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Volumetric measurements of the subcortical structures of healthy adult brains in the Turkish population

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ABSTRACT

Background: The interest in the morphological development of brain structures during childhood and adolescence arises from discussions on subcortical anomalies and sexual dimorphism, from adolescent changes in cognitive functions supported by cortical and subcortical structures to a wide range of childhood neuropsychiatric diseases. This study aims to investigate the relationships subcortical structures regarding age/gender changes in the healthy adult human brain using web-based VolBrain.

Materials and methods: In this study, 303 normal healthy adults [male and female] were obtained using a 1.5 T unit with a 20-channel head coil.

Results: The volumes of White Matter, Gray Matter, Total Brain, Cerebrospinal Fluid, and Total Intracranial Volume were significantly higher in males than those in females. Our analysis revealed a significantly larger accumbens volume for females. With age less than or equal to 50 years, older males were found to have higher total LV, putamen, thalamus, amygdala, cerebrum, White Matter and Gray Matter volumes than females. The age greater than the 50-years-old group resulted in a mean of total thalamus, Globus Pallidus and

accumbens volumes higher in females than those in males. Right hemisphere volumes in younger and older age groups resulted in volumes except caudate in the older age group; the mean of caudate was significantly higher in females than those in males.

Conclusions: These conclusions might have important for the explanation of the effects of gender and age in cross-sectional structural MRI studies. Also, knowing the volume changes of the subcortical structures can provide convenience about the prevention, diagnosis, and treatment of various neuromental disorders.

Key words: cortical volume, subcortical nuclei, sex differences, magnetic resonance imaging, healthy adult brain, VolBrain

INTRODUCTION

Magnetic resonance imaging (MRI) allows examination of brain parts in a noninvasive and in vivo. This is significant in studying the pathogenesis and pathophysiology of neurological disturbance [1]. There are many volumetric brain studies that show neuroanatomical disorders in MRI [2].

Previous studies have reported an increase in the volume of basal ganglia in schizophrenia [3]. However, new volumetric studies have reported a decrease in the volume of basal ganglia such as putamen, caudate, thalamus [4-6].

Autopsy studies show that brain weight decreases by at least 10% in men and women between the ages of 25-75, also in the age range of 50-75, the volume decreases by about 2% every decade [7].

The brain differs from depending on age/gender. Variety can be measured in vivo with magnetic resonance imaging [MRI]. The volumetric MRI analyses indicate that age-associated volume reductions have been reported especially basal ganglia such as the thalamus, caudate, putamen, globus pallidus [7, 8].

There are many studies about basal gray structures volume between age and gender using different methods [4, 5, 9- 11].

Studies on volume indicated a negative proportion among age, sex, and basal ganglia volumes [12]. Male caudate volume is higher than female [13].

There are many reports to support the effect of subcortical volumes in gender-specific neuropsychiatric disturbance [e.g., autism schizophrenia, Parkinson's, ADHD, and addiction] [14-16].

Recently, different techniques have been studied for automatic or semi-automatic of segmentations subcortical structures such as FSL, AFNI [17], BrainVoyager [18], FreeSurfer [19, 20], Mrstudio [21, 22] and SPM [23] – software used to analyze the structural features of the human brain. VolBrain is an automated method where the observer can perform fully automatic segmentation using a web-based user. Recently, VolBrain has been used as a neuroimaging study of MRI data [24].

VolBrain, an automatic and sturdy quantitative analysis system that also gives a result in a short time. In our study, we share the results of the MRI study on the effects of age on subcortical structures using VolBrain. All participant consisted of 303 subjects from 12 to 84 years [113 men, 190 women].

MATERIALS AND METHODS

Participants

All participants provided written informed consent for the relevant studies and ethical approval was obtained from the Dışkapı Training and Research Hospital Clinical Research Ethics Committee.

The study group consisted of healthy volunteers with no history of surgery or trauma of the brain, neurological or psychiatric disease, or substance abuse.

A mini-score assessment was performed in order to rule out psychiatric disease as well as cognitive impairment. Finally, our study group consisted of 303 participants. Participants included 113 men and 190 women with a mean age of 49 years [range: 12 to 84] and 42.5 years [range: 11-82], respectively. Informed consent was obtained from parent and/or legal guardian for human participants under the age of 18. Children under the age of 18 came to the hospital with their parents, informing their parents and brain MRI radiographs were taken.

MRI protocol and segmentation method

MRI of the subcortical structures was acquired on a 1.5 T unit [Magnetom Aera,

Siemens, Erlangen, Germany] with a 20-channel head coil. The subcortical volumetric assessment was conducted on sagittal oblique T1-weighted images obtained perpendicular to the long axis of the subcortical structures. A magnetization prepared rapid acquisition gradient echo sequence [MP-RAGE] was used with the following parameters: TR=2400 ms, TE=3.54 ms, FOV=240 mm, slice thickness=1.2 mm, voxel size=1.3x1.3x1.2 mm.

MRI data processing and subcortical volumetric analyses were performed using VolBrain [v.1.0, <http://volbrain.upv.es>], a free online MRI brain volumetry system. VolBrain is a fully automated segmentation technique of which the algorithm is based on multi-atlas patch-based label fusion segmentation technology [24, 25] [Figure 1, 2].

Statistical analysis

The distributions of age and volume measurements were examined by the Shapiro-Wilk's test and normality plots. All continuous variables were reported as median [range]. Total and side volumes were also summarized by mean \pm standard deviation [mean \pm sd].

Genders were compared by the Mann-Whitney U test for age and volume measurements. Additionally, independent samples t-test was performed in comparison to males and females for normally distributed volumes in the oldest age group. The adjustment of Age and TIC volume was also applied for the comparisons of volumes by GLM procedure. ICV was used as a covariate to compare the volumes of males and females in age groups. The volumes of the left and right hemisfer of the brain were compared by the Wilcoxon test in males and females, separately. A p-value<0.05 was considered as statistically significant.

Statistical analyses were performed via IBM SPSS Statistics 22.0 [IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.].

RESULTS

Global effect in aging

The median age of men and women was 49 [range:12-84] and 42.5 years [range: 11-82], respectively. There was no Significant difference between men and women by age [p=0.071]. The volumes of WM, GM, TB, CF, and TIC were significantly higher in males than females [p<0.001 for all, i.e., Table 1].

Gender differences for subcortical nucleuses

The univariate analysis revealed that the volumes of LV, putamen, GP, amygdala, cerebrum, WM, and GM were significantly higher in men [$p < 0.05$, Table 2]. When the adjustment according to the age and TIC was applied, the only significant difference was in accumbens volume between males and females; it was found to be higher in women compared to males [$p < 0.001$] [i.e., Fig 3].

Sides differences

The right brain volumes were significantly lower for LV, putamen, accumbens and WM, and higher for caudate than those of the left brain in males. The right brain volumes were significantly lower for LV, putamen, thalamus, GP, amygdala, accumbens and WM, and higher for caudate and GM than those of the left volumes in females [i.e., Fig 4, Table 3].

