$				
Putamen				
< 50	8,63 ± 0,95	9,55 ± 1,23	10,755	**0.002**
≥ 50	7,98 ± 0,73	7,63 ± 0,96	1,213	0.274
Test Statistics¥	$F=5,720$; **$p=0,019$**	$F=35,614$; **$p<0,001$**		
Sex: $F=1,801$; $p=0,183$; Age: $F=37,147$; $p=0,001$; Sex*Age: $F=8,968$; $p=0,004$				
Thalamus				
< 50	12,15 ± 1,39	12,80 ± 1,79	2,740	0.102
≥ 50	10,88 ± 0,94	10,45 ± 1,23	0,935	0.336
Test statistics¥	$F=10,81$; **$p=0,001$**	$F=26,916$; **$p<0,001$**		
Sex: $F=0,136$; $p=0,713$; Age: $F=36,99$; $p=0,001$; Sex*Age: $F=3,313$; $p=0,072$				
Hippocampus				
< 50	4,65 ± 0,52	5,03 ± 0,78	4,086	**0.046**
≥ 50	4,32 ± 0,75	4,21 ± 0,53	0,287	0.593
Test statistics¥	$F=2,976$; $p=0,088$	$F=14,696$; **$p=0,001$**		
Sex: $F=0,895$; $p=0,347$; **Age:** $F=16,161$; $p=0,001$; **Sex*Age:** $F=3,049$; $p=0,084$				
CA1				
< 50	1,70 ± 0,21	1,82 ± 0,32	2,662	0,106
≥ 50	1,64 ± 0,30	1,56 ± 0,16	0,993	0,322
Test statistics¥	$F=0,571$; $p=0,452$	$F=9,582$; **$p=0,003$**		
Sex: $F=0,118$; $p=0,732$; **Age:** $F=7,987$; $p=0,006$; **Sex*Age:** $F=3,349$; $p=0,071$				
CA2-CA3				
< 50	0,32 ± 0,06	0,36 ± 0,08	6,706	**0.011**
≥ 50	0,31 ± 0,05	0,30 ± 0,04	0,101	0.751
Test statistics ¥	$F=0,145$; $p=0,705$	$F=8,653$; **$p=0,004$**		
Sex: $F=2,212$; $p=0,141$; **Age:** $F=6,066$; $p=0,016$; **Sex*Age:** $F=3,848$; $p=0,053$				
CA4-DG				
< 50	1,18 ± 0,19	1,27 ± 0,22	2,311	0.132
≥ 50	1,05 ± 0,23	1,03 ± 0,17	0,105	0.747
Test statistics¥	$F=4,680$; **$p=0,033$**	$F=12,693$; **$p=0,001$**		

Table 8 (continued)

Total	Female *n* = 51 Mean ± SD	Male *n* = 39 Mean ± SD	Test statistics † Test value	 *p*
Sex: *F* = 0,594; *p* = 0,443; **Age:** *F* = 16,853; *p* = 0,001; **Sex*Age:** *F* = 1,572; *p* = 0,213				
SR-SL-SM				
< 50	0,87 ± 0,14	0,93 ± 0,16	1,506	0.223
≥ 50	0,80 ± 0,17	0,79 ± 0,17	0,100	0.752
Test statistics$^{¥}$	*F* = 2,215; *p* = 0,140	*F* = 7,317; ***p* = 0,008**		
Sex: *F* = 0,338; *p* = 0,563; **Age:** *F* = 9,092; *p* = 0,003; **Sex*Age:** *F* = 1,110; *p* = 0,295				
Subiculum				
< 50	0,58 ± 0,08	0,65 ± 0,10	7,691	**0.007**
≥ 50	0,51 ± 0,08	0,53 ± 0,09	0,235	0.629
Test Statistics$^{¥}$	*F* = 7,282; ***p* = 0,008**	*F* = 18,827; ***p* = 0,001**		
Sex: *F* = 4,879; *p* = 0,030; **Age:** *F* = 25,419; *p* = 0,001; **Sex*Age:** *F* = 2,205; *p* = 0,141				

F Two-way analysis of variance † Group (Sex) comparison, ¥ Group (Age) comparison, summary statistics are given *as* mean ± standard deviation values. The parts determined in bold are statistically significant ($p < 0.05$)

was higher in males. It was higher in males and females aged 50 years and over. Jernigan et al. (2001) reported that the CSF compartment becomes more extensive with age. Chazen et al. (2017) reported that CSF volume change in healthy individuals did not create a strong correlation with weight and height. The differences may be related to the total brain volume and intracranial cavity.

Soysal et al. (2022) reported that the putamen, thalamus and amygdala volumes were high in men aged 50 and younger in a study conducted with 303 healthy participants (190 females, 113 males) ranging from 20 to 86. In our study, males had higher amygdala, pallidum, putamen, and hippocampus volumes. We think the number of samples, age and gender parameters will create differences in the measurements.

