Normalised MRI Volumetry of the Hippocampus among Normal Malay Children and Adolescents

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Abstract

Background: Magnetic resonance imaging (MRI) is a noninvasive method for determining brain morphology and volumetry. Hippocampal volume changes are observed in conjunction with several diseases. This study aimed to determine the normalised volume of the hippocampus in normal Malay children and adolescents.

Methods: This was a cross-sectional study performed from January 2009 to June 2010. Brain and temporal lobe MRI was performed for 81 healthy normal Malay individuals aged 7–18 years. Manual volumetry was performed. The hippocampal volumes were normalised with the total intracranial volume.

Results: The original right, left, and total hippocampal volumes (mean and standard deviation) were 3.05 (0.48) cm^3, 2.89 (0.44) cm^3, and 5.94 (0.90) cm^3, respectively. Normalised hippocampal volumes for the right, left, and total volume were 3.05 (0.41) cm^3, 2.89 (0.41) cm^3, and 5.94 (0.79) cm^3, respectively. Pearson's correlation coefficient for the right and left hippocampal volumes with intracranial volume were 0.514 and 0.413, respectively ($P < 0.001$). Both the original and normalised hippocampal volumes of the right hippocampus were significantly larger than those of the left ($P < 0.001$).

Conclusion: This is a data set for the local Malay paediatric population. There was no significant difference between the actual and normalised values of hippocampal volume in our study.

Keywords: hippocampus, Magnetic resonance imaging, Malay, normal value

Introduction

The hippocampus is involved in many disease processes, either as an organ of aetiology or as one that is affected by other pathology. In the paediatric population, the hippocampus can be affected by various disorders, including mesial temporal sclerosis (MTS). Many studies have evaluated the normal hippocampal volume in various age groups. There is a need to have local normative data in different geographical regions. This study was carried out in the state of Kelantan, on the east coast of Malaysia and with a predominance of inhabitants of Malay ethnic origin. A normal data set is essential for diagnosis and assisting in patient management in MTS.

Magnetic resonance imaging (MRI) examination has important implications for treatment decisions. The successful outcome of surgical treatment depends on appropriate case selection. Proper understanding and analysis of the hippocampus and temporal lobe are essential for diagnosing the affected side. MRI is sensitive and specific, even for identifying symmetrical bilateral atrophy and mild unilateral disease.

Hippocampal volumes can be calculated using manual, semiautomatic, or fully automatic computer segmentation of sequential magnetic resonance images. However, the manual tracing method is used by 90% of researchers (1) and is considered the gold standard compared to the automated methods (2).

Normalisation of hippocampal volumes with respect to total intracranial volume (ICV) helps to reduce variance and better define subtle differences in total hippocampal volumes, and compensate for growth-related hippocampal volume changes (3).

Our objectives were (1) to determine the original and normalised volume of the hippocampus, (2) to determine the correlation of the original hippocampal volume and ICV, and (3) to compare the right and left hippocampal volumes.

Materials and Method

This is a cross-sectional observational study which included 81 subjects and which was conducted in Hospital Universiti Sains Malaysia. Normal subjects who were Malay and aged between 7–18 years were recruited. Written and verbal consent was obtained from all participants or their guardians. Exclusion criteria were focal neurological deficit, history of psychiatric illnesses, epilepsy, history of head trauma, and abnormal brain MRI findings.

Acquisition of MR Images and Volume Estimation

All MRI examinations were performed using a 1.0 Tesla system (Signa Horizon LX General Electric, Milwaukee, Wisconsin). Brain and temporal lobe series MRI were performed. MRI of the brain consisted of sagittal T1, axial T1, T2, and Fluid Atteunation Inversion Recovery (FLAIR). These sequences were performed with 5 mm thickness and a 2 mm gap. The temporal lobe series consisted of coronal T2, FLAIR, IR, and 3D fast spoiled gradient-recalled echo (SPGR). All coronal series were perpendicular to the long axis of the temporal lobe with 4 mm thickness and a 1 mm gap, except the 3D SPGR, which was carried out with 2 mm thickness and a 1 mm gap. The T1-weighted series used an echo time of 11 ms, repetition time of 420 ms, 20 mm × 20 mm field of view, and 2.0 NEX. The hippocampal volume was measured on coronal IR, and ICV was measured on the T1-weighted sagittal view.