Gender differences in the younger age group

When the individuals with age less than or equal to 50 years old were examined, males were found to have higher total LV, putamen, thalamus, amygdala, cerebrum, WM and GM volumes than females [$p < 0.05$, Table 4]. However, ICV-adjusted total accumbens mean in females was found to be higher than those in males [$p = 0.008$] [i.e., Fig 5, Table 4].

Gender differences in the older age group

In individuals with age greater than 50 years old, the univariate analyses resulted in the same as the younger age group. The ICV-adjusted mean of total thalamus, GP and accumbens volumes were higher in women than in men [$p < 0.05$] [i.e., Fig 5, Table 4].

When left hemisphere volumes in the younger age group were analyzed, males were found to have higher LV, putamen, thalamus, amygdala, cerebrum, WM and GM volumes than females [$p < 0.05$, i.e., Table 5]. However, the ICV-adjusted accumbens mean in females was higher than those in males [$p = 0.038$] [i.e., Fig 6, Table 5]. In the older age group, the univariate analyses resulted in the same as in the younger age group. The ICV-adjusted mean

of thalamus, GP and accumbens volumes were higher in women than in men [$p < 0.05$] [i.e., Fig 6, Table 5].

Right hemisphere volumes in younger and older age groups resulted in almost the same as left hemisphere volumes except caudate in the older age groups [Table 6]. The ICV-adjusted mean of caudate was significantly higher in women than in men [$p = 0.019$, i.e., Fig 7, Table 6].

DISCUSSION

In our study, we measured the subcortical structure volume in healthy adults between the ages of 20-86 and evaluated the data by age and gender.

There are many reports on the brain and subcortical structures volume in both sexes and different ages. The majority of these studies focused on the subcortical structures and examined age-related volume changes of various subcortical structures. It has been reported in various cross-sectional and longitudinal studies that the volumes of caudate, thalamus and putamen decrease with age [5, 26- 32].

Walhovd et al. [26] studied the cortical and subcortical regions of 73 men and women [20-88 years old] using an automated segmentation technique. Except pallidum, they showed age-related volume decrease in cortical gray matter, cerebral white matter, hippocampus, amygdala, thalamus, accumbens, caudate, putamen, pallidus, brainstem, cerebellar cortex and cerebellar white matter. They also found that advanced age was strongly associated with volumes of the thalamus and cortical gray matter, the volume of the thalamus was found with cortical gray matter volume, which showed a linear decline and curvilinear decline with age.

In our study, total thalamus, GP and accumbens volumes older than 50 years were higher in women. In our findings, we did not find an age-related decrease in left thalamus volume in a similarly age range [20-86 years] and a higher thalamus volume in men over the age of 50 years.

Alexander et al. [33] stated that putamen, caudate, accumbens and pallidum, all of which are related to emotional, motor behavior and cognition, are blunted by aging. Basal ganglia reach a peak volume before the age of 20. The youngest participant in our study was 11 [aged 11-84 aged evaluated] according to previous studies. Therefore, the basal ganglia did not go through an atrophy period.

Accumbens and pallidum volumes, which are reported as less stable in the literature than other subcortical structures [28], showed a minimal age effect on pallidum than other structures. Walhovd et al. [34] examined the effects of age on subcortical structures; and they found great differences in putamen, thalamus and accumbens volume due to aging. Regions such as caudate and amygdala were not affected by aging.

In the subcortical regions such as caudate, pallidum and amygdala, a linear decrease in the age-related pattern is shown [30-32]. Pfefferbaum et al. [35] performed MRI studies in 55 men and 67 women [20-85 years], and showed that older age was related to a decrease in thalamus volume, and this decline increased with age [60+ years].

Abedalahi et al. [12] They calculated the caudate volume with the Cavalieri principle. This study was carried out in 120 normal human subjects [60 males, 60 females] divided into young [<40 years] and older [≥ 40 years] groups between the ages of 15-65. The volume of caudate nucleus showed a significant negative correlation with age. Goodre et al. [28] showed that there was a stronger correlation between the age and the structural volume for the hippocampus, amygdala and acumbens in the older group [60-85 years] than the middle-aged [35-60 years] group. Similarly, in our study, 303 normal people [113 men, 190 women] aged 11-84 were divided into young [≤ 50 years old] and elderly [> 50 years old] groups. There was a significant negative correlation between the young group with the volume of the accumbens and the old group with the volume of the thalamus, GP, and accumbens.

Thalamic volumetric analyses showed that thalamus volumes smaller in the elderly adults than younger adults using cross-sectional and automated technique studies [26,29]. Cherebuni et al. [29] found that age showed strong correlation in both striatal structures and thalamic volume. In our study, gender differences in cortical gray matter concentration were older and older than 50 in the advanced age group comparison; LV, putamen, thalamus, amygdala, cerebrum, WM and GM volumes of men were higher than women. However, women had significantly higher accumbens volume. Unlike our findings, Yanpei et al. [27] stated in their study that the volume of accumbens decreased with increasing age. The effect of gender on the volume of subcortical structures may play an important role because basal ganglia have high-density sex steroid receptors [36]. In this period, age and gender interaction showed that the right putamen and right pallidum in men had a marked age progression.

In general, male brains were found to have larger gray matter, white matter, and subcortical structures than women. As a result of the correction of the total intracranial volume, we found that women had a larger volume of acumbens. In addition, in the male

group only, we found a significant large volume effect on the right caudate volume compared to the contralateral structures of the brain hemisphere.

Ruigrok et al [5] found that the total brain volume was on average approximately 8-15% higher in males than females. Yanpei et al. [27] reported that the volume of the right putamen, right pallidum, and right thalamus decreased faster than males, whereas the volume of the left thalamus, bilateral hippocampus and amygdala follow a quadratic model in males and a linear decline model in females. In our study, in men; LV, putamen, accumbens and WM volumes in the right brain were significantly lower than the left brain and higher than the left brain for caudate volume.

Xu et al. [37] found that males had atrophy due to aging in the basal ganglia of the left hemisphere and also the volume of the thalamus and brain in the left hemisphere was significantly smaller than the right hemisphere. Brain atrophy that aging in male subjects was higher than female subjects. We found left hemisphere volumes in both younger age group males and older group ages males were found to have higher LV, putamen, thalamus, amygdala, cerebrum, WM and GM volumes than females. However, accumbens volume mean in females was higher than those in males. Nevertheless, right hemisphere volumes in younger and older age groups resulted in almost the same as left hemisphere volumes except caudate in the older age group. The mean volume of caudate was significantly higher in women than in men.

Goodro et al. [28] found that left and right thalamus volume declined faster than women. Similarly, in our study, the volumes of thalamus in women and men were different in the left and right thalamus. In women between the ages of 20-86, the left thalamic volume was higher than in men.

