MR VOLUMETRY OF INTRACRANIAL AND BRAIN VOLUME IN NORMAL ADULT POPULATION AGED 40 YEARS OLD AND ABOVE

DR. MUHAMAD ZABIDI BIN AHMAD

Dissertation Submitted in Partial Fulfillment of the Requirement for the Degree of Master of Medicine (RADIOLOGY)

2014

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ABBREVIATIONS

BIR	Brain to Intracranial Volume Ratio
BV	Brain Volume
CI	Confidence Interval
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
FDA	United States Food and Drug Administration
GNU	GNU's Not Unix! (a recursive acronym)
IBM	International Business Machines Corporation
ICD	International Classification of Diseases
ITK	Insight Segmentation and Registration Toolkit
IV	Intracranial Volume
MRI	Magnetic Resonance Imaging
PACS	Picture Archiving and Communications System
PET-CT	Positron Emission Tomography and Computed Tomography
RU	Research University
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences, later Statistical Product and Service Solutions
T1WI	T1 Weighted Images
T2WI	T2 Weighted Images
VTK	Visualization ToolKit

ABSTRAK

Tajuk: Pengukuran isipadu intrakranial dan otak menggunakan pengimejan MRI di kalangan orang dewasa berumur 40 tahun ke atas

Pendahuluan:

Magnetic Resonance Imaging (MRI) telah memangkinkan dengan ketara banyak kajian yang melibatkan otak dengan lebih ramai penyelidik mengkaji bukan sahaja aspek anatomi dan struktur otak, tetapi juga aspek fungsi kerana diskriminasi tisu lembut baik (Kennedy *et al*., 2003). MRI juga membolehkan penyelidik untuk mengkaji perubahan yang melibatkan jumlah isipadu intrakranial, otak dan isipadu ruangan dalam otak, memberikan data-data penting mengenai perubahan normal otak manusia dan penyakit degeneratif tertentu atau penyakit psikiatri (Ohnishi *et al*, 2001; Peters, 2006).

Isipadu intrakranial dan otak boleh diperolehi daripada MRI. Secara umum isipadu intrakranial boleh diukur secara manual daripada imej T1.

Kajian ini bertujuan untuk mengkaji isipadu intrakranial, isipadu otak dan nisbah isipadu intrakranial kepada isipadu otak dalam subjek yang sihat. Data yang diperolehi kemudiannya boleh digunakan dalam meramalkan perubahan degeneratif pada pesakit dengan penyakit pesakit dengan penyakit mental seperti skizofrenia dan gangguan bipolar atau Alzheimer.

Objektif:

Untuk menentukan isipadu intrakranial dan isipadu otak yang normal dalam kalangan Melayu dewasa yang sihat yang berumur 40 tahun dan ke atas.

Tatacara:

Ini adalah satu kajian keratan rentas yang melibatkan 58 subjek yang menjalani MRI di bawah penyelidikan sebelumnya. Umur subjek adalah antara 41 hingga 77 tahun.

MRI dilakukan dengan menggunakan pengimbas Signa Horison LX 1.0 Tesla oleh General Electric. Imej MRI diperolehi dalam keratan sagital dan paksi T1 dengan ketebalan 5milimeter dengan jurang 2milimeter. Isipadu intrakranial dan otak diukur secara terapan manual menggunakan kaedah selangan antara keratan. Purata (isipadu sisihan) daripada isipadu intrakranial dan isipadu otak telah dikira dan dianalisis menggunakan IBM SPSS versi 20.

Keputusan:

Purata (isipadu sisihan) isipadu intrakranial adalah 1397.06 cm^3 (132.51 cm^3) bagi semua subjek. Purata isipadu intrakranial bagi subjek lelaki adalah 1496.12 cm^3 (100.08 cm^3) dan subjek wanita adalah 1310.79 cm^3 (90.34 cm^3).

Purata isipadu otak bagi keseluruhan subjek adalah 1245.29 cm^3 (125.34 cm^3). Purata isipadu otak bagi keseluruhan subjek lelaki adalah 1338.05 cm^3 (91.96 cm^3) dan subjek wanita adalah 1164.49 cm^3 (89.61 cm^3).

Purata nisbah isipadu keseluruhan intrakranial kepada isipadu otak untuk semua subjek adalah 0.8911 (0.0245). Purata nisbah isipadu keseluruhan intracranial kepada isipadu otak bagi subjek lelaki adalah 0.8946 (0.0276) dan subjek wanita adalah 0.8881 (0.0214).

Tidak ada perbezaan yang signifikan daripada purata isipadu intrakranial, purata isipadu otak dan nisbah isipadu otak kepada isipadu intrakranial antara subjek lelaki dan perempuan. Terdapat korelasi yang signifikan antara nisbah

isipadu otak kepada isipadu intrakranial dengan umur. Korelasi yang signifikan dilihat antara jumlah purata intrakranial dengan umur dan jantina. Jantina adalah satu faktor yang penting yang berkaitan dengan purata jumlah isipadu otak.

