MR VOLUMETRY STUDY OF HIPPOCAMPUS AND TEMPORAL LOBE IN MALAY ADULTS WITH NORMAL MRI BRAIN IN HUSM

BY
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MR VOLUMETRY STUDY OF HIPPOCAMPUS AND TEMPORAL LOBE IN MALAY ADULTS WITH NORMAL MRI BRAIN IN HUSM.

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Introduction: Volumetry of hippocampus and temporal lobe has been paid attention more and more along with advanced in MRI. Magnetic resonance imaging (MRI) is a non-invasive and provides detailed, accurate morphology of hippocampus and also temporal lobe. MR volumetry of these two structures is important as they are affected by several disease processes. Establishing a normative data for a population is essential so as to refer and diagnose particular illness. There are computer aided automated and semi-automated method available for MR volumetry. This study used manual method for the normative data of hippocampus and temporal lobe.

Volumetric MRI analysis is more sensitive than T2-weighted imaging to atrophy associated with hippocampal sclerosis. It also distinguish volume loss from space occupying lesion as well as may predict a good prognosis following surgery for epilepsy (Bronen, Cheung et al. 1991).

The purpose of this study is to obtain hippocampal and temporal lobes volumes in normal Malay adults as a normative database. Hence, it can be a reference in diagnosing diseases related with these two structures.

Objectives: The aims of this study is to determine the volume of hippocampus and temporal lobe in Malay adult with normal MRI brain.

Methods and materials: This was a cross sectional observational study to determine volume of hippocampus and temporal lobe in Malay adult with normal MRI brain. The age of the patients was range from 21 to 49 years old. The study period was from February 2008 until June 2009 and 51 subjects were included. Majority of them were normal volunteers, and some were patients who had normal MRI brain. MRI of brain and temporal lobe series were performed using a Signa Horizon LX 1.0 Tesla from the Generic Electric Company. Oblique coronal sections perpendicular to the axis of hippocampus were done with 4mm slice thickness and 1mm gap. T1, T2, FLAIR and SPGR series were done. Hippocampal and temporal lobevolumetry were performed. The mean and standard deviation (SD) of hippocampus and temporal lobe volume were calculated using SPSS version 17.

Results: Mean and standard deviation of the total hippocampus volume of normal adult was 6.43 cm^3 (0.80) for all subjects. Mean total hippocampus volume was 6.62 cm^3 (0.87) in male and 6.27 cm^3 (0.71) for female. Mean and standard deviation of hippocampus were 3.35 cm^3 (0.46) on the right and 3.01 cm^3 (0.45) on the left side. Mean hippocampal volume for the right side for male subjects is ranging from 3.21 cm^3 (0.44) to 3.54 cm^3 (0.35) and for the left side is from 2.95 cm^3 (0.30) to 3.32 cm^3 (0.42). Mean hippocampal volume for the right side for female subjects is ranging from

3.07 cm^3 (0.47) to 3.42 cm^3 (0.30) and for the left side is from 2.80 cm^3 (0.36) to 3.08 cm^3 (0.25).

Mean total temporal lobe volume for all subjects was 161.28 cm^3 (19.48). Mean total temporal lobe volume for male and female were 169.23 cm^3 (19.40) and 153.63 cm^3 (16.54) respectively. Mean temporal lobe volume for the right side is ranging from 79.18 cm^3 (8.25) to 87.25 cm^3 (11.11) and for the left side is from 76.79 cm^3 (9.42) to 84.55 cm^3 (11.04).

There was significant correlation between volume of hippocampus and volume of temporal lobe ($r = 0.475$, $p < 0.01$).

Conclusion: These normative data for hippocampus and temporal lobe were useful reference for Malay population. There was significantly larger right hippocampus as compared to left hippocampal volume. There is fairly good association between the temporal lobe and hippocampal volume within normal adult with normal MRI brain.

Dr Salmah Jalaludin @ Win Mar: Supervisor

1 INTRODUCTION

The limbic system comprises components of the brain which are important for memory, emotion and cognitive function. The hippocampus is an important component of this system. It is located within the medial temporal lobe. The hippocampus is a commonly studied structure in MRI morphometry. MRI is an important research tool where brain of neuropsychiatric patients can be investigated in vivo. It is a noninvasive method for investigating brain morphology.

There are many studies where anatomical structures in the brain are measured quantitatively in term of volume, area, width and length. This is because, hippocampal volume and temporal lobe volume varied considerably in various neurological and neuropsychiatric diseases such as Alzheimer (Clifford R. Jack, Ronal C. Petersen *et al*. 1997; Carmichael, Aizenstein *et al*. 2005; Arfanakis, Gui *et al*. 2007; Belaroussi, Bracoud *et al*. 2009), schizophrenia (Bryant, Buchanan *et al*. 1999), major depression (Bremner, Narayan *et al*. 2000), temporal lobe epilepsy (Bonilha, Rorden *et al*. 2004) (Bernasconi, Bernasconi *et al*. 2003), vascular dementia (Barber, Ballard *et al*. 2000), post-traumatic stress disorder (Jatzko, Rothenhöfer *et al*. 2006) and traumatic brain injury (Bigler, Blatter *et al*. 1997; Bigler, Andersob *et al*. 2002). Aging has also been shown to result in gray matter volume loss of the overall brain, including the hippocampus (Allen, Bruss *et al*. 2005).