Hippocampal Volume Measurement

The total area for the region of interest (ROI) was analysed and calculated using the DICOM viewer software OsiriX 3.2.1 workstation. Hippocampal regions were segmented according to the flow chart described by Obenaus et al., (3). The entire hippocampus was measured according to each slice. Measurement of the hippocampal body and tail included the subicular complex, hippocampus proper, dentate gyrus, alveus, and the hippocampal fimbria. Measurement excluded the amygdala, parahippocampal gyrus, isthmus of the cingulate gyrus, and the crus of the fornix.

The anterior limit started from the slice at which the 'pes' or head was visible. The posterior-most section was that on which the crus of the fornix appeared continuous and completely separate from the hippocampus and its fimbria.

Both right and left hippocampi were measured individually. The ROI was manually traced using a computer mouse. Each ROI was traced 3 times for each slice, and the mean (area) was taken. The total area was obtained by summing up all areas (cm^2) from each slice. The entire hippocampal volume (cm^3) was obtained by multiplying the total area with the slice thickness (0.5 cm).

Intracranial Volume Measurement

Intracranial volumetry was performed according to the technique described by Eritaia et al., (4). The total area for the ROI was analysed and calculated using the OsiriX 3.2.1 workstation. ICV is defined as the volume within the cranium, which includes the brain, meninges, and cerebrospinal fluid. Volumetry was performed on T1-weighted images on sagittal view. Manual tracing was performed by following the outlines of the meninges. The bony outline was used when the meninges could not be viewed, especially at the anterior and middle cranial fossa. The inferior limit of segmentation was set as a line drawn between the craniovertebral junctions at the attachment of the dura to the posterior, cutting across to the anterior arch of atlas (C1). Alternate slices were obtained, each slice was measured 3 times, and the mean was taken. The ICV was obtained by multiplying the summed mean with slice thickness (0.5 cm).

Normalisation

Normalisation of the original hippocampal volume with ICV was carried out using the covariance method described by Jack et al. (5), as follows:

NV = OV – Grad (CMi – CM mean)

NV	Normalised hippocampal volume
OV	Original hippocampal volume
Grad	Gradient of the regression line between the hippocampal volume and ICV
CMi	Appropriate ICV measurement for that subject
CM mean	Mean value of all subjects

The gradient of regression line between the hippocampal volume and ICV was obtained using simple linear regression for the right, left, and total hippocampal volumes, which were 0.002, 0.001, and 0.003, respectively.

Statistical Analysis

Data entry and analysis were performed using PASW® Statistics 18 (SPSS, Chicago IL). Mean, standard deviation, and distribution of the data were obtained for the original and normalised hippocampal volumes. For comparison of the right and left hippocampal volumes, distributions of the differences of the original and normalised right and left volumes of each age group were checked. A paired t test was used if data were normally distributed; if data were skewed, the Wilcoxon signed rank test was used, and a *P*-value of less than 0.05 (*P* < 0.05) was considered significant. A simple linear regression test was used to determine the relationship between intracranial and hippocampal volume. Pearson's correlation test was used to determine the original right and left hippocampal volumes.

Results

We recruited 87 subjects. However, 6 were excluded (6.9%) due to abnormal MRI findings in 2 subjects and our inability to retrieve images in 4 subjects. We included 81 subjects in this study. The study group consisted of 46 (56.8%) boys and 35 (43.2%) girls. The mean and standard deviation of age was 12.96 (3.29) years. The subjects' ages were normally distributed. The age and sex distributions are listed in Table 1.

Original and Normalised Hippocampal Volumes

The mean and standard deviation of the original right, left, and total hippocampal volumes are summarised in Table 2 together with the normalised values.

Simple linear regression analysis demonstrated that there was a significant linear relationship between the intracranial, and hippocampal volumes (*P* < 0.001). The gradients of regression lines between the hippocampal and intracranial volumes obtained using simple linear regression for the right, left, and total volumes were 0.002 (95% confidence interval [CI], 0.001, 0.003), 0.001 (95% CI, 0.001, 0.002), and 0.003 (95% CI, 0.002, 0.005), respectively. These results indicate that when ICV increases by 1 cm³, the right, left, and total hippocampal volumes will increase by 0.002, 0.001, and 0.003 cm³, respectively. The variation in the right, left, and total hippocampal volumes by 26.4%, 17.1%, and 22.8%, respectively, can be explained by the total ICV (R^2 = 0.264, 0.171, and 0.228, respectively).

