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Original Article

Radiology Section

Establishment of Age and Gender Specific Normative Hippocampal Volumes Using Magnetic Resonance Imaging: A Cross-sectional Study

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ABSTRACT

Introduction: Mesial Temporal Sclerosis (MTS) is the principal pathological substrate in Temporal Lobe Epilepsy (TLE) and manifests as hippocampal atrophy. Accurate Hippocampal Volumetry on Magnetic Resonance Imaging (MRI) aids seizure localisation, surgical planning, and detection of bilateral lesions. While reference normative Hippocampal Volume (HV) data exist for Western populations, population-specific standards for Indian demographics remain limited.

Aim: To establish age- and gender-stratified normative HV in healthy Indian adults.

Materials and Methods: This was a cross-sectional study conducted at the Department of Radiodiagnosis, Rangaraya Medical College, Kakinada, Andhra Pradesh, India, from January 2023 to December 2024. Two thousand healthy adults aged 18-40 years from diverse Indian regions were enrolled after exclusion of neurological, psychiatric, and substance-related disorders. Subjects underwent a 1.5 Tesla MRI with T1-weighted sequences (1 mm slice thickness). Semiautomated volumetric segmentation of hippocampi was performed on a sagittal image with reconstruction in coronal sections using anatomical landmark-based methodology. Intraobserver reliability was assessed via Intraclass Correlation Coefficient (ICC) values. Group comparisons by gender and age (18-29 vs 30-40 years) employed Independent two-tailed t-tests; age-HV correlations used Pearson's correlation coefficient.

Results: The mean age of the participants 27.3±6.2 years. Mean Right Hippocampal Volume (RHV) was 2.42±0.31 cm^3 and Left Hippocampal Volume (LHV) was 2.40±0.29 overall. Males demonstrated significantly larger HV than females (RHV: 2.48 vs 2.28 cm^3, $p<0.001$; LHV: 2.44 vs 2.23 cm^3, $p<0.001$). Subjects aged 18-29 years had larger RHV (2.43 cm^3) and LHV (2.41 cm^3) compared to the 30-40 year group (RHV: 2.36 cm^3, LHV: 2.34 cm^3; $p<0.001$). Moderate negative correlations between age and HV were confirmed (RHV: r= -0.35, LHV: r= -0.30; $p<0.001$). The 5th percentile cut-offs were RHV 2.25 cm^3 and LHV 2.19 cm^3, useful for identifying hippocampal atrophy. Intraobserver ICC values were 0.92-0.95, indicating excellent reliability.

Conclusion: This study provides population-specific normative hippocampal volume reference values for young to middle-aged Indian adults and highlights the necessity for population-specific standards.

Keywords: Hippocampal atrophy, Mesial temporal sclerosis, Neuroradiology, Normative data, Temporal lobe

INTRODUCTION

The hippocampus, named for its resemblance to a seahorse, is a curvilinear structure of gray matter located within the mesial temporal lobe [1]. It serves critical roles in memory consolidation (short-term to long-term), spatial navigation and learning, emotional regulation, and contextual information processing, with integral involvement in the limbic system linking memory to emotions and behavioural responses [2-4].

The TLE accounts for 40-50% of complex partial-onset seizures and is frequently drug-resistant [5,6]. MTS, characterised by neuronal loss, gliosis, and hippocampal atrophy, is the principal pathological substrate in approximately 60-80% of TLE cases [7]. MRI hippocampal volumetry complements qualitative assessment by aiding seizure lateralisation, surgical planning, and detection of bilateral or MRI-occult lesions [8].

However, volumetric interpretation depends critically on population-appropriate reference standards. Normative HV data have been established for Western populations and UK cohorts [9].

However, previous work by Mohandas S et al., [10] on Indian populations utilised three Tesla MRI with automated segmentation. Additionally, normative data stratified by age, gender, and specific MRI field strength for young to middle-aged (18-40 years) Indian adults remain scarce.

