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Original Article

Effect of Aging on Hippocampal Formation in Normal Human Brains: MRI Study.

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Abstract

Background: The hippocampus, a complex structure with distinct subfields, is involved in memory functions and affected by Alzheimer's disease, aging, and epilepsy. The hippocampal complex is involved in aging processes and volume loss. MRI scans can identify subtle neural damage, but existing knowledge on the anatomical variability and effects of development, aging, and disease on hippocampal subfields is limited.

Objective: We aimed to build a reference for hippocampal volume in the general population using 3D MRI brain.

Methods: The study analyzed hippocampal volume in 105 healthy subjects aged 21-75 using magnetic resonance imaging.

Results: Group 3 [43-53 years] had the biggest volume, followed by groups 1 [21-31 years] and 2 [32-42 years]. The older age groups reported the lowest volume. In 96 healthy individuals between the ages of 18 and 69, the study also discovered substantial negative relationships between age and hippocampus volume. The left and right subiculum had the most noticeable atrophy rates. In older patients, automated hippocampus volume measures are highly reliable; their intraclass correlation is 0.94, whereas manual tracing's is 0.99. Because it is quicker and less prone to rater bias, this approach is especially helpful for examining hippocampus alterations in aging studies, building on earlier research on young adults.

Conclusion: There was a strong correlation between age and hippocampus volume. Additionally, the right hippocampal volume was much greater than the left. Significant correlations between age and hippocampal regions were found in subiculum and CA1 regions.

Keywords: Temporal Lobe; Hippocampus; Brain Volumetry; Aging.

INTRODUCTION

The hippocampus [HC] is one of the most investigated structures in the brain. It is an elongated structure located medially in the temporal lobe. Its resemblance to a seahorse inspired its naming after this sea creature [genus Hippocampus]. It's formed by complex bilaminar grey matter [GM] and plays an important role in cognition, especially in perception, memory, learning, and the control of specific motions and emotional behavior. According to a recent study, the HC can improve the brain's reactivity and regulate the cerebral cortex's overall functional connectivity. The non-dominant right HC primarily mediates non-verbal memory, while the dominant left HC primarily mediates verbal learning and memory in the majority of subjects [1].

Up to the age of two, the hippocampal volume [HV] was observed to rise sharply; after that, it rose gradually. The actual rate of decline may rise with age, especially after the age of 70, even while other studies show declines in the HV with age after the age of 40 [2].

In correlation with handedness, right lateralization in right-handed people is often reported. HC volume alterations in relation to gender have no important value in females, while in males there is significant right lateralization [3].

The hippocampus has three distinct zones: the dentate gyrus, the hippocampus proper, and the subiculum. The dentate gyrus and hippocampus proper [consisting of the Cornu Ammonis, which includes the CA1, CA2, CA3, and CA4 subfields] form two C-shaped rings that interlock. The subiculum is thus a transition zone, linking the hippocampus proper with the dentate gyrus [4].

HC plays an important role in behaviors as well as social interaction; therefore, a decrease in HC volume is related to various neuropsychiatric diseases, such as depression, schizophrenia, epilepsy, Alzheimer's disease, and sleep disorders. So, HV needs to be accurately determined, since volume is important in early diagnoses and assessment of treatments **[5].**

HC has involved in memory functions; cornu ammonis region 1 [CA1] and region 3 [CA3] subfields contribute to long-term memory while CA3 involved particularly in working and short-term memory. The subiculum which connects the HC to parahippocampal regions has been shown to be keystone in learning and memory. The main role of HC in short- and long-term memory has been a matter of discussion; however, the hippocampal lesion leads to anterograde and retrograde amnesia. Measurement of HV can be through many segmentation techniques using magnetic resonance imaging [MRI] sequences, including visual assessment, linear measurements, manual volumetry, automated volumetry, volumetry, signal intensity-based scoring and automated methods. The gall standard method for evaluation of the HV is manual segmentation, although there are no clear protocols that all researchers can apply [6].

Hippocampal volumetric differ greatly between studies, mostly due to the studies inclusion or exclusion of different portions of the HC, i.e., the head, body and tail l; MRI parameters; delineation of structures; and methods of normalization for brain volume.are vary among studies. All of these factors may affect volumetric results [7].

Imaging of the HC and temporal lobe structures depends on image orientation and image sequences optimized to display the anatomy and signal abnormality of hippocampal sclerosis [HS] and temporal pathology. The features of HS are altered signal in a small HC and loss of the normal internal architecture [8].

Both 1.5 T and 3 T enable three-dimensional [3-D] visualization that can be used for volumetric detection of hippocampal volume loss [9].

High-resolution T1-weighted 3D volume sequences can be used quantitatively to measure the volume of any particular region of interest. Volumetric assessment can be done manually or with half- or fully automated software, and increasingly advanced methods of anatomic analysis are being developed and implemented **[10]**.

This study is designed to evaluate the effect of aging on hippocampal volume and any change in shape in both sexes in the general population. using 3D MRI brain; It has been demonstrated that alterations in HV are closely associated with a wide range of neurological and mental conditions.

PATIENTS AND METHODS

Cross-sectional study includes one hundred and five right-handed healthy participants with normal brain MRI [105] who were selected in equal distribution from five age groups. Their age ranges from 21 to 75 years. Participants were attended to diagnostic imaging at Al-Azhar Hospital [New Damietta] during the period from May 2024 to December 2024.The chosen subjects were classified into five age groups, each of which included males and females as follows:

Group I [G I] included 21 persons; 14 males and 7 females aged between 21-31 years old, while **Group II [G II]** included 21 persons; 13 males and 8 females aged between 32-42 years old.

Group III [G III] included 21 persons; 9 males and 12 females aged between 43-53 years old, while **Group IV [G IV]** included 21 persons; 10 males and 11 females aged between 54-64 years old. Finally, **Group V [G V]** included 21 persons; 7 males and 14 females aged between 65-75 years old.

All the cases included in this study underwent brain MRI with manual and automated volumetric analysis.

The inclusion criteria were 1] Participants who are neurologically normal, 2] Cooperative, 3] Aged from 21 to 75 years.

The exclusion criteria were 1] Neurological disorder, 2] post-operative patients, 3] Patients contraindicated to perform MRI, such as those with intraocular metallic foreign bodies, cardiac pacemakers, or non-compatible intracranial clips of arterial brain aneurysms and also claustrophobic patients, 4] Critical illness, 5] Psychiatric disorders, 6] Patients showing structural brain anomaly on the initial conventional MRI study.

Methods:

All participants were subjected to the following battery of assessment:

- Thorough clinical assessment, which included careful history taking from the participant, which included personal history. Name, age, sex and any clinical symptomatology refer to neurological disease, past history of previous injury, operation, or disease of the brain. The participants were routinely questioned about any

conditions that would contraindicate MRI examination, such as metallic prosthesis or implants.

All of the patients have had brain MRI examinations. Hippocampal volumetric analysis and MRI data processing will be carried out both manually using 3D Slicer and automatically utilizing the volBrain brain volumetry system.

Automatic: Voxel-based morphometry was performed automatically utilizing the hippocampus pipeline, a completely automated software analysis suite called volBrain. For automatic HC subfield segmentation of monomodal [T1] or multimodal [T1 + T2] MRI data, HIPS is a pipeline. It generates a PDF report with the volumes of HC subfields after receiving anonymized MRI brain volumes in NIFTI format. Once the automatic process is finished, a notification by e-mail containing a PDF report gathering all the volumetry values calculated from the segmentations. includes patient information, subfield volumes [CA1, CA2-CA3, CA4-DG, SR-SL-SM and Subiculum] and their asymmetries. It also includes several snapshots from the different labeling results as a quality control [11].

All of the volumes are expressed as absolute values in cm^3 as well as relative values in respect to the intracranial volume. Expected limits [95%] of normalized volume in relation to age and sex are shown between brackets for each metric as a reference. Volume over or below the intended volume limitations was shown by the red numbers [12].