Accuracy in detecting these quantitative changes depends on comparison with normative database. A volumetric MRI of hippocampus and temporal lobe were done to obtain normative values of these two important brain structures by many investigators from various regions. Several investigators have defined normal age-specific value for the medial temporal lobe structures in neurologically normal elderly subject, but, to our knowledge, no one has reported values for healthy subjects in our country.

Most published studies had shown significant relationship between volume of hippocampus and temporal lobes and neuropathological condition. Various studies have also been carried out to obtain volume of right and left temporal lobes and hippocampal formation from healthy volunteers. Right-left asymmetry in the volume of temporal lobes and hippocampal formation were normal findings (Jay N, A *et al*. 1996). The right hippocampal formation was larger than the left (mean right-left difference, 0.3 cm^3) and this was statistically significant ($p < 0.001$) (Jack, Twomey *et al*. 1989). They also found that there was no effect of age, sex and handedness was seen in normalized hippocampal formation volumes.

Atrophy of hippocampus and temporal lobes, and increased signal on T2-weighted images of MRI in some neuropathology such as mesial temporal sclerosis, can be determined by qualitative visual analysis. However, visual analysis of MRI may detect gross structural atrophy and small degrees of volume loss may be overlooked. Right-left asymmetry in normal persons can also be misinterpreted as volume loss. Unilateral atrophy of hippocampus and temporal lobes can be identified by side-to-side comparison, but bilateral atrophy requires absolute hippocampal and temporal lobes volume assessment in comparison with normative value available.

Accurate and reproducible in vivo measurement of hippocampal volumes using magnetic resonance (MR) imaging is complicated by the morphological complexity of the structure. Absolute hippocampal volume from fast-spin echoes MRI have been shown to correlate with the neural density in its anatomical division (CA1, CA2 and CA3), which was absent with visual analysis of increased T2 signal (Lee, Tien *et al*. 1995). Volumetric MRI analysis may be more sensitive than T2-weighted imaging of atrophy associated with hippocampal sclerosis, may distinguish volume loss from space occupying lesions, and may predict a good prognosis following surgery for epilepsy (Bronen, Cheung *et al*. 1991).

Based on previous studies, volume of hippocampus and temporal lobes are different among those from various regions. Wide ranges of hippocampal volumes (1.73-5.68 cm^3) were reported previously in both MRI-based and histology-based studies (Hayman, Fuller *et al*. 1998).

The aim of this study is to quantify hippocampal and temporal lobes volume in the normal population, thus establishing a normative value for their volumes on coronal MRI for future reference especially for radiologist in the diagnosis of diseases affecting this structure.

2 LITERATURE REVIEW

2.1 Anatomy of hippocampus and temporal lobe

2.1.1 Hippocampus

The hippocampal formation consists of the hippocampus, the dentate gyrus and the parahippocampal gyrus. The hippocampus is a component of medial temporal lobe. It is a curved elevation of gray matter that extends throughout the entire length of the floor of the inferior horn of the lateral ventricle. The hippocampal complex consist s of head, body and tail (Hayman, Fuller *et al*. 1998). It has a total length of head, body and tail of approximately 4.0 cm (Duvernoy, 1988). It is named hippocampus because it resembles a “sea horse” in coronal section. Its anterior end is expanded to form the pes hippocampus. The convex ventricular surface is covered with ependyma, beneath which lies a thin layer of white matter called the alveus. The alveus consists of nerve fibres that have originated in the hippocampus and these converge medially to form a bundle called the fimbria (Fig 2.1). The fimbria will in turn become continuous with the crus of the fornix. The hippocampus terminates posteriorly beneath the splenium of the corpus callosum. The dentate gyrus is a narrow, notched band of gray matter that lies between the fimbria of the hippocampus and the parahippocampal gyrus. The parahippocampal gyrus is continuous with the hippocampus along the medial edge of the temporal lobe.

The hippocampus consists of two major parts, the cornu Ammonis (hippocampus proper) and the dentate gyrus, which are separated by the hippocampus sulcus. Below the hippocampus sulcus or fissure is the subiculum, which occupies the medial/superior curvature of the parahippocampal gyrus and runs superolaterally to its border with the hippocampus.