Given documented ethnic and anthropometric diversity, this study aimed to establish age- and gender-stratified normative HV ranges for healthy Indian adults.

MATERIALS AND METHODS

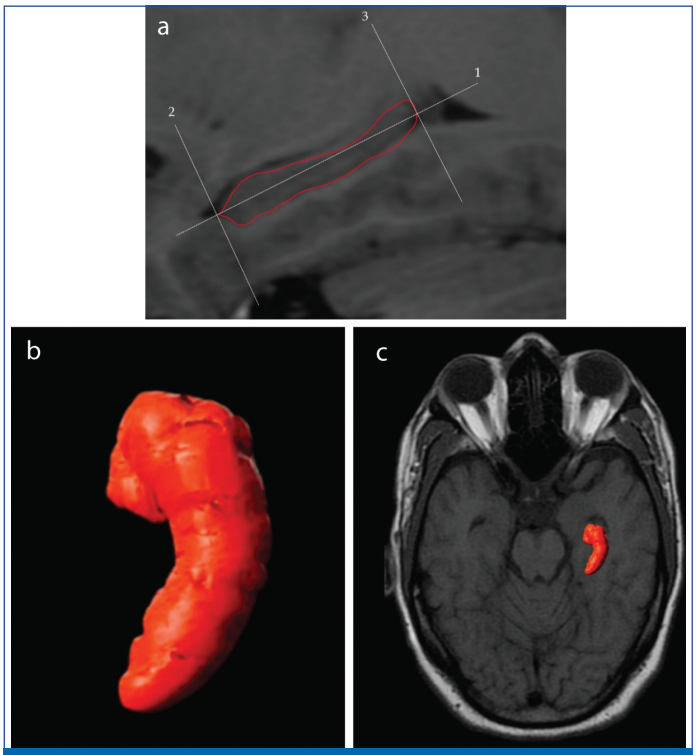
This was a cross-sectional study conducted at the Department of Radiodiagnosis, Rangaraya Medical College, Kakinada, Andhra Pradesh, India, from-January 2023 to December 2024. Prior clearance was obtained from the Institutional Ethics Committee (RMC-EC/2023-039) as per standard Institutional guidelines. Two thousand adults aged 18-40 years from diverse geographical regions across India were enrolled.

Inclusion criteria: Participants aged 18-40 years presenting for MRI evaluation of headache or migraine without structural pathology demonstrated on imaging, with no history of neurological disease, psychiatric disorder, head trauma, or substance abuse, and willing to provide informed consent were included.

Exclusion criteria: It encompassed history of seizures, epilepsy, or neurological/psychiatric disease; previous head trauma or loss of consciousness; history of substance abuse or dependency; contraindications to MRI such as pacemakers, ferrous implants, or claustrophobia; structural brain lesions on MRI including infarcts, tumors, cortical malformations, or haemorrhage; and abnormal global brain volumes or significant brain atrophy on visual inspection.

Study Procedure

Semi-automated volumetric segmentation of the hippocampus was performed on high-resolution T1-weighted images using 3D Slicer with normalisation to intracranial volume to account for individual brain size variation, following planning in the parasagittal plane and reconstruction in coronal planes. Segmentation followed standardised anatomical landmarks as demonstrated in [Table/Fig-1]. White matter, cerebrospinal fluid, and parahippocampal gyrus were carefully excluded. All segmentations were performed on multiplanar views (axial, coronal, sagittal) to ensure accuracy.



[Table/Fig-1a-c]: Anatomical boundaries of Hippocampal Volumetry (HV). (a) Zoomed parasagittal section from high-resolution T1-weighted brain MRI. Dotted line 1 follows the hippocampal long axis; dotted line 2 marks the anterior boundary at the subiculum (rostral end) drawn perpendicular to the line 1; dotted line 3 defines the posterior boundary at the tail (caudal end) drawn perpendicular to line 1. The red line manually outlines hippocampal gray matter; (b) Surface-rendered 3D hippocampal reconstruction from 3D Slicer analysis; (c) T1-weighted MRI brain image with the segmented hippocampus overlaid in its anatomical position.