Although our MRI research cannot identify the mechanism that leads to volume differences due to age, it can provide additional information for the possible mechanism of sex-dependent volume differences in basal ganglia when associated with advanced software technology. Volume analysis of accumbens nucleus helps in the evaluation of neurodegenerative diseases. In this context, our results are of importance for gender-dependent accumbens nucleus volume increase.

Compared to women, men have been found to perform worse in the ongoing response task and visual-spatial learning and planning task, especially in older ages [38, 39]. However,

some studies have not reported age and gender effects or different aging effects on cognition in men and women [40,41].

In this study, we used an automated and reliable analysis to address volumetric changes [24]. We presented a new method, namely, VolBrain. It can be used in place of other volume techniques. VolBrain has several advantages for brain imaging researchers. In addition, it is a less tiring software that can get very fast results in the treatments and clinical studies in neurological disorders.

The main limitation of our study is that it is not a longitudinal study. More participants and more studies are needed to confirm the findings of this study. Another limitation is that it is not done using manual volumetry.

VolBrain can be used to measure volumes of other anatomical areas of the body using radiological images. We believe that our results will provide additional information to volumetric studies evaluating the development, pathology and abnormalities of subcortical structures.

The results of the study demonstrated with age less than or equal to 50 years old, males were found to have higher total LV, putamen, thalamus, amygdala, cerebrum, WM and GM volumes than females. In the age greater than the 50-years-old group, the mean of total thalamus, GP, and accumbens volumes were higher in females than those in males.

CONCLUSIONS

In conclusion, the results of recent research show that brain cortical structures and volume loss of subcortical nuclei are a common finding in a number of neuropsychiatric problems. The data obtained in this study are normal brain data according to age and gender of the adult Turkish population. It can be useful in clinical applications and cognitive disorders of many neuropsychiatric diseases.

Ethics approval and consent to participate

Research was conducted on human participants. All procedures performed in this study comply with the ethical standards of the institution. Approval was obtained from the Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital, indicating that the MR images used in the study were ethically and scientifically safe.

Availability of data and materials

The raw data we used in our study are in the archive of the hospital where the study was performed. Datas can be accessed from the archive of the Radiology Clinic of Dışkapı Yıldırım Beyazıt Training and Research Hospital. Datas are available from the corresponding author on reasonable request. I agree to accept full responsibility for the work submitted in the manuscript, including the accuracy and integrity of the data and data analyses.

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Abbreviations

WM, white matter; GM, gray matter; TB, total brain; CF, cerebrospinal fluid; TIC, total intracranial volume; LV, Lateral Ventricle; GP, globus pallidus; MRI, magnetic resonans imaging; ADHD, attendion deficit hyperactivity disorder; ICV, intracranial volume; MPRAGE, magnetization prepared rapid gradient echo; SPM, statistical parametric maps

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Table 1. Age and volume distributions in males and females

	Male [n=113]	Female [n=190]	Total [n=303]
	Median (min-max)	Median (min-max)	Median (min-max)
Age, years*	49 (12-84)	42.5 (11-82)	45 (11-84)
Volumes, mm ³ **			
WM	530.16 (317.29-785.44)	477.73 (215.18-1,027.72)	493.35 (215.18-1,027.72)
GM	719.07 (401.78-929.19)	661.45 (242.56-903.33)	681.21 (242.56-929.19)
TB	1,241.83 (862.18-1,548.87)	1,151.11 (644.70-1,475.80)	1,183.99 (644.70-1,548.87)
CF	242.30 (101.99-518.05)	178.46 (62.79-596.96)	195.09 (62.79-596.96)
TIC	1,494.78 (1,146.07-1,866.76)	1,329.50 (941.06-1653.44)	1,374.51 (941.06-1,866.76)

WM: white matter, GM: gray matter, TB: total brain, CF: cerebrospinal fluid, TIC: total intracranial;

*p=0.071, **p<0.001

Table 2. Distribution of subcortical volumes in males and females

Total	Male		Female		p-value	Adj. p-value
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)		
LV	23.08±18.04	16.96 (2.20-83.92)	13.48±15.88	9.75 (2.09-149.93)	< 0.001	0.260
Caudate	7.01±1.54	6.81 (4.39-18.92)	6.82±0.97	6.75 (4.41-11.55)	0.354	0.265
Putamen	8.49±1.69	8.31 (5.52-21.97)	8.07±1.08	8.11 (3.60-13.41)	0.012	0.785
Thalamus	11.04±2.13	11.07 (6.86-27.04)	10.69±1.28	10.75 (6.51-14.64)	0.178	0.293
GP	2.39±0.44	2.37 (1.27-5.10)	2.26±0.35	2.27 (0.68-3.14)	0.021	0.276
Amygdala	1.77±0.34	1.78 (0.44-2.60)	1.64±0.31	1.68 (0.04-2.65)	< 0.001	0.635
Accumbens	0.66±0.18	0.67 (0.04-1.08)	0.68±0.16	0.68 (0.07-1.11)	0.347	< 0.001
Cerebrum	1,088.94±119.37	1,090.01 (746.69-1,345.42)	998.02±106.54	1,001.35 (607.16-1,308.94)	< 0.001	0.133
WM	474.60±73.11	484.08 (288.09-701.24)	433.93±72.21	429.58 (170.51-879.07)	< 0.001	0.144
GM	614.34±74.20	609.66 (348.86-814.31)	564.09±70.74	555.75 (214.27-795.99)	< 0.001	0.830

LV: Lateral ventricle, GP: Globus Pallidus ,WM: White matter, GM: Gray matter, Adj. p-value: p-value after total intracranial volume and age adjustment

Table 3. Distribution of right and left sides in males and females.

	<u>Right</u>		<u>Left</u>		p-value
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Male					
LV	10.88±8.69	8.38 (1.26-50.08)	12.20±9.80	8.71 (0.94-43.26)	<0.001
Caudate	3.53±0.80	3.48 (1.98-9.84)	3.48±0.79	3.44 (0.61-9.08)	0.010
Putamen	4.21±0.94	4.11 (2.16-12.05)	4.28±0.80	4.20 (1.89-9.92)	<0.001
Thalamus	5.50±1.13	5.49 (3.3-14.18)	5.54±1.06	5.56 (3.49-12.85)	0.086
GP	1.19±0.24	1.19 (0.57-2.65)	1.20±0.22	1.19 (0.58-2.45)	0.639
Amygdala	0.90±0.19	0.90 (0.22-1.73)	0.88±0.20	0.89 (0.08-1.72)	0.061
Accumbens	0.31±0.09	0.32 (0-0.54)	0.35±0.10	0.35 (0.04-0.60)	<0.001
Cerebrum	544.06±61.08	546.91 (373.2-671.09)	544.88±60.04	544.52 (373.49-681.72)	0.494
GM	307.43±38.41	304.95 (154.96-408.61)	306.92±36.67	305.37 (193.90-413.49)	0.176
WM	236.63±37.87	240.00 (145.54-369.85)	237.96±36.33	240.44 (142.55-351.79)	0.010
Female					
LV	6.35±7.68	4.61 (0.91-77.38)	7.12±8.35	5.10 (0.93-72.55)	<0.001
Caudate	3.43±0.49	3.40 (2.19-6.17)	3.39±0.50	3.33 (2.10-5.39)	<0.001
Putamen	4.01±0.53	4.01 (2.49-6.69)	4.05±0.57	4.08 (1.08-6.72)	<0.001
Thalamus	5.30±0.65	5.34 (2.69-7.30)	5.39±0.68	5.42 (3.33-8.30)	<0.001
GP	1.12±0.18	1.12 (0.13-1.54)	1.14±0.18	1.15 (0.46-1.59)	0.028
Amygdala	0.83±0.15	0.84 (0.04-1.27)	0.82±0.17	0.84 (0.00-1.37)	0.046