Kesimpulan:

Kami telah memperolehi data normatif untuk anggaran dan meramalkan perubahan degeneratif masa depan di kalangan penduduk Melayu. Keputusan ini paling bermanfaat untuk pesakit yang mengalami kemerosotan kognitif ringan atau yang baru didiagnosis gangguan neuropsikiatri seperti penyakit Alzheimer atau skizofrenia. Walaubagaimanapun, terdapat beberapa limitasi di dalam kajian ini seperti jumlah subjek yang sedikit dalam kalangan satu bangsa, terapan manual berserta penggunaan MRI 1 Tesla yang mungkin menyebabkan penggunaan hasil kajian yang terhad.

ABSTRACT

Topic: MR volumetry of intracranial and brain volume in normal adult population aged 40 years old and above.

Introduction:

Magnetic Resonance Imaging (MRI) has significantly accelerated many studies involving the brain with more researchers looking into not only anatomy and structural aspects of the brain, but also functional aspect due to excellent soft tissue discrimination (Kennedy *et al.*, 2003). MRI also enables researchers to study the changes involving intracranial volume, brain volume and compartmental volumes, giving valuable data regarding the normal human brain morphological changes and in certain degenerative diseases or psychiatric illnesses (Ohnishi *et al.*, 2001; Peters, 2006).

Total intracranial volume and brain volume can be obtained from MRI. In general intracranial volume can be measured manually from T1-weighted images.

This study aimed to study the intracranial volume, brain volume and intracranial volume to brain volume ratio in the normal healthy subjects. Data obtained can later be used in predicting degenerative changes in patients with Alzheimer's disease or patients with psychiatric illnesses such as schizophrenia and bipolar disorder.

Objectives:

To determine the intracranial volume and brain volume in normal healthy adult Malay aged 40 years old and above.

Materials and methods:

This was a cross sectional study involving 58 subjects who underwent MRI under previous research. The age of the subjects ranged from 41 to 77 years old.

MRI was performed using Signa Horison LX 1.0 Tesla scanner by General Electric. MRI images were obtained in T1 sagittal and axial sections with 5milimeter thickness with 2 milimeter gap. Intracranial and brain volumes were measured using manually traced alternate slice volumetry method. The mean (SD) of total intracranial volume and total brain volume were calculated and analysed using IBM SPSS version 20.

Results:

Mean (SD) of intracranial volume was 1397.06 cm^3 (132.51 cm^3) for all subjects. The mean intracranial volume for male subjects was 1496.12 cm^3 (100.08 cm^3) and female subjects was 1310.79 cm^3 (90.34 cm^3).

The mean brain volume for all subjects was 1245.29 cm^3 (125.34 cm^3). The mean brain volume for the male subjects was 1338.05 cm^3 (91.96 cm^3) and female subjects was 1164.49 cm^3 (89.61 cm^3).

Mean brain to intracranial volume ratio for all subjects were 0.8911 (0.0245). Mean brain to intracranial volume ratio for male subjects was 0.8946 (0.0276) and female subjects was 0.8881 (0.0214).

There was no significant difference of mean intracranial volume, mean brain volume and intracranial volume to brain volume ratio between male and female subjects. There was significant correlation between brain to intracranial

volume ratio with age. Significant correlation was seen between mean intracranial volume with age and sex, and mean brain volume with sex.

Conclusion:

We have obtained a normative data for estimation and predicting future degenerative events in Malay population. The results gathered would be most beneficial for those patients who are experiencing mild cognitive impairment or newly diagnosed neuropsychiatric disorders such as Alzheimer's disease or schizophrenia. Limitations such as small sample size within single ethnicity, manual tracing method with 1 Tesla MRI machines would however limit the usage of this data.

ABSTRACT

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Associate Professor Dr. Mohd. Shafie Abdullah (Supervisor)

Dr. Win Mar@Salmah Jalaluddin (Co-Supervisor)

1 Introduction

The human brain is an important part of central nervous system which consists of cerebrum, cerebellum and midbrain. Many studies have been published in regards to brain anatomy, physiology and function. With the advent of medical imaging in the last 50 years, the study of the brain has become more intense and detailed, with more researchers looking into more detailed and specific aspects of the human brain (Buckner *et al.*, 2008).

For 100 years prior to the invention of cross sectional imaging such as Computed Tomography (CT), the study of the human brain largely conducted through autopsy (Miller *et al.*, 1980; Hwang *et al.*, 1995). With CT scan, the study of the human brain has accelerated and became more detailed. Researchers such as Abbott *et al.* (2000) and Hahn *et al.* (1984) studied the intracranial cavity using CT scan, although most of their studies involved paediatric population. Nevertheless, with cross sectional imaging, many novel measurement and volumetry techniques were developed and utilized.