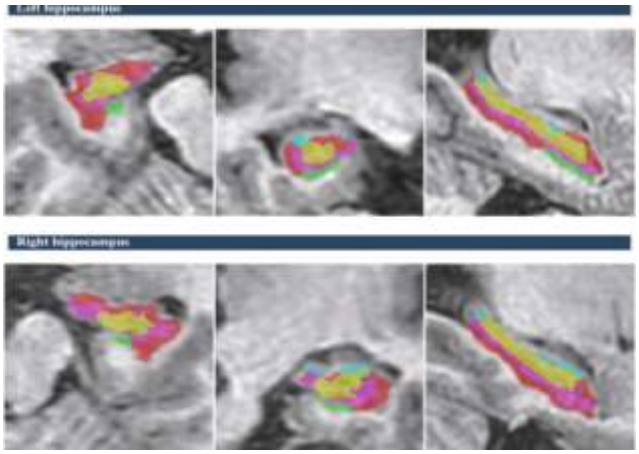


Figure [1]: Automatic by using volbrain brain volumetry system.

Manually: With a slice thickness of 0.5 mm, a three-dimensional, T1-weighted [3D T1] sequence was performed. A personal computer [PC] workstation was equipped with Slicer 5.6.1 software, which offers accurate morphometry of regions of interest by manual and semiautomated tracing of the brain MRI, including coronal, axial, and sagittal T1 [13].

The HC was the structure under study. Axial, coronal, and sagittal 3D T1-weighted images were used for volumetric analysis. By multiplying the trace area of each slice by the thickness of the slice, the volume was automatically determined. After carefully tracing the left and right sides of each chosen location, the total volumes were determined. A percentage of the traced intracranial volume was used to represent the traced volumes of each region of interest [14].

Delineation is the process of manually or with the use of semi-automated techniques creating labels to identify the areas of interest inside a brain [15].

By using the three orthogonal orientations to identify and demarcate the edges of the structures. In addition, use the anatomical descriptions for each selected structure to detect the location and boundaries of each one referenced. Usually, the actual manual segmentations were performed on the coronal scans by using a specific slice that was often located in the middle part for each structure as a reference, when it is at its largest, its background and intensity are much different [GM versus WM].

In order to make it simpler and usually possible to identify the region of interest based just on visual appearance, this study began by looking for pixels in the image of the structure that had sharp intensity fluctuations.

To establish demarcation points, which show up as dots or lines on the coronal scans and act as threshold boundaries for the real segmentation process, the structure on the orthogonal slices [sagittal and coronal] was then sketched. Following the demarcation of the structures' boundaries on the orthogonal pictures, the coronal scans were manually outlined and the inside of the path filled, always staying inside the lines [because we only intended to include GM and not WM].

Slice after slice, this process was performed while adhering to the, respecting the anatomy and boundaries for each region of interest. The manual segmentations of the structure were continued using the coronal scans as far as the interested structure was seen and differentiated and never went any higher or lower than that. The line [the edge] was left unchanged unless GM tissue can still be identified. The subicular complex, dentate gyrus, alveus, and fimbria were included for the measurement of the hippocampus body and tail in order to define the HC proper. The amygdala, parahippocampal gyrus, isthmus of the cingulated gyrus, and crus of fornix were not included in the measurement. It creates the lateral ventricle's inferior horn floor [16].

The HC's anterior, posterior, superior, and inferior borders were identified using the coronal view by locating a scan of its central section, when the GM and WM can be easily separated and the hippocampus is at its biggest size. That acts as a cutoff point for the coronal scan segmentation procedure; the region where the HC was most obvious was looked for to start delineation. The manual segmentations were performed on the coronal scans by using a specific slice as a reference where it has the largest size, and its intensity [GM] differs from the surrounding background [WM]. Repeated HC delineation in several slices. After complete HC delineation in all slices [about 20 slices], the 3D view of the HC appeared. The volumes were computed automatically by multiplying the thickness of each slice by the sum of its HC. The HV calculation is shown in cm^3.

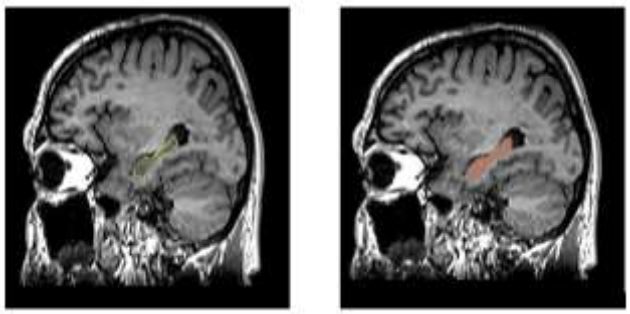


Figure [2]: Normal T1-weightedcoronal and sagittal MRI of brain showing outlines of the hippocampus.

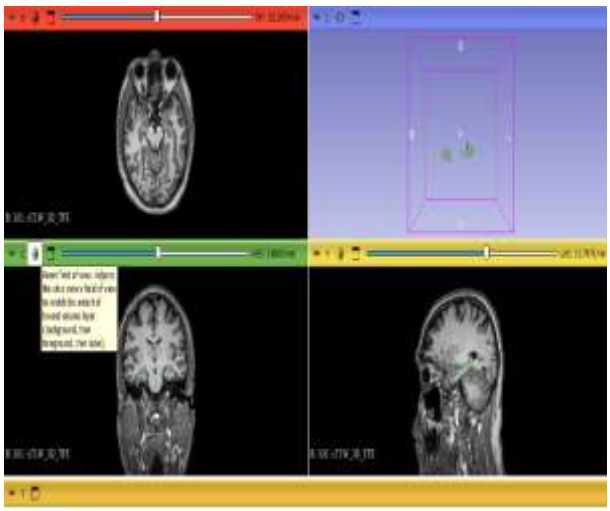


Figure [3]: Normal T1-weighted MRI of brain showing outlines of the hippocampus in coronal, sagittal and axial and 3D view.

Statistical analysis

Collected data was revised, coded, tabulated and introduced to a PC using the Statistical Package for Social Science [IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.]. Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Descriptive statistics included mean ± standard deviation [SD] for parametric quantitative data, while frequency and percentage were used for categorical data. Then, the analysis phase of analysis was conducted and included the following:

- **Analysis of variance [ANOVA or F test]:** For continuous data, one-way ANOVA tests were employed to check for significant differences between groups that were more than two times normally distributed. The Shapiro-Wilk and Levine's tests were used to confirm the assumptions of homogeneity of variances and normality in each group, respectively.

- **Post Hoc tests:** Following a significant ANOVA test to determine which significant differences existed between pairs of groups, the Tukey honestly significant difference [Tukey-HSD] test was employed as a post hoc test to account for multiple comparisons.

- **Chi-Square test** was used to examine the relationship between two or more qualitative variables.

Level of significance: Two-tailed probabilities are used to quote the findings of significance tests. The significance level was assessed for each of the aforementioned tests, represented by the likelihood of the p-value, and the findings were described as follows: Non-significant if the p value is > 0.05, and significant if the p value is ≤ 0.05.

RESULTS

In the current work, there was non significant differences between study groups regarding patient gender. Males represented 66.7%, 61.7%, 42.9%, 47.6% and 33.3% respectively [Table 1].

In the current study, the automatic right and hippocampal volumes showed statistically significant variance between study groups. However, with paired comparison the differences between groups 2 and 3 in relation to group 1 showed non significant differences. But, groups 3 and 4 were significantly lower than groups 1, 2 and 3 [Table 2]. The manual right and left hippocampal volumes showed significant variances between study groups. The main differences were significant reduction in groups 4 and 5 than other study groups [Table 3]. In addition, the automatic and manual right and left hippocampal volumes showed similar results as manual volumes when categorized by subject gender [Tables 4, 5, 6 and 8].