Accumbens	0.32±0.08	0.32 (0.01-0.50)	0.36±0.09	0.35 (0.02-0.64)	<0.001
Cerebrum	498.57±53.79	500.42 (269.6-652.79)	498.69±52.41	499.91 (337.56-656.14)	0.689
GM	282.32±35.83	279.21 (109.51-398.88)	281.77±35.10	279.03 (104.76-397.11)	0.012
WM	216.24±35.70	214.20 (84.72-430.87)	216.92±35.59	216.41 (85.79-448.20)	0.021

LV: Lateral ventricle, GP: Globus Pallidus, WM: white matter, GM: gray matter

Table 4. Distribution in males and females in younger and older age group (≤ 50 years old and $+50$ years old in total)

Age Groups	Total	Male		Female		p-value	Adj. p-value
		Mean \pm SD	Median (min -max)	Mean \pm SD	Median (min -max)		
Younger Age	LV	15.71 \pm 12.65	11.27 (2.20-61.82)	10.84 \pm 13.91	8.35 (2.09-149.93)	0.001	0.301
	Caudate	7.46 \pm 1.82	7.26 (4.39-18.92)	7.07 \pm 1.01	6.97 (4.92-11.55)	0.122	0.563
	Putamen	8.95 \pm 2.03	8.71 (5.53-21.97)	8.43 \pm 1.04	8.36 (3.60-13.41)	0.030	0.803
	Thalamus	11.94 \pm 2.31	11.59 (8.87-27.04)	11.18 \pm 1.1	11.05 (6.51-14.64)	0.002	0.803
	GP	2.48 \pm 0.48	2.42 (1.27-5.10)	2.31 \pm 0.38	2.35 (0.68-3.14)	0.057	0.681
	Amygdala	1.84 \pm 0.3	1.80 (0.87-2.60)	1.69 \pm 0.32	1.72 (0.04-2.65)	<0.001	0.875
	Accumbens	0.72 \pm 0.18	0.73 (0.04-1.08)	0.72 \pm 0.16	0.72 (0.07-1.11)	0.769	0.008
	Cerebrum	1127.02 \pm 104.65	1114.85 (873.65-1345.4)	1029.7 \pm 97.57	1031.47 (607.16-1308.94)	<0.001	0.133
	WM	488.91 \pm 64.15	489.75 (360.10-701.24)	445.36 \pm 73.99	436.82 (170.51-879.07)	<0.001	0.532
	GM	638.11 \pm 79.41	623.75 (348.86-814.31)	584.34 \pm 73.66	579.80 (214.27-795.99)	<0.001	0.536
Older Age	LV	31.73 \pm 19.63	27.27 (5.91 -83.92)	18.1 \pm 18.04	13.04 (3.11 -114.58)	<0.001	0.068
	Caudate	6.48 \pm 0.89	6.55 (4.57 -8.77)	6.39 \pm 0.73	6.34 (4.41 -8.17)	0.551	0.072
	Putamen	7.95 \pm 0.94	8.01 (5.52-10.13)	7.44 \pm 0.83	7.52 (5.08 -10.61)	0.002	0.594
	Thalamus	9.99 \pm 1.26	9.9 (6.86 -12.68)	9.82 \pm 1.09	9.99 (6.61 -11.75)	0.433	<0.001
	GP	2.28 \pm 0.36	2.3 (1.48 -3.38)	2.17 \pm 0.24	2.17 (1.53 -2.67)	0.066	0.037
	Amygdala	1.7 \pm 0.38	1.69 (0.44-2.52)	1.56 \pm 0.28	1.61 (0.72 -2.06)	0.013	0.123
	Accumbens	0.59 \pm 0.14	0.60 (0.12-0.87)	0.61 \pm 0.14	0.63 (0.34 -1.11)	0.502	0.007
	Cerebrum	1044.27 \pm 121	1058.10 (746.69 -1328.12)	942.47 \pm 99.16	939.27 (712.33 -1173.36)	<0.001	0.176
	WM	457.8 \pm 79.79	452.80 (288.09 -630.98)	413.88 \pm 64.73	408.89 (245.55 -582.04)	0.001	0.096
	GM	586.47 \pm 56.6	579.86 (458.6 -740.8)	528.59 \pm 48.23	534.87 (350.09 -638.26)	<0.001	0.969

LV: Lateral ventricle, GP: Globus Pallidus ,WM: White matter, GM: Gray matter, Adj. p-value: p-value after total intracranial volume adjustment
 Bold measurements are significantly higher in females than those in males after

Table 5. Distribution in males and females in younger and older age group (≤ 50 years old and $+50$ years old) in left hemisphere

Age Groups	Left hemisphere	Male		Female		p-value	Adj. p-value
		Mean \pm SD	Median (min-max)	Mean \pm SD	Median (min-max)		
Younger Age	LV	8.37 \pm 7.31	5.61 (0.94-35.01)	5.65 \pm 6.89	4.40 (0.93-72.55)	0.003	0.256
	Caudate	3.69 \pm 0.94	3.61 (0.61-9.08)	3.53 \pm 0.50	3.49 (2.53-5.39)	0.119	0.520
	Putamen	4.50 \pm 0.94	4.43 (1.89-9.92)	4.23 \pm 0.56	4.19 (1.08-6.72)	0.008	0.800
	Thalamus	5.99 \pm 1.15	5.91 (3.49-12.85)	5.65 \pm 0.60	5.63 (3.82-8.30)	0.003	0.947
	GP	1.24 \pm 0.24	1.20 (0.58-2.45)	1.17 \pm 0.19	1.20 (0.46-1.59)	0.167	0.464
	Amygdala	0.91 \pm 0.19	0.91 (0.08-1.31)	0.84 \pm 0.18	0.86 (0-1.37)	<0.001	0.900
	Accumbens	0.38 \pm 0.10	0.37 (0.04-0.60)	0.38 \pm 0.09	0.37 (0.02-0.63)	0.578	0.038
	Cerebrum	563.46 \pm 53.99	555.28 (434.27-681.72)	514.43 \pm 47.27	514.91 (337.56-656.14)	<0.001	0.219
	WM	244.64 \pm 31.60	245.31 (179.41-351.79)	222.43 \pm 36.28	219.81 (85.79-448.20)	<0.001	0.651
	GM	318.82 \pm 39.49	310.69 (193.90-413.49)	291.99 \pm 36.38	290.19 (104.76-397.11)	<0.001	0.554
Older Age	LV	16.70 \pm 10.48	14.91 (2.38-43.26)	9.69 \pm 9.98	6.44 (1.34-58.48)	<0.001	0.088
	Caudate	3.23 \pm 0.46	3.27 (2.29-4.33)	3.16 \pm 0.39	3.12 (2.10-4.27)	0.393	0.227
	Putamen	4.02 \pm 0.50	4.04 (2.51-5.16)	3.73 \pm 0.42	3.77 (2.58-5.26)	0.001	0.857
	Thalamus	5.02 \pm 0.64	4.95 (3.53-6.38)	4.93\pm0.56	4.99 (3.33-6.11)	0.440	0.002