The hippocampus proper consists of six-layers: the alveus, stratum oriens, stratum pyramidale, stratum radiatum, stratum lacunosum and stratum moleculare. The alveus covers portion of the hippocampus that protrudes into the temporal horn of the lateral ventricle and is main efferent path followed by hippocampal and subicular axons. The alveus continues medially to form the fimbria of the hippocampus, which in turn joins the fornix. Stratum lacunosum contains some of the efferent fibers to the hippocampus. The remaining four layers of the hippocampus are gray matter consisting primarily neurons, dendrites and collateral axons. Because of different appearances and different connections of the pyramidal neurons, the cornu Ammonis is usually divided into four fields, CA1, CA2, CA3 and CA4. The dentate gyrus envelops fields CA4 and the subiculum by the hippocampal fissure (Fig 2.2). The hippocampal fissure is usually obliterated during development, although persistent cavity often remain.

The main blood supply for the hippocampus is from the posterior circulation via single or multiple middle and posterior hippocampal arteries, branches of the posterior cerebral artery. Small blood vessels also enter the hippocampal from adjacent subarachnoid space by penetrating the dentate gyrus.

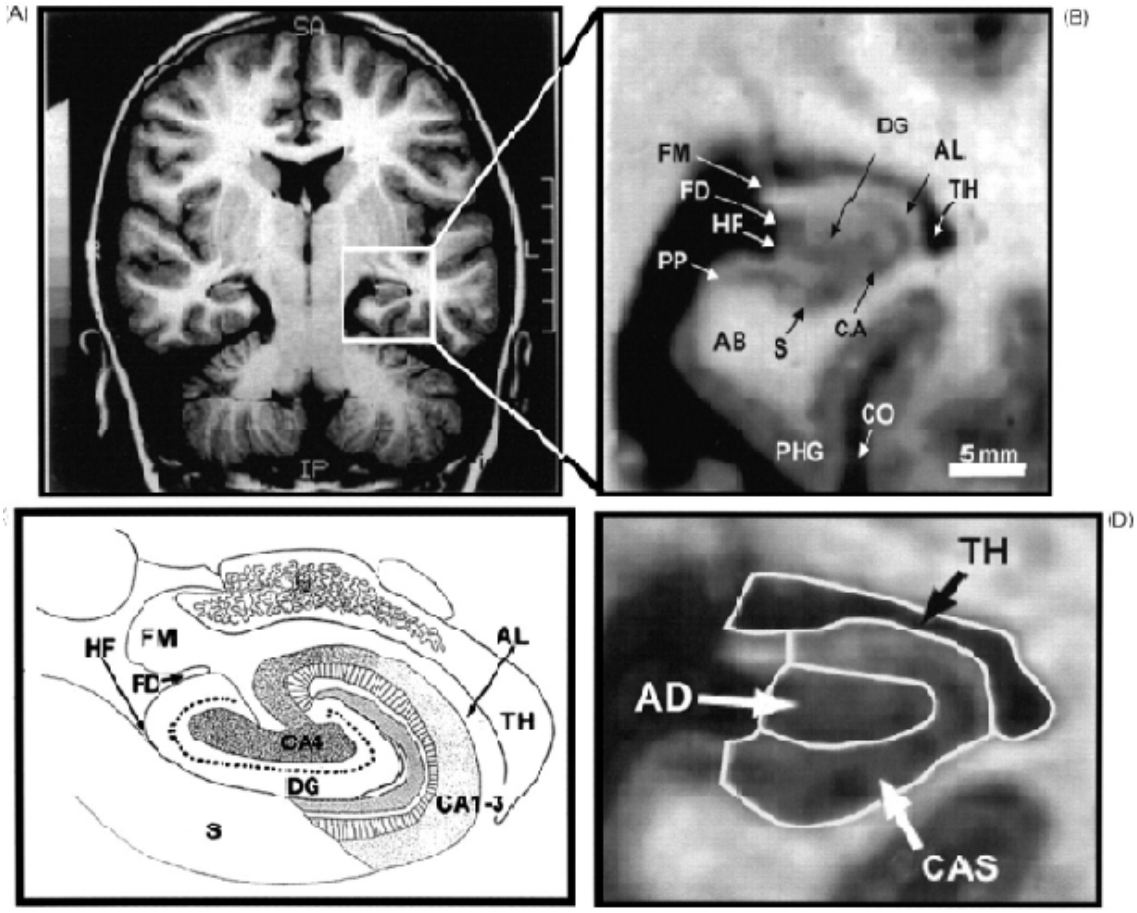

Fig 2.1: The hippocampal formation in the coronal plane.

(Source: Development of the hippocampal formation from 2 to 42 years; MRI evidence of smaller area dentata in autism; Brain 124(7):1317-1324, Osamu Saitoh *et al*.)

(A) T1-weighted coronal image. The left hippocampal formation is indicated with a box. The image is from a 6-year old autistic boy.