Table [1]: Analysis of the sex distribution in the study groups according to age groups**.**

Sex	Group 1 [21-31 years] [N= 21]	Group 2 [32-42 years] [N= 21]	Group 3 [43-53 years] [N= 21]	Group 4 [54-64 years] [N= 21]	Group 5 [65-75 years] [N= 21]	Test of significance
Males	**14 [66.7%]**	**13 [61.9%]**	**9[42.9%]**	**10 [47.6%]**	**7 [33.3%]**	**χ^2= 6.324 P = 0.176**
Females	**7 [33.3%]**	**8 [38.1%]**	**12 [57.1%]**	**11 [52.4%]**	**14 [66.7%]**	

P: probability; Categorical data expressed as Number [%]; χ2: Chi-square test.

Table [2]: Analysis of the automatic hippocampal volume in the study groups according to age groups.

	Group 1 [21-31 years] [N= 21]	Group 2 [32-42 years] [N= 21]	Group 3 [43-53 years] [N= 21]	Group 4 [54-64 years] [N= 21]	Group 5 [65-75 years] [N= 21]	Test of significance
Right hippocampal volume	2.73±0.42	2.42± 0.33	2.89± 0.42	2.18± 0.32	2.05± 0.49	F= 16.717; P < 0.001*
P1		0.100	0.694	< 0.001*	< 0.001*	
P2			0.002*	0.303	0.023*	
P3				< 0.001*	< 0.001*	
P4					0.794	
Left hippocampal volume	2.73±0.37	2.26± 0.37	2.77± 0.43	2.04± 0.28	1.68± 0.48	F= 29.276; P < 0.001*
P1		0.002*	0.995	< 0.001*	< 0.001*	
P2			< 0.001*	0.389	< 0.001*	
P3				< 0.001*	< 0.001*	
P4					0.031*	

P: probability; Quantitative data are expressed as mean ± SD; F: One-way ANOVA test; P1: Significant difference in relation to Group 1 [21-31 years]; P2: Significant difference in relation to Group 2 [32-42 years]; P3: Significant difference in relation to Group 3 [43-53 years]; P4: Significant difference in relation to Group 4 [54-64 years].

Table [3]: Analysis of the manual hippocampal volume in the study groups according to age groups.

	Group 1 [21-31 years] [N= 21]	Group 2 [32-42 years] [N= 21]	Group 3 [43-53 years] [N= 21]	Group 4 [54-64 years] [N= 21]	Group 5 [65-75 years] [N= 21]	Test of significance
Right hippocampal volume	2.87±0.42	2.61± 0.34	3.07± 0.43	2.29± 0.33	2.17± 0.58	F= 16.092; P < 0.001*
P1		0.304	0.591	< 0.001*	< 0.001*	
P2			0.008*	0.119	0.011*	
P3				< 0.001*	< 0.001*	
P4					0.894	
Left hippocampal volume	2.79±0.49	2.39± 0.38	2.92± 0.44	2.16± 0.28	1.76± 0.48	F= 26.255; P < 0.001*
P1		0.026*	0.833	< 0.001*	< 0.001*	
P2			0.001*	0.376	<0.001*	
P3				< 0.001*	< 0.001*	
P4					0.024*	

P: probability; Quantitative data are expressed as mean ± SD; F: One-way ANOVA test; P1: Significant difference in relation to Group 1 [21-31 years]; P2: Significant difference in relation to Group 2 [32-42 years]; P3: Significant difference in relation to Group 3 [43-53 years]; P4: Significant difference in relation to Group 4 [54-64 years].

Table [4]: Analysis of the automatic hippocampal volume in the study groups according to age groups [male cases].

	Group 1 [21-31 years] [N= 14]	Group 2 [32-42 years] [N= 13]	Group 3 [43-53 years] [N= 9]	Group 4 [54-64 years] [N= 10]	Group 5 [65-75 years] [N= 7]	Test of significance
Right hippocampal volume	2.86±0.38	2.49± 0.25	3.01± 0.33	2.18± 0.43	2.37± 0.39	F= 9.357; P < 0.001*
P1		0.067	0.876	< 0.001*	0.034*	
P2			0.014*	0.246	0.950	
P3				< 0.001*	0.008*	
P4					0.813	
Left hippocampal volume	2.82±0.34	2.33± 0.43	2.80± 0.52	2.04± 0.32	1.69± 0.22	F= 14.846; P < 0.001*
P1		0.016*	0.999	< 0.001*	< 0.001*	
P2			0.049*	0.388	0.008*	
P3				0.001*	< 0.001*	
P4					0.362	

P: probability. Quantitative data are expressed as mean ± SD. F: One-way ANOVA test. P1: Significant difference in relation to Group 1 [21-31 years]. P2: Significant difference in relation to Group 2 [32-42 years]. P3: Significant difference in relation to Group 3 [43-53 years]. P4: Significant difference in relation to Group 4 [54-64 years].

Table [5]: Analysis of the manual hippocampal volume in the study groups according to age groups [male cases].

	Group 1 [21-31 years] [N= 14]	Group 2 [32-42 years] [N= 13]	Group 3 [43-53 years] [N= 9]	Group 4 [54-64 years] [N= 10]	Group 5 [65-75 years] [N= 7]	Test of significance
Right hippocampal volume	3.01±0.39	2.68± 0.25	3.18± 0.34	2.29± 0.44	2.36± 0.36	F= 11.345; P < 0.001*
P1		0.151	0.778	< 0.001*	0.003*	
P2			0.019*	0.084	0.322	
P3				< 0.001*	< 0.001*	
P4					0.994	
Left hippocampal volume	2.93±0.35	2.47± 0.43	2.95± 0.53	2.16± 0.33	1.77± 0.22	F= 15.240; P < 0.001*
P1		0.030*	0.999	< 0.001*	< 0.001*	
P2			0.047*	0.335	0.003*	
P3				< 0.001*	< 0.001*	
P4					0.270	

P: probability. Quantitative data are expressed as mean ± SD; F: One-way ANOVA test. P1: Significant difference in relation to Group 1 [21-31 years]. P2: Significant difference in relation to Group 2 [32-42 years]. P3: Significant difference in relation to Group 3 [43-53 years]. P4: Significant difference in relation to Group 4 [54-64 years].

Table [6]: Analysis of the automatic hippocampal volume in the study groups according to age groups [female cases].

	Group 1 [21-31 years] [N= 7]	Group 2 [32-42 years] [N= 8]	Group 3 [43-53 years] [N= 12]	Group 4 [54-64 years] [N= 11]	Group 5 [65-75 years] [N= 14]	Test of significance
Right hippocampal volume	2.47±0.37	2.31± 0.43	2.81± 0.47	2.19± 0.20	1.88± 0.46	F= 8.904; P < 0.001*
P1		0.946	0.413	0.610	0.024*	
P2			0.075	0.962	0.134	
P3				0.006*	< 0.001*	
P4					0.348	
Left hippocampal volume	2.55±0.40	2.13± 0.23	2.75± 0.38	2.04± 0.25	1.68± 0.57	F= 13.034; P < 0.001*
P1		0.293	0.839	0.086	< 0.001*	
P2			0.014*	0.978	0.101	
P3				0.001*	< 0.001*	
P4					0.196	

P: probability. Quantitative data are expressed as mean ± SD. F: One-way ANOVA test. P1: Significant difference in relation to Group 1 [21-31 years]. P2: Significant difference in relation to Group 2 [32-42 years]. P3: Significant difference in relation to Group 3 [43-53 years]. P4: Significant difference in relation to Group 4 [54-64 years].

Table [7]: Analysis of the manual hippocampal volume in the study groups according to age groups [female cases].

	Group 1 [21-31 years] [N= 14]	Group 2 [32-42 years] [N= 13]	Group 3 [43-53 years] [N= 9]	Group 4 [54-64 years] [N= 10]	Group 5 [65-75 years] [N= 7]	Test of significance
Right hippocampal volume	2.60±0.38	2.50± 0.44	2.98± 0.48	2.30± 0.21	2.08± 0.66	F= 6.182; P < 0.001*
P1		0.994	0.480	0.680	0.145	
P2			0.208	0.888	0.287	
P3				0.012*	< 0.001*	
P4					0.792	
Left hippocampal volume	2.51±0.63	2.27± 0.24	2.90± 0.39	2.16± 0.25	1.76± 0.58	F= 11.133; P < 0.001*
P1		0.837	0.373	0.488	0.006*	
P2			0.027*	0.983	0.092	
P3				0.002*	< 0.001*	
P4					0.194	

P: probability. Quantitative data are expressed as mean ± SD. F: One-way ANOVA test. P1: Significant difference in relation to Group 1 [21-31 years]. P2: Significant difference in relation to Group 2 [32-42 years]. P3: Significant difference in relation to Group 3 [43-53 years]. P4: Significant difference in relation to Group 4 [54-64 years].