Older Age	GP	1.15±0.19	1.14 (0.72-1.66)	1.09±0.13	1.09 (0.67-1.32)	0.046	0.047
	Amygdala	0.83±0.21	0.82 (0.22-1.72)	0.78±0.15	0.79 (0.20-1.01)	0.082	0.168
	Accumbens	0.31±0.08	0.32 (0.09-0.53)	0.33±0.08	0.33 (0.19-0.64)	0.423	0.016
	Cerebrum	523.09±59.90	532.08 (373.49-662.49)	471.08±49.77	471.04 (350.15-588.37)	<0.001	0.301
	WM	230.14±40.10	227.97 (142.55-316.04)	207.24±32.37	205.90 (122.11-292.40)	0.001	0.126
	GM	292.95±27.39	289.34 (230.94-371.23)	263.84±24.02	265.02 (171.92-317.10)	<0.001	0.675

Bold measurements are significantly higher in females than those in males after total intracranial volume adjustment

LV: Lateral ventricle, GP: Globus Pallidus, WM: white matter, GM: gray matter, Adj. p-value: p-value after total intracranial volume adjustment

Table 6. Distribution in males and females in younger and older age group (≤ 50 years old and $+50$ years old) in right hemisphere

Age Groups	Right hemisphere	Male		Female		p-value	Adj. p-value
		Mean±SD	Median (min-max)	Mean±SD	Median (min-max)		
	LV	7.34±5.72	5.50 (1.26-28.33)	5.19±7.12	4.19 (0.91-77.38)	0.001	0.370
	Caudate	3.77±0.95	3.70 (1.98-9.84)	3.55±0.52	3.51 (2.19-6.17)	0.055	0.635
	Putamen	4.45±1.16	4.29 (2.16-12.05)	4.19±0.50	4.14 (2.52-6.69)	0.052	0.812
	Thalamus	5.95±1.25	5.78 (3.60-14.18)	5.53±0.58	5.51 (2.69-7.30)	<0.001	0.686
Younger Age	GP	1.24±0.26	1.20 (0.59-2.65)	1.14±0.20	1.14 (0.13-1.54)	0.015	0.907

Older Age	Amygdala	0.93±0.14	0.90 (0.47-1.29)	0.85±0.16	0.86 (0.04-1.27)	0.001	0.857
	Accumbens	0.34±0.09	0.34 (0-0.54)	0.35±0.08	0.34 (0.01-0.50)	0.859	0.002
	Cerebrum	563.56±53.68	559.56 (413.08-671.09)	514.07±49.95	515.50 (269.60-652.79)	<0.001	0.220
	WM	244.28±34.36	245.42 (151.33-369.85)	221.72±36.41	220.98 (84.72-430.87)	<0.001	0.653
	GM	319.28±41.18	317.76 (154.96-408.61)	292.35±37.48	289.57 (109.51-398.88)	<0.001	0.528
	LV	15.03±9.73	12.58 (3.31-50.08)	8.39±8.26	6.04 (1.54-56.10)	<0.001	0.058
	Caudate	3.25±0.45	3.23 (2.25-4.44)	3.22±0.35	3.20 (2.31-4.01)	0.697	0.019
	Putamen	3.93±0.46	3.98 (2.91-4.97)	3.70±0.43	3.70 (2.49-5.35)	0.005	0.383
	Thalamus	4.97±0.67	4.92 (3.30-6.31)	4.89±0.55	4.99 (3.28-5.75)	0.651	0.001
	GP	1.14±0.19	1.15 (0.57-1.73)	1.09±0.12	1.09 (0.82-1.35)	0.058	0.046
	Amygdala	0.87±0.22	0.86 (0.22-1.73)	0.79±0.14	0.81 (0.30-1.05)	0.025	0.181
	Accumbens	0.27±0.07	0.28 (0-0.42)	0.28±0.07	0.29 (0.14-0.48)	0.660	0.005
	Cerebrum	521.18±61.75	527.69 (373.20-665.65)	471.39±49.61	471.10 (362.18-584.99)	<0.001	0.098
	WM	227.66±40.11	224.25 (145.54-314.94)	206.64±32.48	204.41 (123.44-289.64)	0.002	0.075
GM	293.52±29.65	290.40 (227.66-369.58)	264.75±24.42	268.09 (178.17-321.15)	<0.001	0.729	

Bold measurements are significantly higher in females than those in males after total intracranial volume adjustment

LV: Lateral Ventricle, GP: Globus Pallidus, WM: white matter, GM: gray matter, Adj. p-value: p-value after total intracranial volume adjustment