(B) Magnified coronal images of left hippocampal formation. AB=angular bundle; AL= alveus; CA=cornu ammonis; CO=collateral sulcus; DG=dentate gyrus; FM= fimbria; FD= fimbriodentate sulcus; HF= hippocampal fissure; PHG = parahippocampal gyrus, PP= perforant path; S= subiculum; TH= temporal horn of the lateral ventricle.

(C) Drawing of the hippocampal formation adapted from Duvernoy (Duvernoy, 1988). The cross –sectional areas of the area dentata, AD (AD; dentate gyrus + CA4) and combined subiculum and CA1-CA3 (CAS = Cornu ammonis subiculum). Abbreviations as in B.

(D) Magnified coronal images of left hippocampal formation with lines depicting anatomical boundaries of AD and CAS. Line thickness was increased for illustrative purpose. Abbreviation as in B and C.

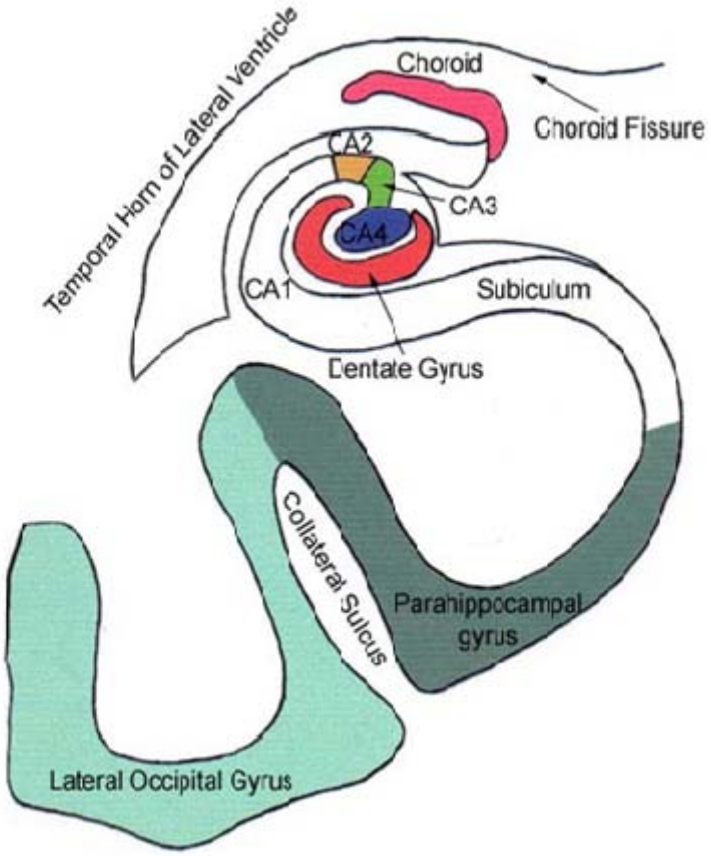

Figure 2.2: Specific anatomic features of hippocampus represent four regions of cornu Ammonis. (Adapted from website http://emedicine.medscape.com/)

2.1.2 Temporal lobe

There are two temporal lobes, one on each side of the brain located at about the level of the ears. Temporal lobe is associated with 3 functions. A small area of that portion of the superior temporal gyrus that lies in the lateral sulcus is the primary auditory cortex. The parahippocampal gyrus and hippocampus are part of limbic system. Temporal lobe is also involved in complex aspect of learning and memory. The left temporal lobe is mainly involved in verbal memory and specific language functions such as the comprehension of words. The right temporal lobe participates in visual memory, musical abilities and in the identification of visual objects. The temporal lobes rest on top of and are connected to the limbic system, which is considered the seat of raw emotions. Temporal lobe damage most often occurs in cases of traumatic brain injury, stroke, and encephalitis, but these symptoms may occur following any neurologic condition that leads to damage within the temporal lobes or their connections with other parts of the brain.

The temporal lobe extends superiorly to the lateral sulcus and the line forming the inferior boundary of the parietal lobe. Posteriorly it extends to the line connecting the top of the parietoocipital sulcus and the preoccipital notch. For the medial surface, its posterior boundary is an imaginary line from the preoccipital notch to the splenium of the corpus callosum.

The human temporal lobe is divided into five gyri and sulci (Bigler, Andersob *et al*. 2002). The five gyri are the superior, middle, inferior, fusiform and parahippocampal gyri. The five sulci are the superior, middle, inferior and rhinal sulci, with the sylvian fissure defining the CSF space dorsal to the superior temporal gyrus.

The temporal horn is formed as longitudinal and downward extension of the lateral ventricular system that is centrally located in the temporal lobe. In the floor of the temporal horn sits the hippocampus. Since hippocampal input is provided predominantly via the fusiform and parahippocampal gyri, changes in these gyri may provide additional information about the intergrity of important temporal-limbic areas of the brain.