Case presentation

Case 1

Group 1 [21-31 years]

Male participant 25 old complaining from headache clinically free with normal brain MRI. The automatic measurement using volbrain were 4.99 cm^3, 2.43 cm^3 and 2.56 cm^3 for total hippocampus volume, right and left hippocampus, respectively. On the other side, the manual measurements using third slicer 5.6.1 were **5**.26 cm^3, 2.55 cm^3 and 2.7 cm^3 total hippocampus volume, right and left hippocampus, respectively [figure 4a,b and c].

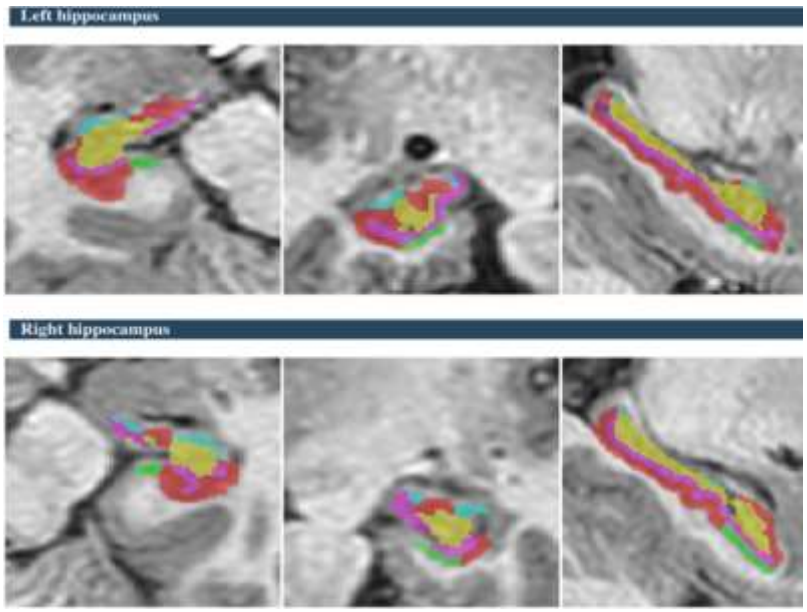


Figure [4a]: Hippocampal segmentation for the control group using the Winterburn procedure. Green: CA2/CA3, Yellow: CA4/dentate gyrus [DG], Red: Cornu Ammonis [CA]1, Pink: subiculum; blue: stratum radiatum, lacunosum, and moleculare [SR/SL/SM].

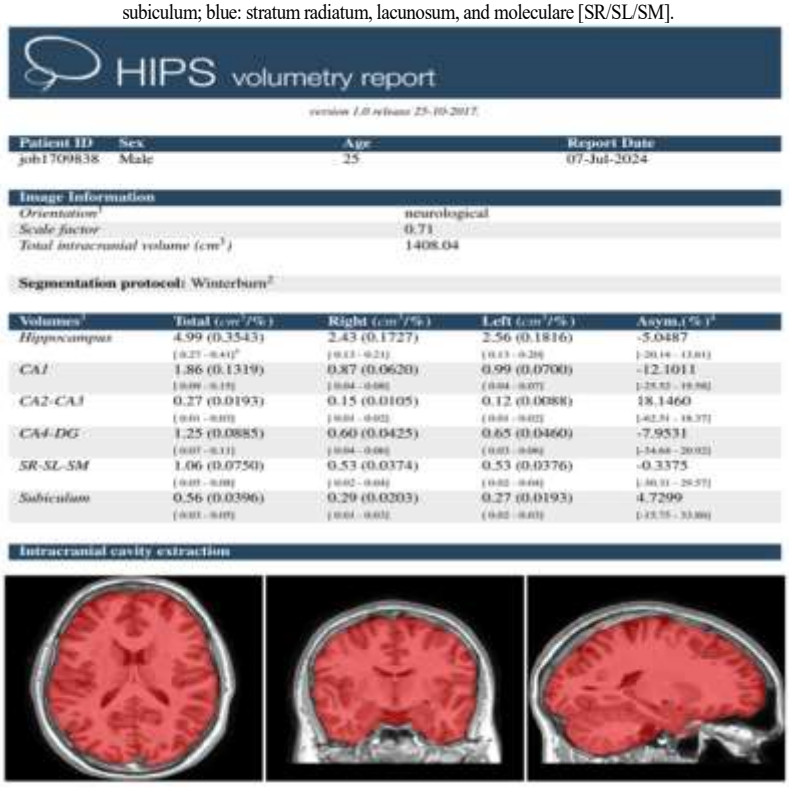


Figure [4b]: volBrain report for automatic measurement of hippocampus and its subfield using hippocampus pipeline and Winterburn segmentation protocol.

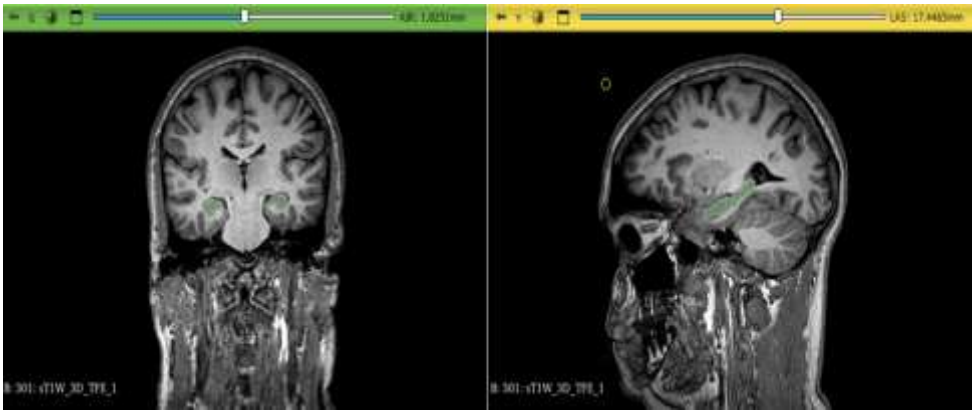


Figure [4c]: Coronal and sagittal T1-weighted MRI image manual measurement.

Case 2

Group 2 [32-42 years]: Male participant 33 old complaining of migraine clinically free with normal brain MRI. The automatic measurement using volbrain were 5.26 cm³, 2.64 cm³ and 2.62 cm³ for total hippocampus volume, right and left hippocampus, respectively. On the other side, the manual measurements using third slicer 5.6.1 were 5.55 cm³, 2.78 cm³ and 2.77 cm³ total hippocampus volume, right and left hippocampus, respectively [Figures 5a, b and c].