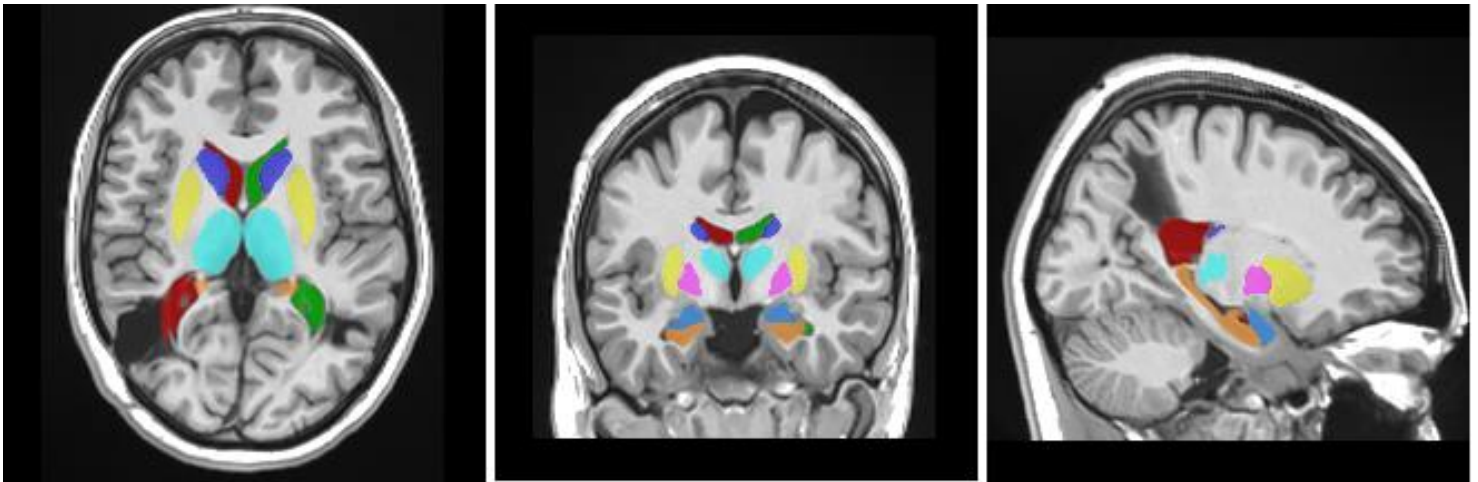


Figure 1. Fully-automated subcortical segmentation by volBrain.

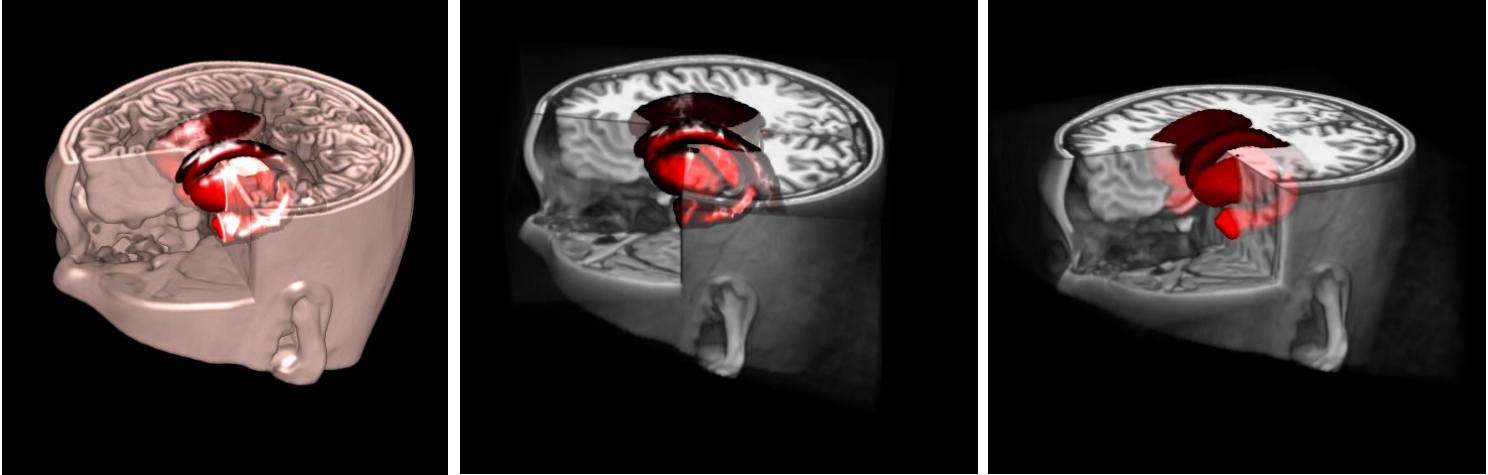


Figure 2. 3D visualization of volBrain data.