Main blood supply to the temporal lobe is middle cerebral artery. It arises from internal carotid artery and continues into the lateral sulcus where it branches and projects to many parts of the lateral cerebral cortex. The artery extends from the sphenoidal segment of the MCA via the operculum inferior surface and supplies the polar and anterior lateral portion of the temporal lobe (temporopolar portion). For the anterior temporal region, this artery extends in the similar fashion with the temporopolar and vascularises the same regions. The artery extends from the Sylvian fissure opposite to the inferior frontal gyrus and supplies the superior and middle portion of the middle temporal lobe. The middle cerebral artery branches extends out and away from the operculum and turns in a step-wise manner first inferiorly then posteriorly into the superior temporal sulcus then to the middle temporal sulcus. This vessel supplies the posterior portion of the temporal lobe and is the origin of several perforating arteries that irrigate the insula. The medial and inferior surface of temporal lobe is supply by posterior cerebral artery.

2.2 Imaging of hippocampus and temporal lobe

Magnetic resonance imaging has demonstrated abnormalities of brain structures, particularly of the temporal lobes and hippocampus. Differences in MRI magnet field strength and slice thickness values might differentially contribute to volumetric asymmetry estimates (Pedraza, Bowers *et al.* 2004). The MR imaging of hippocampus is best performed in a slightly oblique coronal plane, perpendicular to the long axis of hippocampus (Atlas, 2009).

The use of different protocols for measuring the volume of the hippocampal formation led to important variations in the absolute values of the calculated volumes. For both hippocampus, there were significant differences of mean volume between acquisition not perpendicular to axis of the hippocampal formation and on section obtained from coronal 3-D acquisition perpendicular to axis of the hippocampal formation obtained with the patient's head tilted backward (Hasboun, Chantome *et al.* 1996).

Coronal, T1- weighted, three dimensional volume gradient echo is optimal for quantitative volumetry, whereas high-resolution fast spin echo and inversion recovery sequences are important for depiction of hippocampal architecture. Conventional or fast spin echo T2-weighted acquisition is sensitive for assessing hippocampal signal changes and for detecting focal abnormalities in the rest of the brain. FLAIR may provide better T2-weighted signal detection (Jack, Rydberg *et al.* 1996) . Gadolinium-DTPA does not appear to increase the diagnostic yield of MRI in the presurgical evaluation of patients with partial epilepsy if the unenhanced MRIs are normal. (Gregory D. Cascino, Kathryn A. Hirschorn *et al.* 1989).

Current methods of measuring hippocampal volume require manually tracing of the boundary of the hippocampus. This method was considered to be the goal standard as compared to the automated methods (Hsu, Schuff *et al*. 2002). A new developed system for a fully automated measurement of segmented brain structures including hippocampus was developed by (Ishii, Soma *et al.* 2006). They used automatic volumetric segmented brain image system (AVSIS) for 15 healthy volunteers and found that each volume measure by AVSIS and semiautomatic method were correlated with the measurement by manual method. However, the system cannot be applied to a severely atrophied brain.

In diagnosing bilateral hippocampal atrophy, hippocampal volume and T2 relaxometry are routinely used even without visually appreciable signal changes. Qualitative evaluation of hippocampal volume has been found to marginally increase the sensitivity over visual analysis in detection of hippocampal sclerosis (Jack 1994). Visual inspection of the hippocampus was neither sensitive nor specific for the detection of hippocampal atrophy, which was detectable by volumetric methods (Reutens, Stevens *et al.* 1996). Quantitative evaluation of hippocampal volume has been found to marginally increase the sensitivity over visual analysis in detection of hippocampal sclerosis (Jackson, Berkovic *et al.* 1990).

2.3 Hippocampus and temporal lobe in normal population

The quantitative estimation of the volume of brain structures become an important part of diagnostic procedure, especially when disease causes poorly noticeable macroscopic changes (Jack, Twomey *et al.* 1989). The hippocampus shows fast growth early infancy and remains stable throughout after 2 years old. The volume of the hippocampal formations increased sharply until the age of 2 years, and continues to increase slowly thereafter (Utsunomiya H, T.K *et al.* 1999). In view of that, disease related to hippocampus and temporal lobe will give a significant decrease in volume quantification.

In Asia, there are few studies done for normative volumetric measurement of hippocampus from MR imaging in normal adults. In China, for subjects aged 20 to 60 years, the volume of hippocampal formation range from 2.52 to 3.33cm^3 on the right and 2.40 to 2.98 cm^3 on the left (Zou L, X.J *et al.* 2003). For subjects aged more than 60 years, the volume of hippocampal formation ranged from 2.33 to 2.65 cm^3 on the right and 1.98 to 2.64 cm^3 on the left. They also found that there was no significant difference in the volumes of hippocampal formations in subjects aged less than 60 years. The decrease of the volumes of hippocampal formations was seen in the subject aged 60 years old and above. A study using 1.0T magnetic strength MRI in Hungary showed that mean right and left hippocampal volumes were 2.12 cm^3(0.31) and 2.07 cm^3(0.3) (Horvath K, Kover F *et al*. 2002). This study involved 40 healthy volunteers with age range 19 to 26 years.