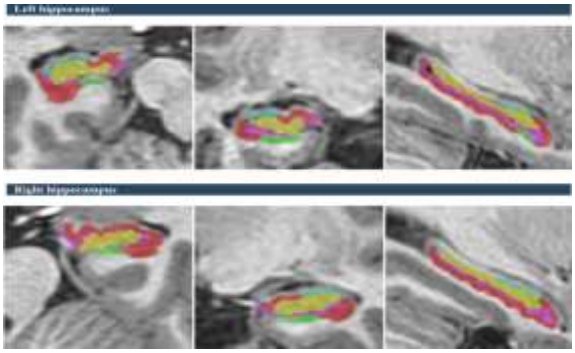
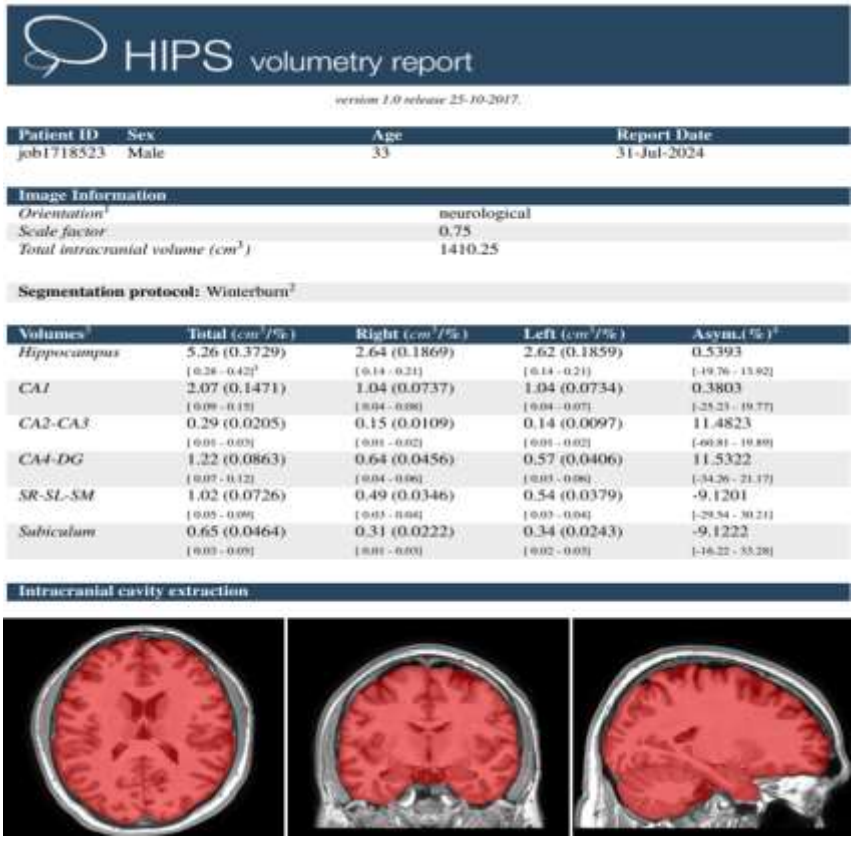


Figure [5a]: Hippocampal segmentation for the control group using the Winterburn procedure. Green: CA2/CA3, Yellow: CA4/dentate gyrus [DG], Red: Cornu Ammonis [CA]1, Pink: subiculum; blue: stratum radiatum, lacunosum, and moleculare [SR/SL/SM].



HIPS volumetry report

version 1.0 release 25-10-2017.

Patient ID	Sex	Age	Report Date
job1718523	Male	33	31-Jul-2024

Image Information

Orientation[1]	neurological
Scale factor	0.75
Total intracranial volume (cm³)	1410.25

Segmentation protocol: Winterburn[2]

Volumes[3]	Total (cm³/%)	Right (cm³/%)	Left (cm³/%)	Asym.(%)[3]
Hippocampus	5.26 (0.3729) [0.28 - 0.42][3]	2.64 (0.1869) [0.14 - 0.21]	2.62 (0.1859) [0.14 - 0.21]	0.5393 [-19.76 - 13.92]
CA1	2.07 (0.1471) [0.09 - 0.15]	1.04 (0.0737) [0.04 - 0.08]	1.04 (0.0734) [0.04 - 0.07]	0.3803 [-25.23 - 19.77]
CA2-CA3	0.29 (0.0205) [0.01 - 0.03]	0.15 (0.0109) [0.01 - 0.02]	0.14 (0.0097) [0.01 - 0.02]	11.4823 [-60.81 - 19.89]
CA4-DG	1.22 (0.0863) [0.07 - 0.12]	0.64 (0.0456) [0.04 - 0.06]	0.57 (0.0406) [0.03 - 0.06]	11.5322 [-34.26 - 21.17]
SR-SL-SM	1.02 (0.0726) [0.05 - 0.09]	0.49 (0.0346) [0.03 - 0.04]	0.54 (0.0379) [0.03 - 0.04]	-9.1201 [-29.54 - 30.21]
Subiculum	0.65 (0.0464) [0.03 - 0.05]	0.31 (0.0222) [0.01 - 0.03]	0.34 (0.0243) [0.02 - 0.03]	-9.1222 [-16.22 - 33.28]

Intracranial cavity extraction

Figure [5b]: volBrain report for automatic measurement of hippocampus and its subfield using hippocampus pipeline and Winterburn segmentation protocol.

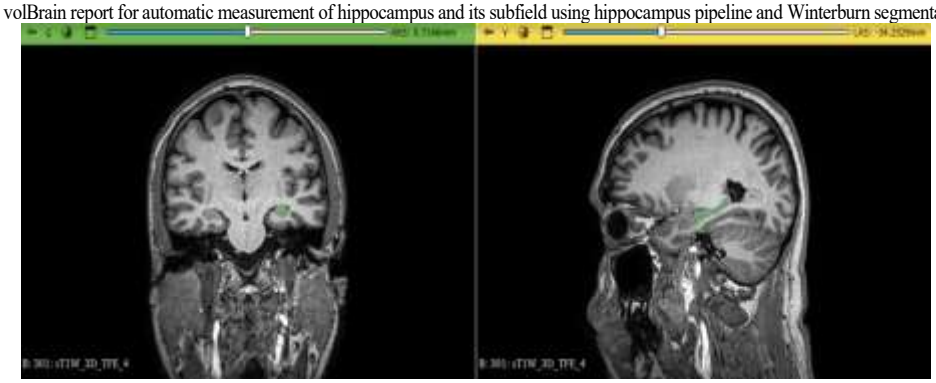


Figure [5c]: Coronal and sagittal T1-weighted MRI image manual measurement.

Case 3

Group 3 [43-53 years]: Female participant 47 old complaining of dizziness clinically free with normal brain MRI. The automatic measurement using volbrain were 4.42 cm³, 2.16 cm³ and 2.06 cm³ for total hippocampus volume, right and left hippocampus, respectively. On the other side, the manual measurements using third slicer 5.6.1 were 4.47 cm³, 2.30 cm³ and 2.17 cm³ total hippocampus volume, right and left hippocampus, respectively [Figures 6 a,b and c].

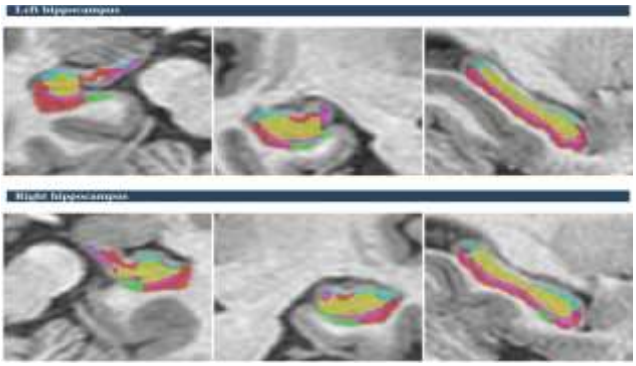
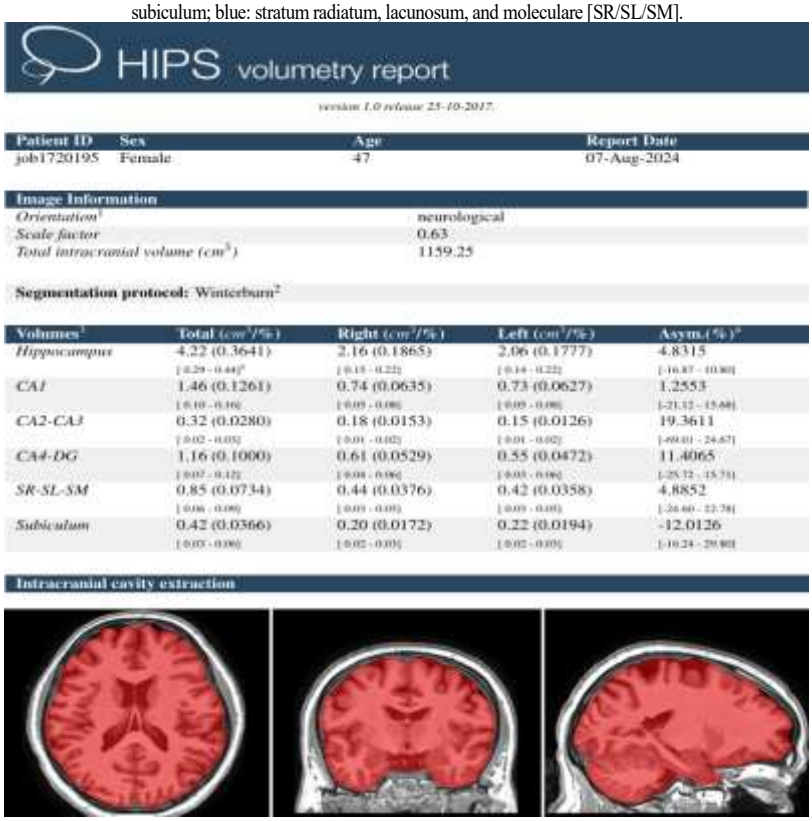