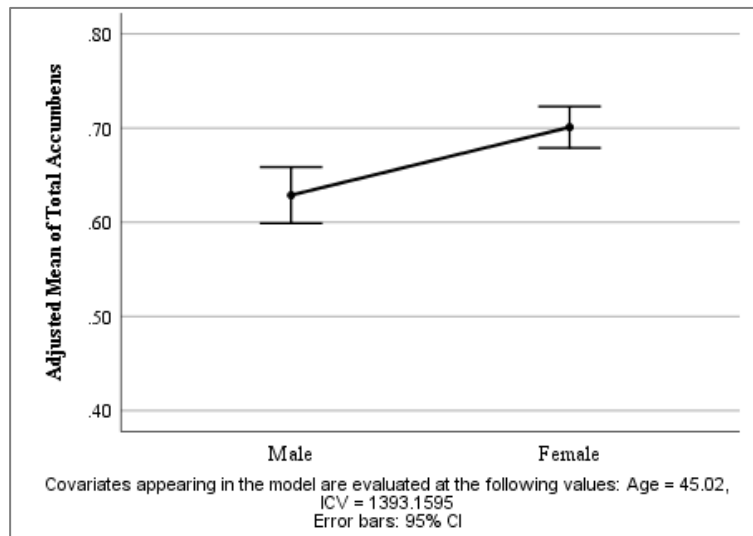


Figure 3. ICV and Age-adjusted mean of total accumbens in males and females

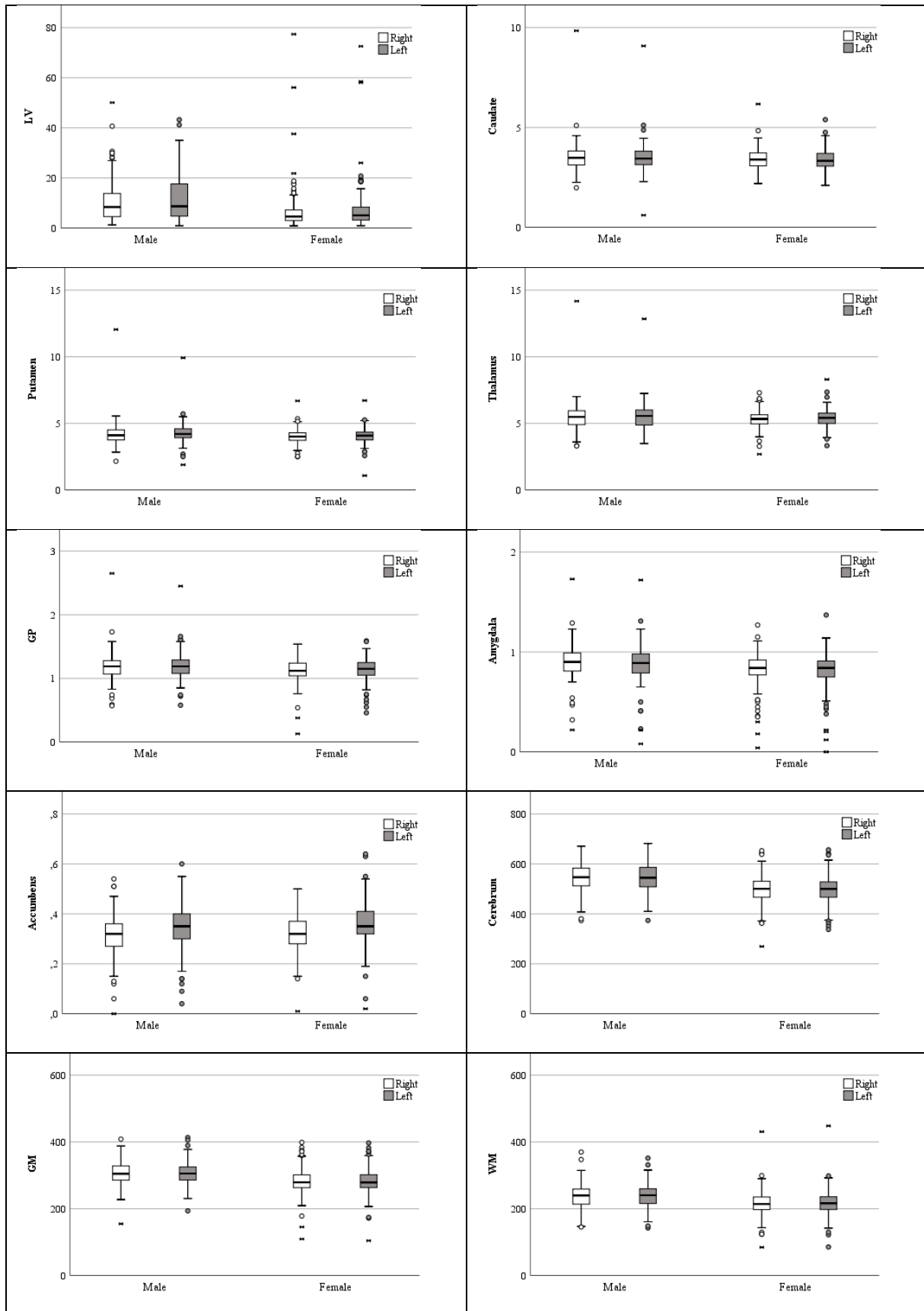


Figure 4. Distribution of right and left sides in males and females.

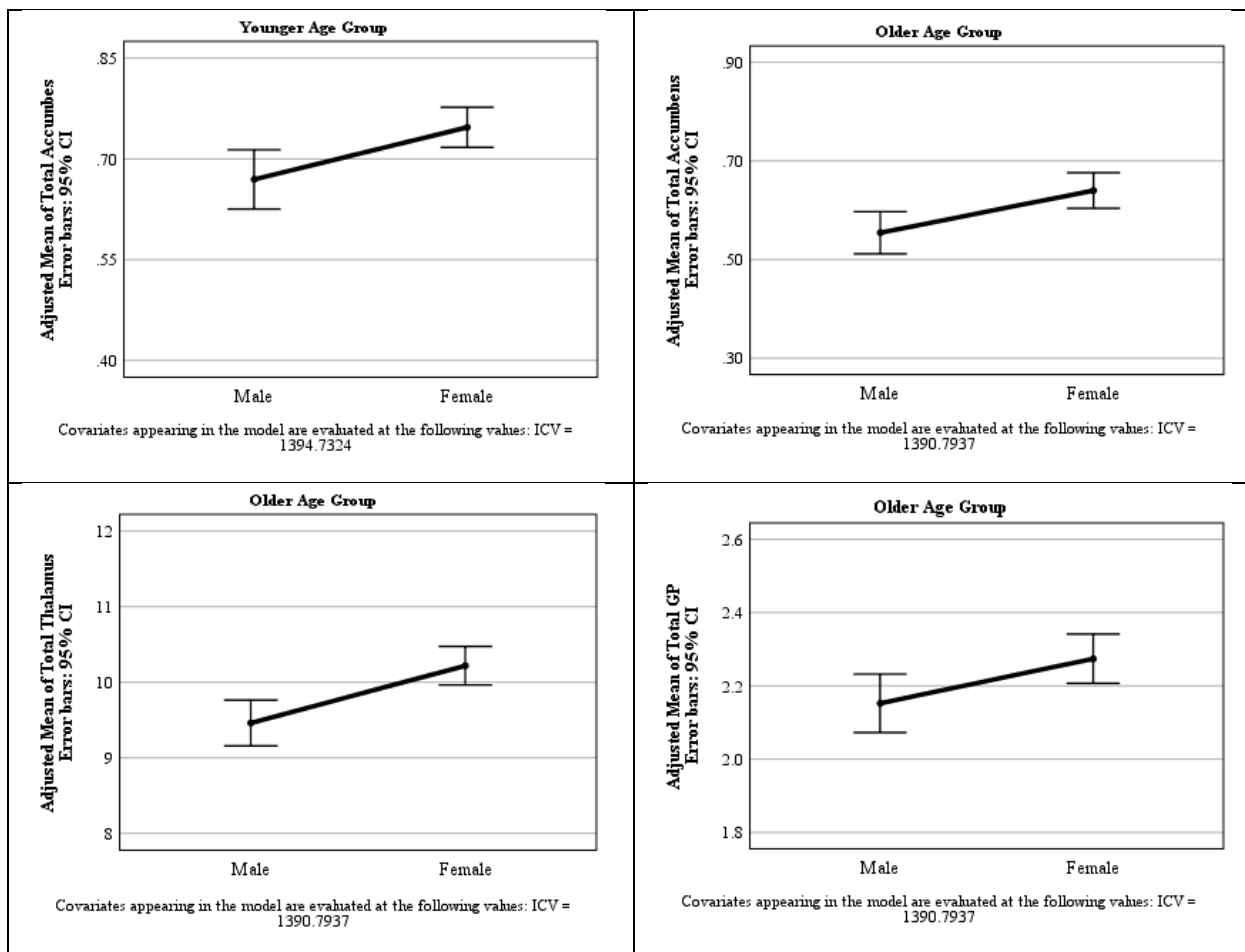


Figure 5. ICV-adjusted mean of total accumbens, thalamus and GP volumes in males and females of younger and older age groups