Reliability assessment: Intraobserver reliability was assessed by randomly re-segmenting n=200 (10%) of scans 2 weeks after initial measurement. Intraclass Correlation coefficient (ICC 3, 1 for two-way mixed effects, absolute agreement) was calculated; ICC >0.90 was considered excellent.

Parameters studied were comparison of RHV in cm^3, LHV in cm^3, Total Hippocampal Volume (THV)= RHV + LHV between genders and age group (18-29 years vs 30-40 years). Correlation between age (continuous, in years) and HV was also performed.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences (SPSS) for windows, version 30.0 (IBM Corp., Armonk, NY, USA) was used. Descriptive Statistics i.e., Mean, Standard Deviation (SD), and 95% Confidence Intervals (CI) were calculated for HV overall and stratified by gender and age group. Independent two-tailed t-tests compared RHV and LHV between males and females. Independent two-tailed t-tests compared RHV and LHV between 18-29 and 30-40 year groups. Pearson's correlation coefficient assessed the relationship between age (continuous) and HVs; significance was assessed at α=0.05 (two-tailed). A 5th percentile threshold for RHV and LHV were calculated to define hippocampal atrophy in clinical contexts.

RESULTS

Of 2100 individuals screened, 2000 were enrolled (100 excluded due to structural brain pathology) [Table/Fig-2].

Parameters	Value
Total participants	2000
Males (n, %)	1040 (52.0%)
Females (n, %)	960 (48.0%)
Age 18-29 years (n, %)	1200 (60.0%)
Age 30-40 years (n, %)	800 (40.0%)
Mean age ±SD (years)	27.3±6.2
Age range (years)	18-40

[Table/Fig-2]: Baseline demographic characteristics of study participants (N=2000).

Right hippocampus was marginally larger than left (mean difference: 0.02 cm^3, p=0.18, not significant) [Table/Fig-3].

Parameters	Mean±SD	95% CI
Right Hippocampal Volume (RHV) (cm^3)	2.42±0.31	2.40-2.44
Left Hippocampal Volume (LHV) (cm^3)	2.40±0.29	2.38-2.42
Total Hippocampal Volume (THV) (cm^3)	4.82±0.59	4.78-4.86

[Table/Fig-3]: Hippocampal Volumes (HV) in study participants.

Males demonstrated significantly larger HVs than females (RHV: 2.48 vs 2.28 cm^3, p <0.001; LHV: 2.44 vs 2.23 cm^3, p <0.001) [Table/Fig-4].

Parameters	Males (Mean±SD)	Females (Mean±SD)	t-value	df	p-value	Cohen's d
RHV (cm^3)	2.48±0.32	2.28±0.25	14.88	1998	<0.001	0.68
LHV (cm^3)	2.44±0.30	2.23±0.24	15.93	1998	<0.001	0.72
THV (cm^3)	4.92±0.60	4.51±0.48	16.42	1998	<0.001	0.72

[Table/Fig-4]: Gender differences in Hippocampal Volume (HV).

Younger adults (18-29 years) had significantly larger HVs than those aged 30-40 years [Table/Fig-5].

Parameters	18-29 years (Mean±SD)	30-40 years (Mean±SD)	t-value	df	p-value	Cohen's d
RHV (cm^3)	2.43±0.29	2.36±0.33	4.84	1998	<0.001	0.23
LHV (cm^3)	2.41±0.27	2.34±0.31	5.57	1998	<0.001	0.25
THV (cm^3)	4.84±0.55	4.70±0.63	5.21	1998	<0.001	0.24

[Table/Fig-5]: Age-group differences in Hippocampal Volume (HV).

Simple linear regression analysis demonstrated that age explained 12% (R^2=0.12) of the variance in RHV and 9% (R^2=0.09) in LHV [Table/Fig-6].