Figure [6a]: Hippocampal segmentation for the control group using the Winterburn procedure. Green: CA2/CA3, Yellow: CA4/dentate gyrus [DG], Red: Cornu Ammonis [CA]1, Pink: subiculum; blue: stratum radiatum, lacunosum, and moleculare [SR/SL/SM].



HIPS volumetry report

version 1.0 release 25-10-2017

Patient ID	Sex	Age	Report Date
job1720195	Female	47	07-Aug-2024

Image Information

Orientation[1]	neurological
Scale factor	0.63
Total intracranial volume (cm^3)	1159.25

Segmentation protocol: Winterburn[2]

Volumes[3]	Total (cm^3/%)	Right (cm^3/%)	Left (cm^3/%)	Asym.(%)[4]
Hippocampus	4.22 (0.3641) [0.29 - 0.44][5]	2.16 (0.1865) [0.15 - 0.22]	2.06 (0.1777) [0.14 - 0.22]	4.8315 [-16.87 - 10.80]
CA1	1.46 (0.1261) [0.10 - 0.16]	0.74 (0.0635) [0.05 - 0.08]	0.73 (0.0627) [0.05 - 0.08]	1.2553 [-21.32 - 15.68]
CA2-CA3	0.32 (0.0280) [0.02 - 0.03]	0.18 (0.0153) [0.01 - 0.02]	0.15 (0.0126) [0.01 - 0.02]	19.3611 [-99.01 - 24.67]
CA4-DG	1.16 (0.1000) [0.07 - 0.12]	0.61 (0.0529) [0.04 - 0.06]	0.55 (0.0472) [0.03 - 0.06]	11.4065 [-25.72 - 15.71]
SR-SL-SM	0.85 (0.0734) [0.06 - 0.09]	0.44 (0.0376) [0.03 - 0.05]	0.42 (0.0358) [0.03 - 0.05]	4.8852 [-24.60 - 22.78]
Subiculum	0.42 (0.0366) [0.03 - 0.06]	0.20 (0.0172) [0.02 - 0.03]	0.22 (0.0194) [0.02 - 0.03]	-12.0126 [-16.24 - 29.80]

Intracranial cavity extraction

Figure [6b]: volBrain report for automatic measurement of hippocampus and its subfield using hippocampus pipeline and Winterburn segmentation protocol.

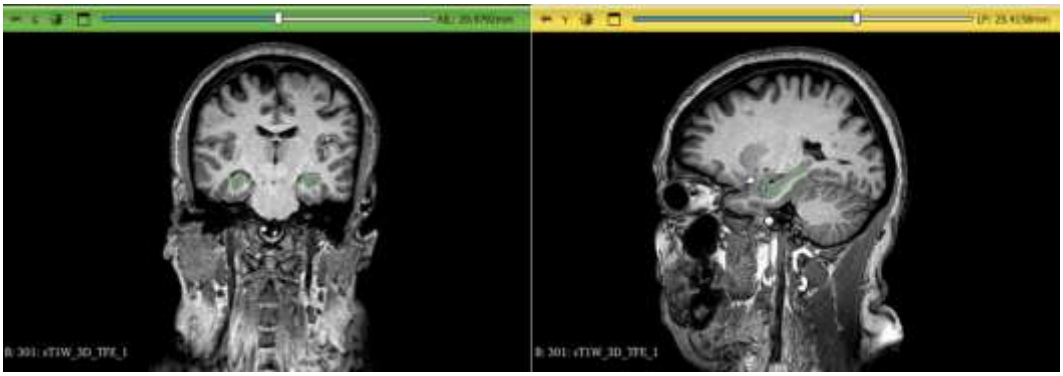


Figure [6c]: Coronal and sagittal T1-weighted MRI image manual measurement.

Case 4

Group 4 [54-64 years]: Male participant 54 old complaining of dizziness clinically free with normal brain MRI. The automatic measurement using volbrain were 5.51 cm³, 2.81 cm³ and 2.70 cm³ for total hippocampus volume, right and left hippocampus, respectively. On the other side, the manual measurements using third slicer 5.6.1 were 5.8 cm³, 2.90 cm³ and 2.80 cm³ total hippocampus volume, right and left hippocampus, respectively [Figures 7 a,b and c].

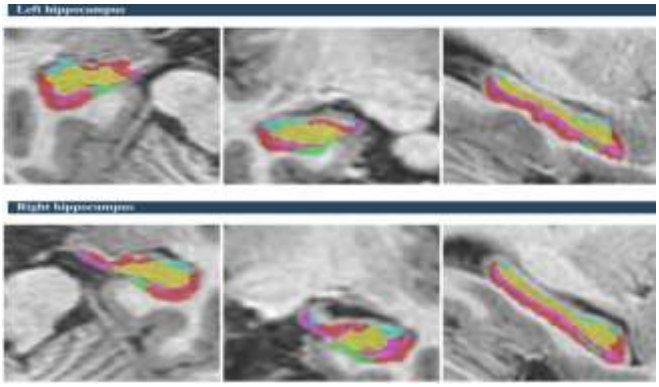


Figure [7a]: Hippocampal segmentation for the control group using the Winterburn procedure. Green: CA2/CA3, Yellow: CA4/dentate gyrus [DG], Red: Cornu Ammonis [CA]1, Pink: subiculum; blue: stratum radiatum, lacunosum, and moleculare [SR/SL/SM].

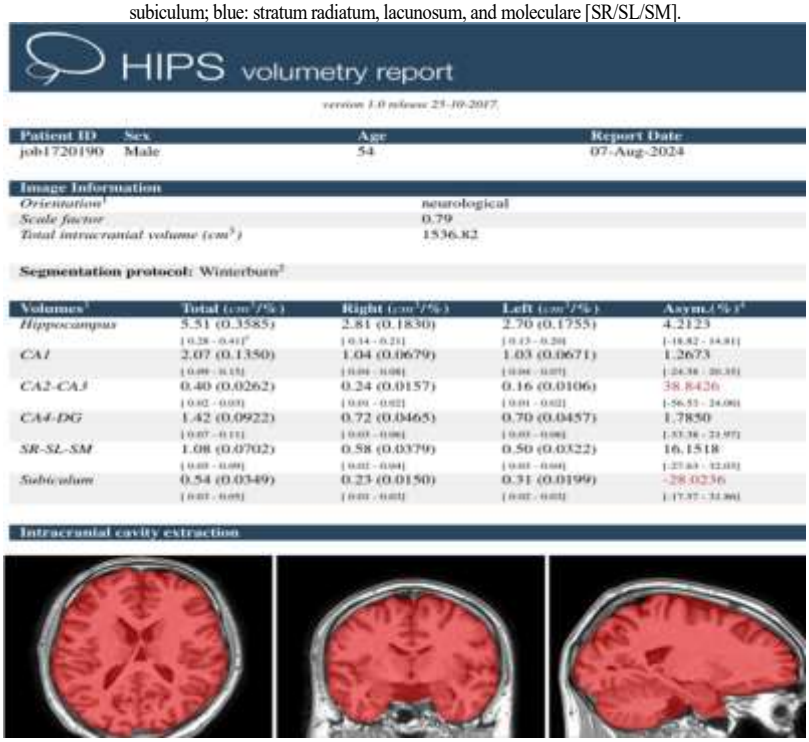


Figure [7b]: volBrain report for automatic measurement of hippocampus and its subfield using hippocampus pipeline and Winterburn segmentation protocol.