Autopsy studies and MRI have shown that there is a decrease in brain volume in individuals over the age of 60 years. The brain regions that mostly affected are the hippocampus and frontal lobe (Anderton 2002). The age-related hippocampal volume reduction was similar to the grey matter reduction, and the hippocampal volume was lateralized, where the right side was greater than left ($p < 0.01$) (Miyahira Y, Yu J *et al.* 2004).

Asymmetrical appearance of both hippocampus can be a normal finding. This has been reported in many studies on healthy volunteers. A study in Portugal found that right-left asymmetry in the volumes of hippocampus and entorhinal cortex was a normal finding (Goncalves-Pereira PM, Olieveira E *et al.* 2006). This study involved 34 healthy volunteers with age ranged 19 to 52 years. However, another study by (Bhatia, Bookheimer *et al.* 1993) has reported a different result. Their study involved 29 normal adults with age range 22 to 47 years old and found no side to side differences in the sizes of the temporal lobes or hippocampus.

Various studies reported different result of both hippocampus and temporal lobe between male and female. A study involved 40 healthy adults showed no significant volume differences between male and female (McHugh TL, S.A *et al.* 2007). Hippocampal volume was also found not to be associated with handedness in men. However, the absolute and normalized hippocampal volume were larger in left-handed women than right-handed women (Anstey KJ, Maller JJ *et al.* 2004). A study in Chinese population by (Zou L, X.J *et al*. 2003) involved 102 normal adults also found that no significant different of hippocampal formation was seen in the sex group.

2.4 Hippocampus and temporal lobe associated with pathological disorder.

2.4.1 Normal aging and traumatic brain injury

Age related changes can cause minimal temporal lobe gyral, hippocampal, temporal horn and white matter atrophy. Trauma produced disproportional white matter loss associated with increased temporal horn and sulcal CSF volumes; it caused substantial hippocampal atrophy, which was related to memory impairment (Bigler, Andersob *et al.* 2002).

Age related shrinkages occur in the medial temporal lobes of healthy adults, with significant hippocampal decline and minimal entorhinal changes. The rate of decline accelerates with age, although the role of pathologic factors in age-related increase of volume loss merits further investigations (Raz, Rodrigue *et al*. 2004).

2.4.2 Mesial temporal sclerosis and Temporal lobe epilepsy

Hippocampal volumetric measurement based on magnetic resonance images is important in the diagnosis and treatment of patient with mesial temporal lobe epilepsy. A radiological *in vivo* diagnosis of mesial temporal sclerosis is possible by demonstrating atrophy of the mesial temporal lobe structures on T1-weighted anatomical MR images and increased signal on conventional spin-echo T2 MRI sequences (Jackson, Berkovic *et al.* 1990; Duncan, Bartlett *et al.* 1996).

There is widespread temporal lobe volume loss in patients with intractable mesial temporal lobe epilepsy associated with mesial temporal sclerosis. For whole temporal lobe, the mean volume loss was 13% (Moran, Lemieux *et al.* 2001). In mesial temporal sclerosis, atrophy is due to neuronal death, which , the weight of evidence suggest, is a result of excitotoxicity produced by excessive electrical activity occuring in epileptic changes, rather than the effects of metabolic derangements associated with clinical seizures (Meldrum 1990).

Extrahippocampal volume abnormality were bilateral and occured in both temporal and extratemporal cortical regions in temporal lobe epilepsy, where as hippocampal deficits were related to the side of the epileptogenic focus. Brain abnormality in temporal lobe epilepsy are not limited to epileptogenic region (Marsh, Morrell *et al*. 1997).

2.4.3 Schizophrenia

Structural magnetic resonance imaging of the brain at baseline revealed that people at high risk has smaller mean volume of the amygdala-hippocampal complex than those of healthy participants (Lawrie and Abukmeil 1998). However, when comparing with patient with first-episode schizophrenia, the mean volume of hippocampus was found to be larger in people at high risk of this disease.

Temporal lobe abnormalities are present in schizophrenic patient with first hospitalization. A study by (Hirayasu, Shenton *et al*. 1998) found that low volume of the left posterior superior temporal gyrus gray matter is specific to schizophrenia. The volume reduction of grey matter at this gyrus was progressive and seen in patients with first episode schizophrenia but not in first-episode affective psychosis (Kasai, Shenton *et al*. 2003).

There is unique interaction between gender and the pathophysiological process that lead to altered temporal lobe volume in patients with schizophrenia. Temporal lobe volume on the left was significantly smaller in male subject than male healthy volunteers. Female patients and female volunteers demonstrated no significant difference in temporal lobe volume (Bryant, Buchanan *et al.* 1999).