Zheng et al. (2018) reported that the thalamus volume decreased with age in 54 healthy individuals (28 females, 26 males) aged between 21 and 71 years. In addition, it was reported that putamen, pallidum, accumbens, amygdala and caudate did not show significant age-related significance. Similarly, in our study, the thalamus volume decreased with age, but the volumes of other parameters were higher in individuals under 50 years. Zheng et al. (2018) reported that the volumes of the GC-DG, CA2-3, and CA4 parts of the hippocampus initially increased and decreased after age 50. Similarly, in our study, it was found to be higher in individuals under 50. However, the volume of the CA1, CA2-CA3 and subiculum parts of the hippocampus were higher in males under 50 years of age. In addition, CA4-DG volume was higher in individuals under 50 years in both genders.

Cherubini et al. (2009) reported large age-related differences in the thalamus, putamen, and caudate volume. On the other hand, Jernigan et al. (2001) reported that the amygdala was unaffected, while the volume of the accumbens and caudate decreased moderately with age. This finding is consistent with our study. However, it has been determined that the amygdala value differs depending on age.

Another study stated that the hippocampus volume increased until age 40 and rapidly decreased after age 50 (Long et al. 2012). On the other hand, Jernigan et al. (2001) reported that the hippocampus volume increased slightly until age 40, and a serious decrease was observed after age 60 (Jernigan et al. 2001). While our study was consistent with the findings of Long et al. (2012), it was observed to be partially consistent with Jernigan et al. (2001). Decreased hippocampus volume with aging may indicate changes in memory and cognitive status. Because the hippocampus is important in the functioning of memory and cognitive functions (O'Shea et al. 2016). Furthermore, Goto et al. (2011) reported that the hippocampus volume decreased in males over age 60. Similarly, our study found that the hippocampus volume decreased in males aged 50 years and older. The difference in hippocampus volume by gender is associated with stress and sex hormones. Because there is information in the literature that stress affects memory and can increase hippocampus-related memory, especially in males. (Andreano and Cahill 2006; Galea et al.2014). It has been reported that hippocampus volume reduction is seen earlier in females, and it occurs later and progresses more rapidly in males (Wang et al. 2019).

Wang et al. (2019) reported a linear decrease in caudate and hippocampus asymmetry due to age and that hippocampal asymmetry decreased in females. In the same study, accumbens and pallidum asymmetry were also examined. Accumbens asymmetry increases in females up to the age of 39.26 on average and then decreases; It was determined that there was a linear decrease in males. In our study, accumbens asymmetry results did not differ for genders under 50. However, it was higher in males aged 50 and over. Hippocampus and caudate asymmetry did not differ according to age and gender. We think there will be differences in the measurements in the number of samples, average age, and gender parameters. Wang et al. (2019) reported that pallidum asymmetry decreased in both sexes until the age of 45 and then increased. Unlike this study, there was no statistical difference in the asymmetry values of the pallidum and amygdala in our study. Guadalupe et al. (2017), according to the results of their large-scale meta-analysis, hippocampus, pallidum, putamen and thalamus asymmetry show differences according to gender. It has been reported that there are changes in the putamen asymmetry with age. In our study, there was no change in the hippocampus, pallidum, putamen and thalamus asymmetry in age and gender parameters. Studies reporting that factors such as genetics, age, gender, and hand preference affect brain asymmetries are in the literature (Guadalupe et al. 2017). In another study, it was reported that asymmetry values differ according to gender. However, it was stated that it is difficult to statistically evaluate gender differences because a limited number of articles analyse asymmetry based on voxels (Ruigrok et al. 2014).

We think more comprehensive studies should be done according to age-gender parameters using up-to-date voxels or web-based software programs of brain structures. We believe that these studies will be especially important for neuropsychiatric diseases.

Conclusion

Studies evaluating the volumetric analysis and asymmetry of hippocampus subbranches and other subcortical structures in adults are very limited. However, in healthy individuals, the parameters of these structures are essential for diagnosing possible diseases. In our study, the morphometry of the hippocampus sub-branches and other subcortical structures of healthy individuals was examined in detail. It was determined that the structures differed according to age, gender and body side.

The total averages of the amygdala, pallidum, putamen and subiculum right and left regions were statistically lower in females than in males. In all subcortical structures examined, the total mean of the right and left regions was statistically higher in individuals under 50 years of age. Asymmetry values did not differ statistically in age categories. In the gender category, the SR-SL-SM asymmetry value of males had a higher average than females. It is thought that measurements of subcortical structures will be important for clinical diagnosis and treatment. In addition, asymmetry values will contribute to future studies on genetics.

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Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest The authors declared that they had no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Non-Intervention Clinical Research Ethics Committee of the Medical Faculty gave ethical approval (approval number 2022–09/95).

Informed consent A formal informed consent procedure was waived due to the retrospective nature of this study.

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