The mean ICV for all subjects was 1418.3 (130.7) cm³, with a minimum and maximum value of 1085.7 cm³ and 1817 cm³, respectively. The mean and standard deviation of the normalised right and left hippocampal volumes were 2.97 (0.42) cm³. Comparison revealed no significant difference between the original and normalised mean hippocampal volumes for all subjects (*P* > 0.05) (Table 3).

Correlation between Original Hippocampal Volume and Intracranial Volume

There was a moderate correlation and linear relationship between the original right and left hippocampal volumes and ICV (Table 4).

Table 1: Distribution of age and gender

Age group	Total (*n* = 81)	Male (*n* = 46)	Female (*n* = 35)
7−9	16	8	8
10−12	20	14	6
13−15	22	9	13
16−18	23	15	8

Table 2: The original and normalised hippocampal volume

Hippocampal volume	Mean (SD) (cm³)		
	Right	**Left**	**Total**
Original	3.05 (0.48)	2.89 (0.44)	5.94 (0.90)
Normalised	3.05 (0.41)	2.89 (0.41)	5.94 (0.79)

Comparison of the Right and Left Hippocampal Volumes

The original hippocampal volume of the right hippocampus was significantly larger ($P < 0.05$) than that of the left in 85% of subjects. The comparison of the mean differences of the right and left hippocampi is summarised in Table 5. Similarly, there was a significant difference between the mean normalised hippocampal volume of the right and left hippocampi ($P < 0.05$).

Discussion

It is well established that various types of neuropsychiatric disorders, especially MTS and temporal lobe epilepsy, affect hippocampal volume. Hippocampal volumetric measurement is not presently practical in a clinical setting and for now remains a research tool. However, it can provide valuable information and function as a supplementary test to support decisions in cases where hippocampal changes are subtle or bilateral and in cases where quantitative correlation with clinical or pathological factors is desired. Since very limited studies have been performed in the normal paediatric population, it is crucial to establish normative data for this population as a reference.

Hippocampal Volume

The mean original right and left hippocampal volumes for our study group were 3.05 (0.48) cm^3 and 2.89 (0.44) cm^3, respectively. The total hippocampal volume was 5.94 (0.90) cm^3. Our results report larger hippocampal volumes as

Table 3: Comparison of original and normalised mean hippocampal volume

All, $n = 81$		Mean (SD) cm^3	Mean difference* (95% CI)	t statistic* (df)	P value*
Right hippocampal volume	Original	3.05 (0.48)	2.0×10^{-5} (−0.06, 0.06)	0.001 (80)	0.999
	Normalised	3.05 (0.41)			
Left hippocampal volume	Original	2.89 (0.44)	0.00000 (−0.03, 0.03)	0.000 (80)	1.000
	Normalised	2.89 (0.41)			
Total hippocampal volume	Original	5.94 (0.90)	-1.0×10^{-5} (−0.09, 0.09)	0.000 (80)	1.000
	Normalised	5.94 (0.79)			

Paired−sampled t test.

Table 4: Pearson's correlation coefficient between hippocampal volume and intracranial volume

	Right	Left
Pearson correlation coefficient (r) **	0.514	0.413
P value	< 0.001	< 0.001

** $P < 0.01$ indicates significant by Pearson's correlation test.

Table 5: Comparison means of right and left hippocampal volumes for all subjects

		Mean (SD) cm^3	Mean difference* (95% CI)	t statistic* (df)	P value*
Original	Right	3.05 (0.48)	0.16 (0.11,0.21)	6.89 (80)	0.001
	Left	2.89 (0.44)			
Normalised	Right	3.05 (0.41)	0.16 (0.11,0.21)	6.87 (80)	< 0.001
	Left	2.89 (0.41)			

*** $P < 0.05$ indicates significant by paired-sampled t test.

compared to the study by Obenaus et al. (3), in which the same segmentation method was used. That study involved 6 children (aged 1 month to 16 years), and non-normalised hippocampal volume ranged 3.85–6.38 cm³. Their mean right and left hippocampal volumes were 2.44 cm³ and 2.59 cm³, respectively, and the total hippocampal volume was 5.04 cm³.