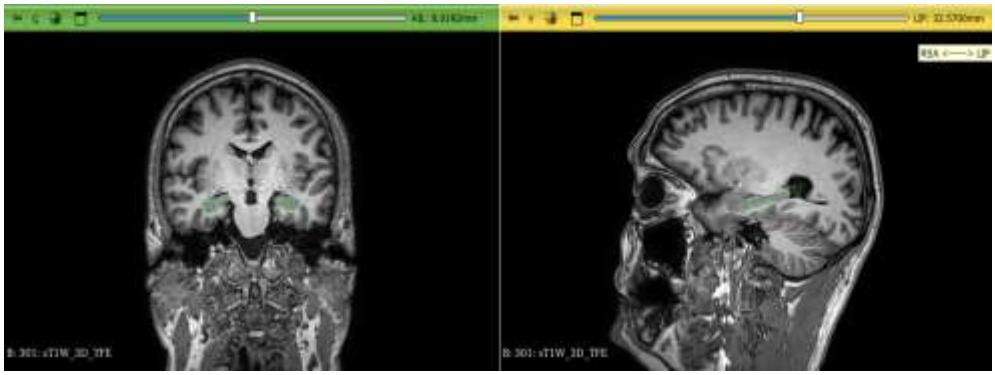


Figure [7c]: Coronal and sagittal T1-weighted MRI image manual measurement.

Case 5

Group 5 [65-75 years]: Female participant 67 old complaining from migraine clinically free with normal brain MRI. The automatic measurement using volbrain were 4.3 cm³, 2.17 cm³ and 2.13 cm³ for total hippocampus volume, right and left hippocampus, respectively. On the other side, the manual measurements using third slicer 5.6.1 were 4.5 cm³, 2.28 cm³ and 2.22 cm³ total hippocampus volume, right and left hippocampus, respectively [Figures 8 a,b and c].

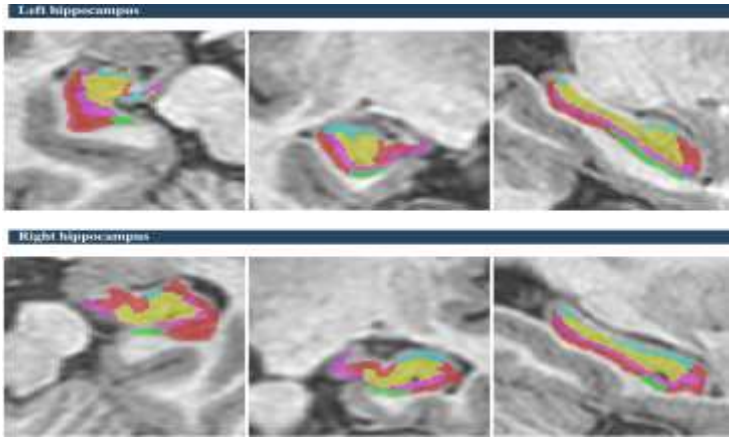


Figure [8a]: Hippocampal segmentation for the control group using the Winterburn procedure. Green: CA2/CA3, Yellow: CA4/dentate gyrus [DG], Red: Cornu Ammonis [CA]1, Pink: subiculum; blue: stratum radiatum, lacunosum, and moleculare [SR/SL/SM].

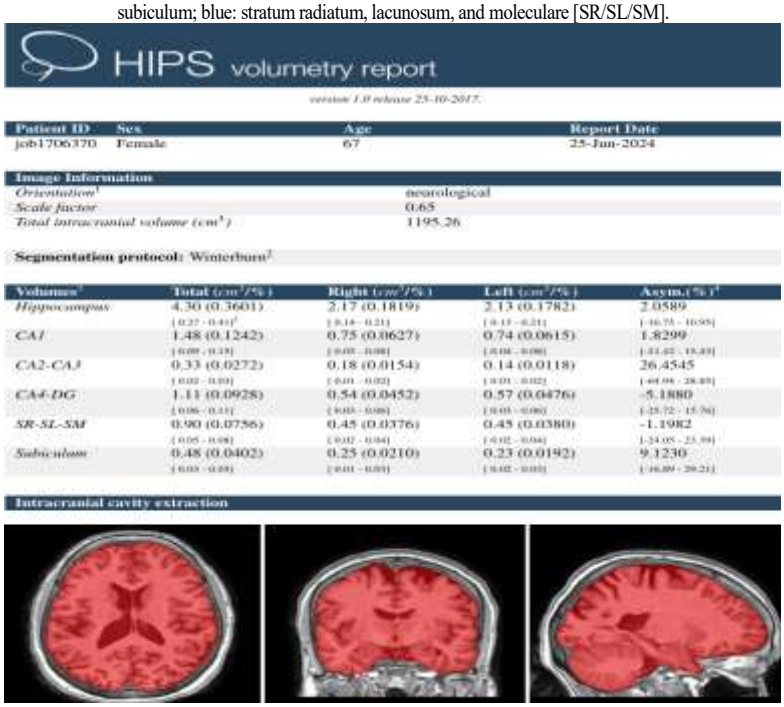


Figure [8b]: volBrain report for automatic measurement of hippocampus and its subfield using hippocampus pipeline and Winterburn segmentation protocol.

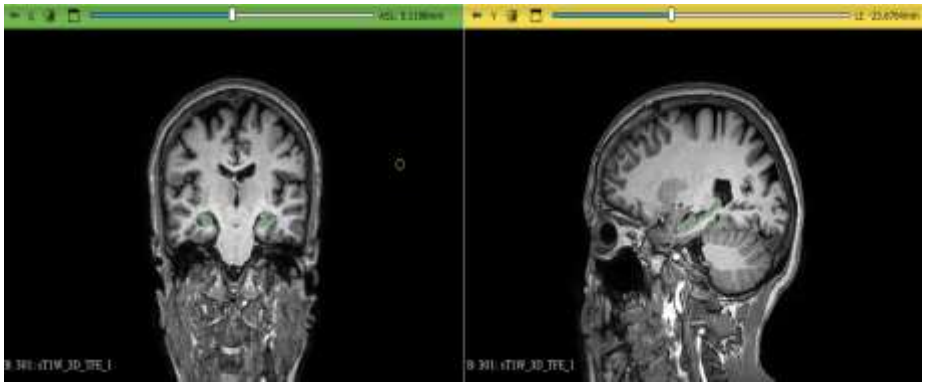


Figure [8c]: Coronal and sagittal T1-weighted MRI image, manual measurement.

DISCUSSION

The HC is a multilayered structure with a complicated geometric pattern of interlocking layers. It is thought that AD, aging, epilepsy, and other conditions preferentially impact the cytoarchitecturally and connectionally distinct subfields of the HC, which are defined by the neuroanatomy literature. These subfields are thought to be differentially involved in memory tasks [17].

Kurth *et al.* [18] shown that the aging process is closely linked to the hippocampus complex, and that the age-related volume loss of its subregions varies.

Additionally, **Kurth and Luders** [19] proved that there is some evidence of asymmetric atrophy later in life.

Diers *et al.* [20] reported that the MR-based shape analysis approach may improve the sensitivity and specificity of structural hippocampal analysis as it can extract three-dimensional features of the hippocampus's form. To investigate the aging impact, we have presented a comprehensive series of conducive shape analysis of human HC MRI images in this work.