2.4.4 Major depressive disorder

Previous studies showed smaller hippocampus were found in depressed subjects compared to healthy volunteers. Few studies in depressive disorder found different findings in male and female. Depressed females showed a trend towards a smaller normalised volume of the left hippocampus compared with male depressed subjects (Vakili , Pillay S.S *et al.* 2000). Another study reported smaller hippocampus volume in depressed or healthy female, compared with depressed or healthy males (Steffens DC, Byrum C.E *et al.* 2000). Smaller hippocampus volume in female depressed subjects when compared with female healthy controls are also found in another study (Meena, Eric *et al.* 2000).

Patients with remitted major depression had a 19% smaller volume of the left hippocampus than matched comparison subjects (Bremner, Narayan *et al.* 2000). They also reported both males and females had smaller volumes in the hippocampus. This is the evidence that sex influences the volumetric changes in the hippocampus in depression.

2.4.5 Dementia

Vascular diseases such as ischemia, haemorrhage or anoxia can lead to dementia. This is because vascular disease causes brain damage and consequently impaired mental and cognitive functions. A study by (Laakso, Lehtovirta et al. 2000), revealed that there was significant differences in hippocampal volume of both hemispheres between ischemic vascular dementia and age-matched control group.

Previous study analysed MR-based volume measurement of the whole brain, ventricles, frontal and temporal lobes, hippocampus and amygdale. This study found significant smaller normalized volume of the whole brain, temporal lobe, hippocampus and amygdala in patients with dementia compared with control group (Barber R, Ballard C *et al*. 2000).

Magnetic resonance imaging based volumetric measurements of medial temporal lobe structures can discriminate between normal elderly controls and patients with Alzheimer's disease of moderate to advanced severity. The volume of each medial temporal lobe structures declined with age in patients with AD and is significantly smaller than control subject ($p < .001$) (Clifford R. Jack, Ronal C. Petersen *et al.* 1997).

2.5 Importance of volumetry hippocampus and temporal lobe.

Mean difference (95% confidence interval) between right and left temporal lobe volume was 7 cm^3 (6-9 cm^3) (Jack, Gehring *et al.* 1988). Unilateral temporal lobe atrophy, particularly in patients with TLE, should be interpreted from MR images with this range of discrepancy in normal left-right size in mind.

Right-left asymmetry in the volume of temporal lobe and hippocampal formation was a normal finding (Jay N, A *et al.* 1996). Unilateral atrophic of hippocampus and temporal lobes can be identified by side-to-side comparison, but bilateral atrophy requires absolute hippocampal and temporal lobes volume assessment in comparison with normative value available.

2.6 Method of segmentation

MRI uses magnetic fields and radio waves to produce high quality three-dimensional images of brain structures without use of ionizing radiation (X-ray) or radioactive tracer. It is an important research tool where brain of neurological and neuropsychiatric patients can be investigated *in vivo*. The use of data from MR imaging rather than CT scan for volumetric measurement of brain is intrinsically appealing due to the superior soft tissue contrast, multiplanar imaging capability, and absence artifact from dense calvarium achievable with spin-echo MR imaging (Jack, Theodore *et al.* 1995). Accurate and efficient MRI segmentation of hippocampus is still a challenging issue. Although experienced anatomic trace can be reliable, manual segmentation is a time consuming process and may not be feasible for large-scale neuroimaging studies.

For volumetry measurements, segmentation of grey matter, white matter and cerebral fluid space is important because the actual value of the volume depends on how correctly each area is segmented. Manual tracing of hippocampal boundaries is the 'gold standard' method for volumetry.

Manual tracing of the hippocampus to determine volume changes requires extensive rater training and has potential risk of rater bias. There are other methods using semiautomated and automated software for hippocampal volumetry. A study by (Hsu, Schuff *et al*. 2002) was done to compare the ability of automatic and manual hippocampal volumetry in differentiating between normal ageing, cognitive impairment (CI) and AD. They found that the differences in hippocampal volume among normal, CI and AD subjects are determined using both manual and automatic procedure.

3 OBJECTIVES

3.1 General Objectives

To determine the volume of hippocampus and temporal lobe in Malay adult patients with normal MRI brain.

3.2 Specific Objectives

1. To determine the volume of hippocampus and temporal lobe in adult patients aged 20 to 49 years old.
2. To compare the volume of right and left hippocampus in adult patients of different age and sex groups.
3. To determine the correlation between volume of hippocampus and volume of temporal lobe in normal adult.

3.3 Research hypothesis

There is no difference in volume of right and left hippocampus in normal adult patient.

There is no correlation between volume of hippocampus and volume of temporal lobe in normal adult patient.