The arrival of Magnetic Resonance Imaging (MRI) has significantly accelerated many studies involving the brain with more researchers looking into not only anatomy and structural aspects of the brain, but also functional aspect. This is partly because MRI allows excellent soft tissue discrimination (Kennedy *et al.*, 2003). MRI also enables researchers to study the changes involving intracranial volume, brain volume and compartmental volumes, giving valuable data regarding the normal human brain morphological changes and in certain

degenerative diseases or psychiatric illnesses (Ohnishi *et al.*, 2001; Peters, 2006).

Intracranial volume measurement has long been studied by researchers because of its usefulness in recognizing changes within the human brain. Intracranial volume is defined as the total volume within the cranial space, which includes the brain, meninges and cerebrospinal fluid. Previously data gathered from autopsies considered to be the gold standard in measuring total intracranial volume. However, problems surrounding the autopsy process in regards to presence of concomitant illness, long intervals between death and brain removal and weighing in different conditions may or may not affect the data gathered. MRI as a non-invasive method of study has eliminated inherent difficulties that come with autopsy process, thus making the measurement of brain and its anatomical parts much more accurate.

Intracranial volume measurement provides stable and accurate data in studying and estimating the volumetric changes within the cranium and its contents. Intracranial volume measurement can be used as a predictor to degenerative brain disease in early stages when measured together with total brain volume or ventricular volume, such as in patients with Alzheimer's disease, schizophrenia, bipolar disorders or other conditions such as Huntington's disease (Fox and Freeborough, 1997). It can also be used as a predictor for severity in patients with these conditions (Kruggel, 2006; El-Sayed, 2010; Reite *et al.*, 2010; Giorgio and De Stefano, 2013).

Intracranial volume and brain volume can be obtained from MRI. MRI itself can be performed in various planes such as sagittal and coronal or axial.

Studies showed that there are no differences in intracranial volume measured in T1-weighted or T2-weighted images (Keller and Roberts, 2009). However, in general intracranial volume can be measured manually from T1-weighted images although there are studies being done to compare between automatic and manual measurements (Kennedy *et al.*, 2009).

This study aimed to study the intracranial volume as well as the brain volume in the normal healthy patients to provide normative data about intracranial volume/total brain volume ratio. This data can later be used later in predicting degenerative changes in patients with Alzheimer's disease or patients with psychiatric illnesses such as schizophrenia and bipolar disorder.

2 Literature review

2.1 Intracranial anatomy

The intracranial cavity is a volume enclosed by the frontal, occipital, sphenoid and ethmoid bones with a pair of parietal and temporal bones on its sides. It is occupied by the human brain and its associated vascular supply. In humans, the size and shape of the brain is partly determined by the size and shape of the human skull.