However, similar results were reported in a study carried out in an Indian population, where the subjects' ages ranged 6–12 years. Their mean right and left hippocampal volumes were 2.75 (0.45) cm³ and 2.49 (0.43) cm³, respectively (6). The study used the hippocampal segmentation of Honeycutt et al., (7), where the boundary criteria are almost similar to that in our study.

In our study, the original right and left hippocampal volumes ranged 1.95–4.27 cm³ and 2.12–3.88 cm³, respectively, with a total volume range of 4.07–8.15 cm³. The volumes we obtained are smaller compared to that of the study by Szabo et al., (8). Their right and left hippocampal volumes were 2.70–4.86 cm³ and 2.58–5.01 cm³, respectively, with a total volume range of 5.28–9.87 cm³. The study involved 11 control patients aged 1–7 years. Although the average patient age was younger than that of our study, the hippocampal volume was larger. This could probably have been due to geographical variation.

Another study by Varho et al. (9), comprising 8 European children, also reported a larger mean hippocampal volume of 3.25 (0.46) cm³. Therefore, the hippocampal volume in Asian populations generally appears to be smaller than that of Western populations.

However, a difference can still be observed among Asian regions. Factors such as non-standardised volumetry technique and neuroanatomic boundaries criteria contribute to this variability of hippocampal volume. Different boundaries were used to define the hippocampus in different studies. There are marked differences in the anterior and posterior boundaries between several published reports (10).

Differences in image acquisition plane also could be one of the reasons for the variability. A few different imaging planes are used in MR volumetry. Jack et al., (11) used orientation perpendicular to the long axis of the hippocampus, and others (12,13) have used the anterior and posterior commissure (AC–PC) line.

Inter-institutional variability could also be due to differences in neuroanatomical boundaries and other technical differences such as slice thickness and the strength of the MR machine. Thicker slices decrease spatial resolution, increase the effects of volume averaging, and increase differences between studies on the anatomic boundaries of each structure. However, contrary to this, Laakso et al., (14) found that there was no significant difference in the hippocampal volume measurement when examination was performed with slice thicknesses of 1 mm, 3 mm, or 5 mm. Some studies have stated that MRI performed with 3 Tesla has a higher signal-to-noise ratio, better image quality, and is more sensitive in delineation of the hippocampus than 1.5 Tesla (15).

Some sources of error may be movement artefacts, alterations in magnetic field in homogeneity, machine-dependent image-to-image variation in MR image intensity scales, and voxel size variations due to drifts in imager calibration (16).

Intracranial Volume

The mean ICV for all subjects was 1418.28 (130.69) cm³. Our ICV findings are larger than those obtained from a study carried out in China by Wu et al. (17), where the total ICV was 965 (241) cm³. The study comprised 16 subjects with an age range similar to that of our study (3 to 15 years). The authors measured the ICV manually on axial images. Similar results were reported in a study carried out at the Los Angeles Children's Hospital, USA (18). The mean ICV was 1390 (90) cm³. That study included 7 control subjects aged 8 to 18 years and used the semiautomatic method on 3D SPGR with 1.2 mm slice thickness. A study by Free et al. (19) on an adult population aged 20 to 53 years determined that the mean ICV was 1753 (154) cm³, larger than that of our paediatric age group.

Correlation between Hippocampal Volume and Intracranial Volume

Obenaus et al. (3) reported that the best normalisation was found when estimating the ICV from MRI data for the paediatric population. ICV has been described for adult hippocampal volumes, and provides an excellent method for correcting age and head size (20–22).

In the study by Free et al., (19), good correlation was demonstrated between the right and left hippocampal volumes and ICV.

Regression analysis was applied for the ICV in relation to the right and left hippocampal volumes, and determined that the R^2 values of the regression analysis were 0.264 and 0.171,

respectively. This indicates that 26.4% and 17.1% of the hippocampal volume variance could be predicted from the ICV. Therefore, this result supported the strength of the linear relationship between ICV, and hippocampal volume, which is an important factor for the normalisation process. The regression line indicated that both right and left hippocampi increase with ICV and thus the data require normalisation for accurate inter-individual comparison. Therefore, ICV could be used as a normalisation factor for future research.