Hussain *et al.* [21] noted that the process of visually representing the various human tissues and organs in order to track both normal and pathological bodily architecture and physiology is known as medical imaging. MRI is one of the medical imaging methods used for this. There are several uses for these cutting-edge medical imaging methods in the detection of neurological diseases and other severe illnesses. High resolution, increased safety, and improved reliability are provided by advanced medical imaging modalities like MRI for the diagnosis, management, and treatment of complicated patient problems. These methods have given us a fresh perspective on the brain. using MRI to measure hippocampus volume revealed crucial details regarding a number of neuropsychiatric conditions. It is essential to make sure that new, precise imaging instruments with enhanced resolution, sensitivity, and specificity are produced. With growing technological developments and improvements, the area of medical diagnostics will eventually assess a variety of complicated disorders on a daily basis and offer healthcare treatments.

Although the current work has generated a lot of attention, little is known about the anatomical diversity of the hippocampus area and how development, age, and illness affect its subfields. This was confirmed by **Adler *et al.*** [17] who noted that while the HC is one of the most researched brain structures, little quantitative information is available about its 3D structure, anatomical diversity, and how illness affects its subregions. Because histological investigations are 2D, they only offer limited reference data.

For this, the purpose of this research was to use 3D MRI brain imaging to provide a reference for hippocampus volume by age and sex in the general population. The current study included 105 healthy participants who were selected in equal distribution from five age groups. Group 1 [21-31 years], group 2 [32-42 years], group 3 [43-53 years], group 4 [54-64 years] and group 5 [65-75 years]. The current study showed that the age group 3 [43-53 years] had the largest volume by both manual and automatic hippocampal volume assessment. The next group regarding the largest volume was Group 1 [21-31 years], then Group 2 [32-42 years] as the third rank. The lowest volume was reported in the older age groups.

The current findings agreed with **Kurth *et al.*** [18] who showed that by utilizing enhanced conventional MR-based information to examine the impact of aging on the hippocampus complex in a carefully chosen group of 96 healthy individuals [48 men and 48 women] between the ages of 18 - 69. They reported notable negative associations between age and the volumes of the entorhinal cortex but not the CA, fascia dentata, subiculum, or hippocampus-amygdaloid transition region. At -0.23% and -0.22%, respectively, the left and right subiculum had the highest estimated age-related yearly atrophy rates.

In a previous meta-analysis of 28 studies, **Fraser *et al.*** [22] reported that hippocampal atrophy increased with increasing age, from 0.38% annual atrophy in subjects younger than 55 years to 1.12% in subjects older than 70 years.

In the current study, the decrease in the volume continued to be noticed in the elderly female subjects rather than males. In male subjects, group 5 had larger right hippocampal volume as compared to group 4.

In prior research of 19,793 healthy people [mean age 62.95, SD 7.48], **Nobis *et al.*** [7] showed that females had accelerated hippocampus volume reduction more than males.

Ruigrok *et al.* [23] done meta-analysis of brain structure verified that, throughout the adult lifetime, male and female hippocampi differed significantly in regional volume and tissue density, with the men having a greater volume and higher tissue density. Age and sex interact in a way that makes disparities in hippocampus volume more noticeable in later life.

These differences might result from the age ranges of the patients included in the study, the inclusion/exclusion criteria used, the kind of image data processing [such as tissue categorization and spatial normalization], and the analytic methodology.

In female rats, **Driscoll *et al.*** [24] found a link between a decrease in hippocampus volume and age-related deterioration in hippocampus-dependent learning and memory. The Morris water maze and the transverse pattern learning tests were used to test hippocampal-dependent memory in young-adult [3-month-old], middle-aged [12-month-old], and old [24-month-old] female rats. A visual discrimination task was used to test hippocampal-independent memory.

Age-dependent impairments in hippocampal-dependent memory and spatial memory formation were discovered, as anticipated, with abnormalities in both cognitive processes being most noticeable in middle-aged and elderly rats. Additionally, the 24-month-old age group showed an overall reduction in hippocampus volume, which lends greater credence to the hypothesis that hippocampus volume and hippocampus-dependent cognitive functioning are related.

However, contradictory findings have also been reported by **Maheswaran *et al.*** [25], who did a longitudinal study that failed to detect significant changes in hippocampal size with MRI in wild-type mice from 6 to 14 months of age. Although the results from this study did not exclude the possibility that changes in hippocampal volume could still be detected in mice older than 14 months of age. These differences might result from the age ranges of the patients included in the study, the inclusion/exclusion criteria used, the kind of image data processing [such as tissue categorization and spatial normalization], and the analytic methodology.

In the current study with regard to automatic and manual measurement, reliability was determined, and the result showed that for computerized hippocampus volume calculations, the intraclass correlation was 0.94; for manual tracing, it was 0.99. Compared to human tracing, automated warping produced lower volumes since it excluded the alveus and fimbria. This work shows that automated HC volumetry may be carried out in elderly patients with a high degree of reliability.

Extending previous MRI studies of young adults by **Myszczynska *et al.*** [26] found that in older patients, who may have tiny, irregularly shaped, and challenging-to-measure hippocampus, automated warping assessments of hippocampus volumes maintained a significant correlation with the "gold standard" of hand tracing. This automated approach is anticipated to be highly helpful for examining hippocampus alterations in aging research as the computations were quicker and less prone to rater bias than human tracing.

Also, in the current study, we should point to the fact that significant associations between the HC and age are linked to a reduction in the overall volume of the hippocampus [HVs]; there were certain subregions, such as the subiculum and CA1.According to the "Winterburn" protocol in hippocampal segmentation automatic method, which divides the HC into five segments: CA1, CA2/CA3, SR-SL-SM, CA4/dentate gyrus, and subiculum. In an agreement study done by **Zammit *et al.*** [27], it has been shown that there are significant differences in total HVs, especially in CA1 and total subiculum volumes**.**

The current study has some limitations:

First, the study is a single-center study**,** and this is mostly not suitable for this kind of study that requires assessment of wide geographical areas for better assessment of variations between regions.

Second, the included sample size is relatively small, but it is due to the high cost of performing MRI **,**as these investigations are mostly afforded by the researcher and the included subjectsTo validate the results of this study, more research with a greater sample size is required.

Third, we aim to know how the age factor affects the HC. Nonetheless, a number of other elements may contribute to the HC's structural alterations. A realistic model that takes into account additional risk variables [such as the genetic influence, learning, social, environmental, and so on] has to be developed in the future; this was not the main focus of this study.

Fourth, the age impact may be overstated or understated since this study is cross-sectional rather than longitudinal. In order to get a more sensitive association between recognized risk factors and changes in brain morphology, the longitudinal course of disease and age may help us better understand how changes in brain structure occur during the clinical stage.

Conclusion:

MRI hippocampal volumetry has a significant role in the assessment of hippocampal volume. and monitoring changes with age. This can lead to early and more accurate diagnosis of many pathological diseases related to aging. The process of aging would be more objective with the help of volumetric MRI diagnosis models according to analysis of the results in different age groups regarding the many implicated brain structures.

The effects of gender, hemisphere differences and normal aging were noted. The derived results provide baseline information that might be applied to additional statistical research since the HV is thought to be a practical and accessible substitution for assessing the course of aging, especially in treatment trials. Accurate assessments of HV could potentially aid in early detection of many aging diseases. Indeed, it seems that baseline hippocampal volume and atrophy rate could be a better way to differentiate between MCI and controls than whole brain volume. It is now recognized that estimating HV may be helpful for determining the degree of illness or how other illnesses are progressing.

We discovered a substantial correlation between hippocampus volume and age. Furthermore, the right HC's volume was noticeably greater than the left HC's. The subiculum and CA1-consistent regions showed the strongest correlations between HC and age.

The study found high reliability in automated hippocampal volume with an intraclass correlation of 0.94 compared to 0.99 for manual tracing. Automated warping, which excludes the alveus and fimbria, showed smaller volumes. The quickness and decreased rater bias of this approach should make it helpful for examining hippocampus alterations in aging research.

According to the current investigation, shape analysis may be used to develop theories about various brain structural vulnerabilities.

Financial and non-financial activities and relationships of interest: None

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