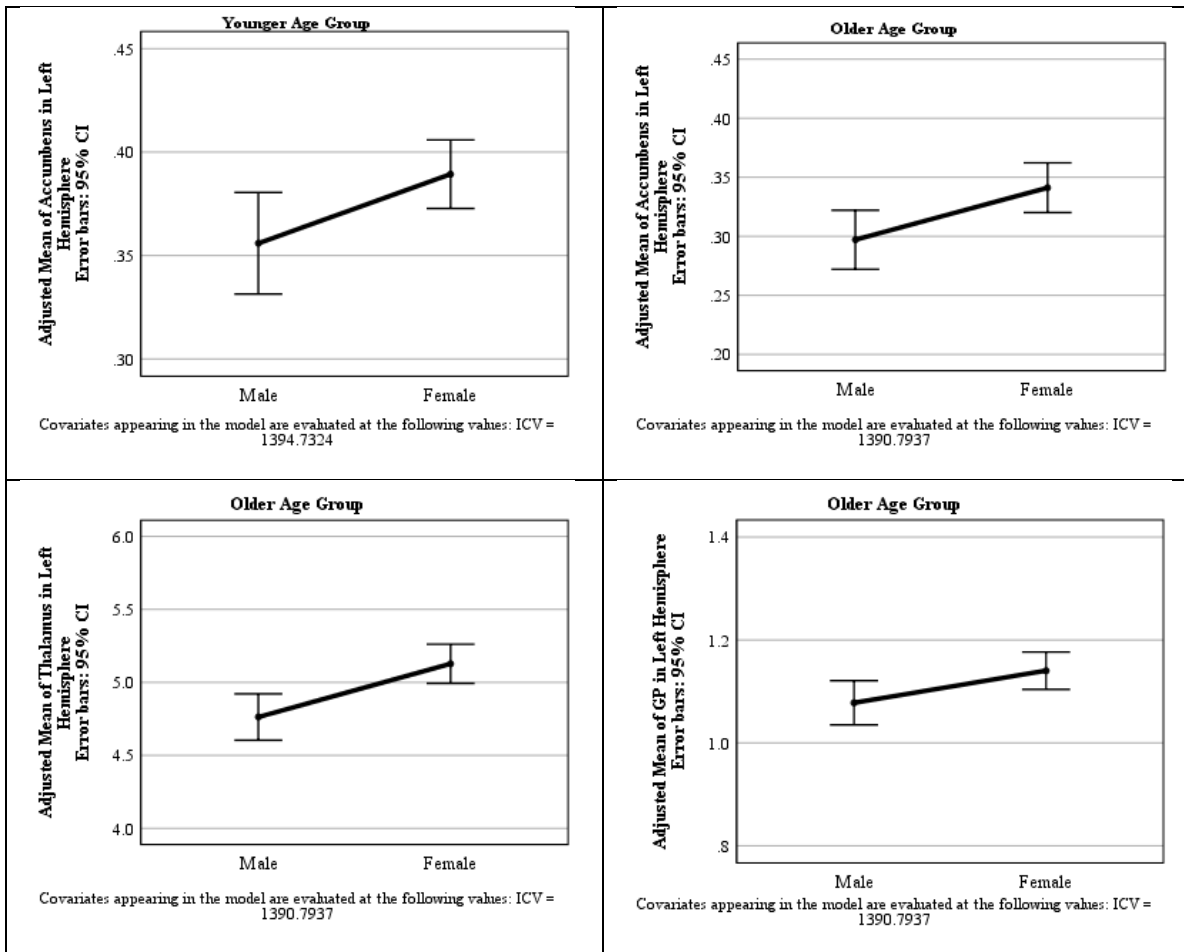


Figure 6. ICV-adjusted mean of left hemisphere accumbens, thalamus and GP volumes in males and females of younger and older age groups

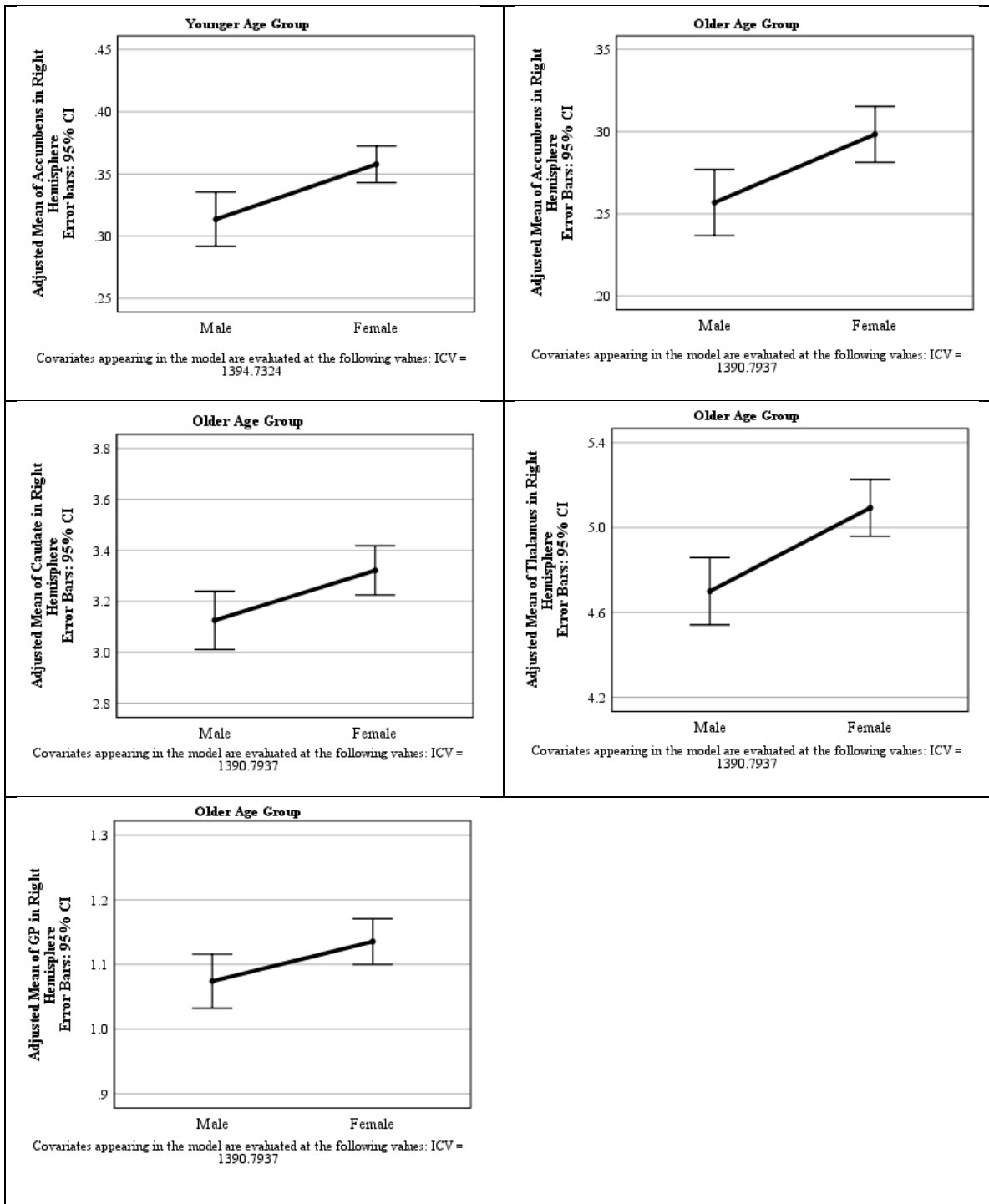


Figure 7. ICV-adjusted mean of right hemisphere accumbens, caudate, thalamus and GP volumes in males and females of younger and older age groups