In this study, corrections were applied using the covariance method (5), with the strength of the linear relationship being based on the hippocampal volume and the correction factor.

Normalised Hippocampal Volume

In this study, the mean corrected left and right hippocampal volume for all subjects were 3.05 (0.41) cm^3 and 2.89 (0.41) cm^3, respectively. The mean total hippocampal volume was 5.94 (0.79) cm^3.

Wu et al. (17) found that the mean normalised right and left hippocampal volumes was 2.61 (0.21) cm^3, with an average ICV of 965 (241) cm^3. Their study had 16 subjects aged 3 to 15 years (mean age 9.1 ± 3.6 years). Our study revealed larger normalised right and left hippocampal volumes of 2.97 (0.42) cm^3, which could probably be attributed to the larger average ICV of 1418.3 (130.7) cm^3.

In our study, there was no significant difference between nonnormalised and normalised values. However, the correction via the covariance method in this study produced a consistent reduction in standard deviation for the hippocampal volume.

A study in Turkey by Eroglu et al. (23) that used normalisation with ICV found that the normalised total hippocampal volume was smaller than the original volume. The study consisted of 13 normal children aged between 3 and 18 years (mean age 10.4 years). The total hippocampal volume was 4.59 (0.68) cm^3. The original right and left hippocampal volumes were 2.29 (0.37) cm^3 and 2.28 (0.34) cm^3, respectively. The normalised total, right, and left hippocampal volumes were 4.17 (0.60) cm^3, 2.08 (0.30) cm^3, and 2.08 (0.31) cm^3, respectively. As in the present study, ICV was measured from sagittal images but a different normalisation formula was applied and the study used a 1.5-Tesla MRI.

Free et al. (19) also observed a difference between original and normalised hippocampal

volumes in a study using the covariance method in the 20 and 53-year-age group. However, their ICV measurement was different, using 9 coronal sections.

Mean Differences of Right and Left Hippocampal Volumes

This study revealed the difference between right, and left original hippocampal volumes. The difference was small but statistically significant ($P < 0.05$). The difference remained significant for the normalised values ($P < 0.05$).

Several studies have revealed a difference between right and left hippocampal volumes, with the right hippocampus being larger. Obenaus et al. (3) revealed that the right hippocampus was 10% larger than the left in 4 of 6 subjects. Pfluger et al. (25) observed a significant difference, with the right hippocampus being larger on average by 0.10 cm^3. In our study, the right hippocampus was larger on average by 0.16 cm^3. Jack et al. (5) revealed that the right hippocampus was larger by 0.3 cm^3 in 52 healthy subjects. A study by Utsunomiya et al. (26) reported the same result in 91% of study subjects ($n = 39$). In our study, 85% of the subjects ($n = 69$) had a larger right hippocampus. Szabo et al. (8) demonstrated the difference between the right and left sides using a ratio. In that study, the ratio of mean right to left hippocampal volume was 1.03 (0.06), indicating that the right side was larger. The ratio in our study was 1.06 (0.07), indicating a greater difference.

A few studies have reported no significant difference between the right and left hippocampal volume. Studies by Varho et al. (9) and Cook et al. (24) identified no significant difference between the right and left hippocampi. Overall, most studies report that the right hippocampus is larger, which is consistent with the findings of the present study.

Conclusion

We determined the hippocampal volume of the normal Malay paediatric population. In this study, there were no significant differences between normalised and original volumes. Right and left hippocampal volumes were significantly different; both the original and normalised volumes of the right hippocampus were larger. There was good correlation between the right and left hippocampal volumes and ICV. These findings can be used as a reference in studies of diseases related to the hippocampus.

Authors' Contributions

Conception and design: WM, NMJ
Analysis and interpretation of the data: NMJ,AHAK
Drafting of the article, obtaining of funding, administrative, technical or logistic support: WM, MSA
Critical revision of the article for the important intellectual content: WM, AHAK
Provision of study materials or patient, collection and assembly of data: NMJ
Statistical expertise: AKG

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