Parameters	Correlation coefficient (r)	p-value	Interpretation
Age vs RHV	-0.35	<0.001	Moderate negative correlation
Age vs LHV	-0.30	<0.001	Moderate negative correlation
Age vs THV	-0.33	<0.001	Moderate negative correlation

[Table/Fig-6]: Correlation between age and Hippocampal Volume (HV).

The 5th percentile cut-offs were RHV 2.25 cm^3 and LHV 2.19 cm^3, useful for identifying hippocampal atrophy [Table/Fig-7].

Parameters	5th percentile (cm^3)
Right Hippocampal Volume (RHV)	2.25
Left Hippocampal Volume (LHV)	2.19

[Table/Fig-7]: Percentile cut-offs for hippocampal atrophy.

The ICC values from re-segmentation of 200 randomly selected scans demonstrated excellent reliability: RHV 0.94 (95% CI: 0.91-0.96), LHV 0.92 (95% CI: 0.89-0.95), and THV 0.93 (95% CI: 0.90-0.95). These ICC values (>0.90) indicate robust and reproducible semiautomated segmentation methodology.

Study/Population	Sample size	Age range (years)	RHV mean (cm^3)	LHV mean (cm^3)	5th %ile RHV (cm^3)	5th %ile LHV (cm^3)	MRI field strength	Measurement method
Current study (Indian, 1.5T, Semiautomated)	2000	18-40	2.42	2.40	2.25	2.19	1.5T	Semiautomated segmentation
UK Biobank [9] (Nobis et al., 2019)	19,793	45-80	3.97	3.86	3.10	3.03	3T	Automated FreeSurfer
Mohandas S et al., [10] (2014) Indian, 3T, Automated	150	20-50	3.18	3.04	—	—	3T	Automated segmentation

[Table/Fig-8]: Detailed comparison of the current Indian cohort with published international datasets [9,10].
3T= 3Tesla

DISCUSSION

The current study employed semiautomated anatomically-guided segmentation on 1.5 Tesla MRI- a pragmatic approach reflecting clinical reality in many Indian centers. While 3 Tesla (3T) MRI and automated segmentation offer superior image quality and standardisation, not all institutions have access to 3T systems. Mohandas S et al., utilised 3T and automated methods, yielding larger volumes (RHV 3.18 vs current 2.42 cm^3) [10]. This difference is attributed to field strength, segmentation methodology, and potentially age range differences [Table/Fig-8] [9,10].

Males exhibited significantly larger HVs than females across all three measures (large effect sizes, Cohen's d >0.68), consistent with documented gender-related neuroanatomical differences mediated by genetic, hormonal, and developmental factors. This finding is consistent with extensive neuroimaging literature documenting sexual dimorphism in brain structure [11]. This difference is mediated by genetic factors (XY chromosome dosage compensation), hormonal factors (androgen receptor distribution), and developmental factors (differential synaptic pruning and myelination) [11].

Limitation(s)

Single-centre study: Data from one Institution may not capture full geographic/ethnic diversity across India; multicentre validation is warranted.

Semiautomated segmentation: While partly operator-dependent, rigorous anatomical protocols and excellent ICC values (>0.90) mitigate this concern; however, inter-observer validation is recommended.

Limited age range: Normative data restricted to 18-40 years; paediatric and geriatric cohorts require separate investigation.

1.5 Tesla only: Findings not directly applicable to 3T systems; field-strength-specific cut-offs should be derived separately.

Selection bias: Cohort limited to headache/migraine presentations; generalisability to entirely asymptomatic or non headache populations requires caution.

CONCLUSION(S)

Mean RHV and LHV were smaller than Western cohorts, reflecting both age and potential ethnic–anthropometric differences. Significant sexual dimorphism and age-related volume decline were documented. The derived 5th percentile cut-offs (RHV 2.25 cm^3, LHV 2.19 cm^3) provide a quantitative clinical baseline for detecting hippocampal atrophy in MTS and TLE evaluation, addressing the inadequacy of indiscriminate application of Western normative standards in Indian neuroradiology practice.

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