4 RESEARCH DESIGN AND METHODOLOGY

This was a cross sectional observational study to obtain volume of hippocampus and volume of temporal lobes in normal adult Malay age 20 to 49 years old. The study was conducted from February 2008 until June 2009 at Hospital Universiti Sains Malaysia (HUSM). Ethical clearance was obtained in February 2008.

All the adult patients who underwent MRI brain in HUSM were included in this study, if they fullfilled the inclusion and exclusion criteria. The volunteers were among hospital staff, their friends and relatives, and they were recruited via advertisement done in HUSM. They are eligible for the study if they fulfilled the inclusion and exclusion criteria.

Inclusion criteria

1. Age: 20 to 49 years old
2. Malay ethnicity
3. Normal MRI brain

Exclusion criteria

1. Focal neurological deficit
2. History of psychological illness
3. History of epilepsy
4. Alcohol abuse
5. History of head trauma

4.1 Sample size

For the first objective, calculation of sample size were made based on formula for single mean proportion, using standard deviation (SD) for hippocampus is 0.61 and standard deviation (SD) for temporal lobe is 11.09 (Bhatia, Bookheimer *et al.* 1993). Precision of the study was taken as 0.25 for hippocampus and $5cm^3$ for temporal lobe. Therefore, for above parameter the calculation gives a sample size of 22 patients for hippocampal volume and 18 patients for temporal lobe volumes. Taking the non response rate of 10%, the total sample size will be 24 patients for hippocampus and 20 patients for temporal lobe.

For the second objective, calculation is also done by using PSsoftware DUPPORT using the following parameters: Alpha error was taken as 0.05, Beta error was taken as 0.20 (power of 80%), standard deviation (SD) was 0.5 and detectable differences is 0.2 (Pedraza, Bowers *et al.* 2004). Therefore, for the above parameters the calculation gives a sample size of 51 patients. Taking the non response rate of 10%, the total sample size will be 56 patients.

For the third objective, the calculation is done by using STATA 10 software using following parameter: Alpha was taken as 0.05 (two-tailed), power of 80%, null Rho was taken as 0.00 and alternative Rho was taken as 0.50. Therefore, estimated sample size for Pearson Correlation gives a sample size of 29. Taking the non response rate of 10%, the total sample size will be 32 patients.

4.2 Methodology

All brain MRI examination was performed using a Signa Horizon LX 1.0 Tesla from the General Electric Company. The MRI examinations follow the MRI protocol for epilepsy surgery that has been developed in our department (Table 4.1). Scout images were obtained to ensure proper positioning of the patient's head. A preliminary sagittal T1-weighted sequence performed. Based on this sagittal images, a coronal oblique scan for the temporal lobe were obtained perpendicular to long axis of the hippocampus, to include all the hippocampal area and whole temporal lobe (Fig 4.1). It starts from the most anterior part of the temporal lobe, extends posteriorly to the end of sylvian fissure.

The sequences had the following parameters; IRT1-weighted: TR of 2000, TE of 15.0 and field of view was 20 x 20, T2-weighted: TR of 4020, TE of 80.0, field of view was 20 x 20, FLAIR: TR of 9000, TE of 147.0 and field of view was 20 x 20. These parameters were found to give the best resolution which enabled differentiation of hippocampal complex structure from the adjacent white matter and cerebrospinal fluid surrounding it (Fig 4.2). No contrast given if there was no lesion found. A scan for the whole brain also performed to exclude any concomittant lesion in the brain parenchyma.

After completion of all sequences, the images obtained were reviewed to confirm that all the region of interest was included. The acceptibility of the images was also evaluated prior to discharging patient from the MRI suite.

Table 4.1: MRI protocol for Epilepsy Surgery

Whole brain:
T1WI axial, 3mm thickness, no gap, zero gantry
T2WI axial, 3mm thickness, no gap, zero gantry
Temporal lobe:
T2WI coronal, 4mm thickness, 1mm gap
FLAIR coronal, 4mm thickness, 1mm gap
T1WI (inversion recovery), 4mm thickness, 1mm gap
SPGR coronal, 2mm thickness, 1mm gap
(The coronal plane must be perpendicular to the long axis of the hippocampus)
** contrast study should be performed in vascular or tumoural lesion

In this study we used images with slice thickness of 4 mm with 1 mm gap in coronal images. This is because there was no significant difference in the hippocampal volume measurement when the examination performed with the slice thickness of 1mm, 3mm and 5mm as showed in previous study by (Laakso, Juottonen *et al.* 1997). Thicker slice thickness means a shorter duration of scanning per sequences. This was particularly important to shorten the time of examination therefore keeping the trauma of MRI's experience to its least. Other than that, this slice thickness is also closely related with gross anatomy. Anatomic details of hippocampus shown on T1-weighted images (5-mm thick sections) correlates closely with anatomic findings in cadaveric section (Naidich., Daniels. *et al*. 1987).