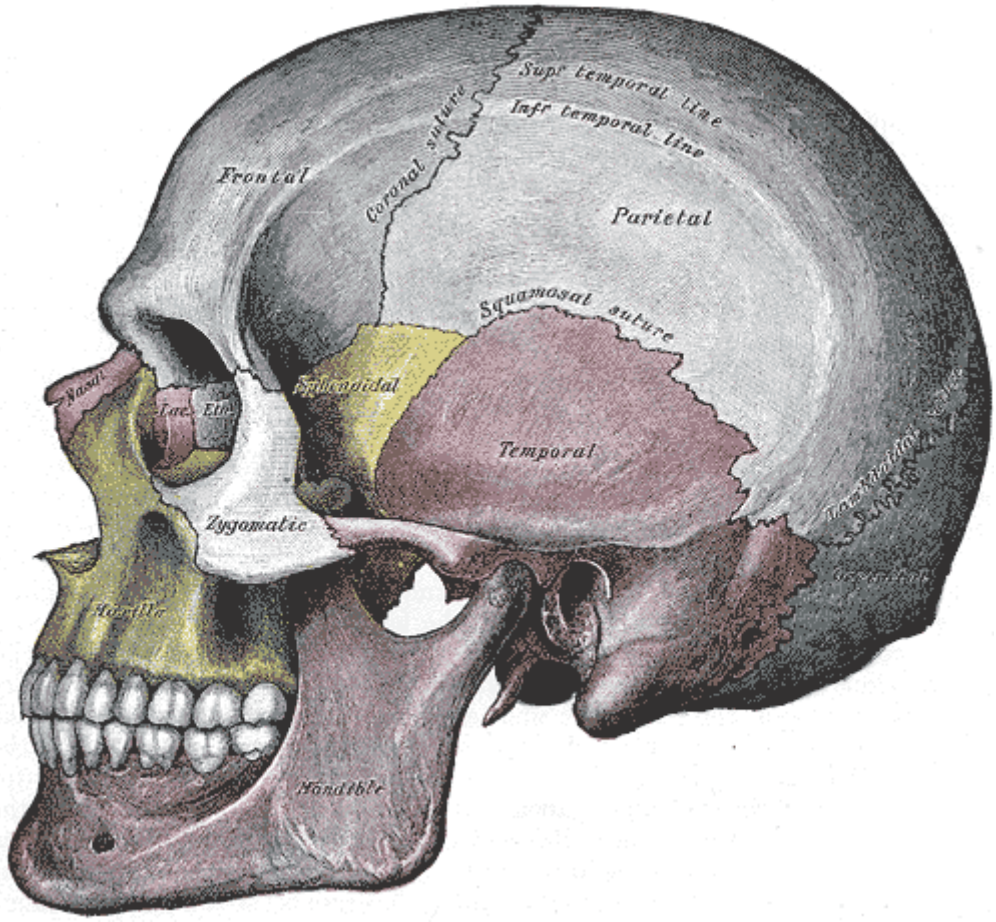

Figure 2.1. Lithograph plate of the human cranium (Adapted from Gray and Lewis (1924))

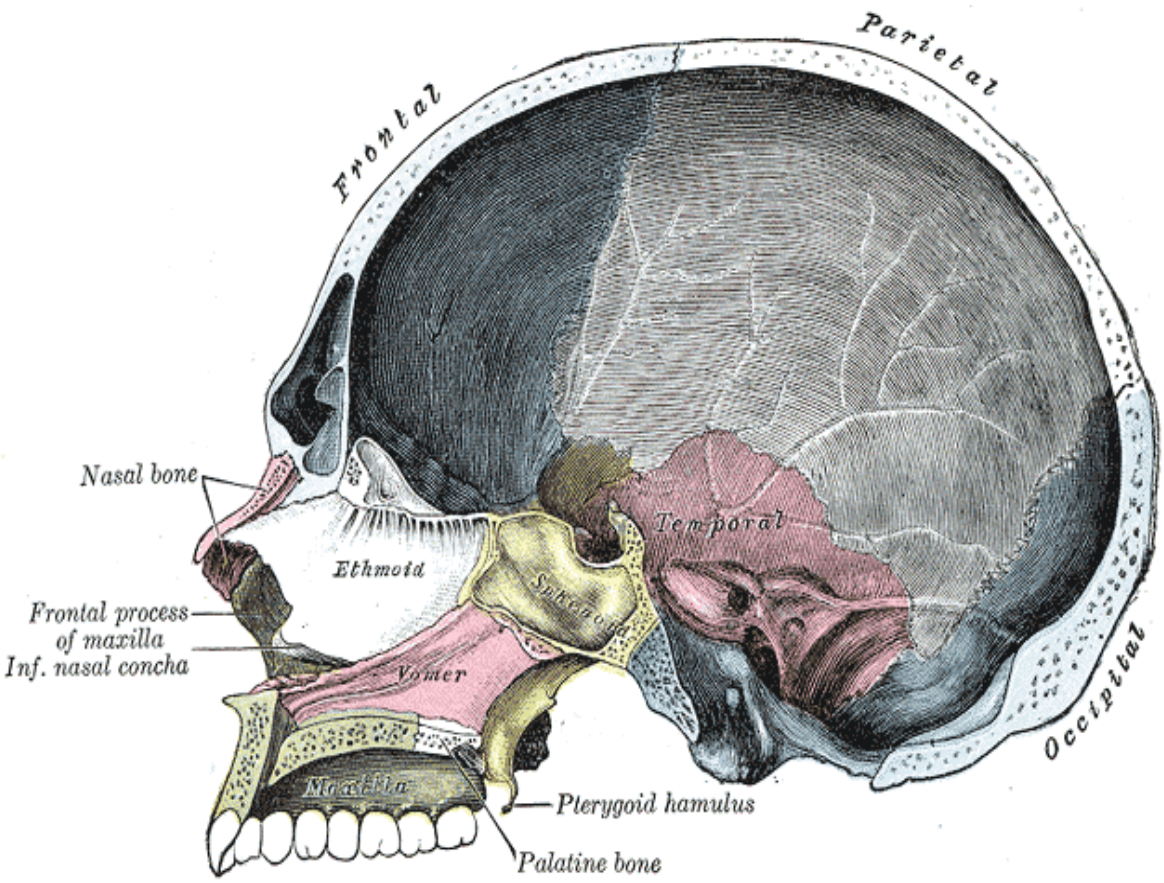

Figure 2.2. Lithograph plate showing the inside of the human cranium (Adapted from Gray and Lewis (1924))

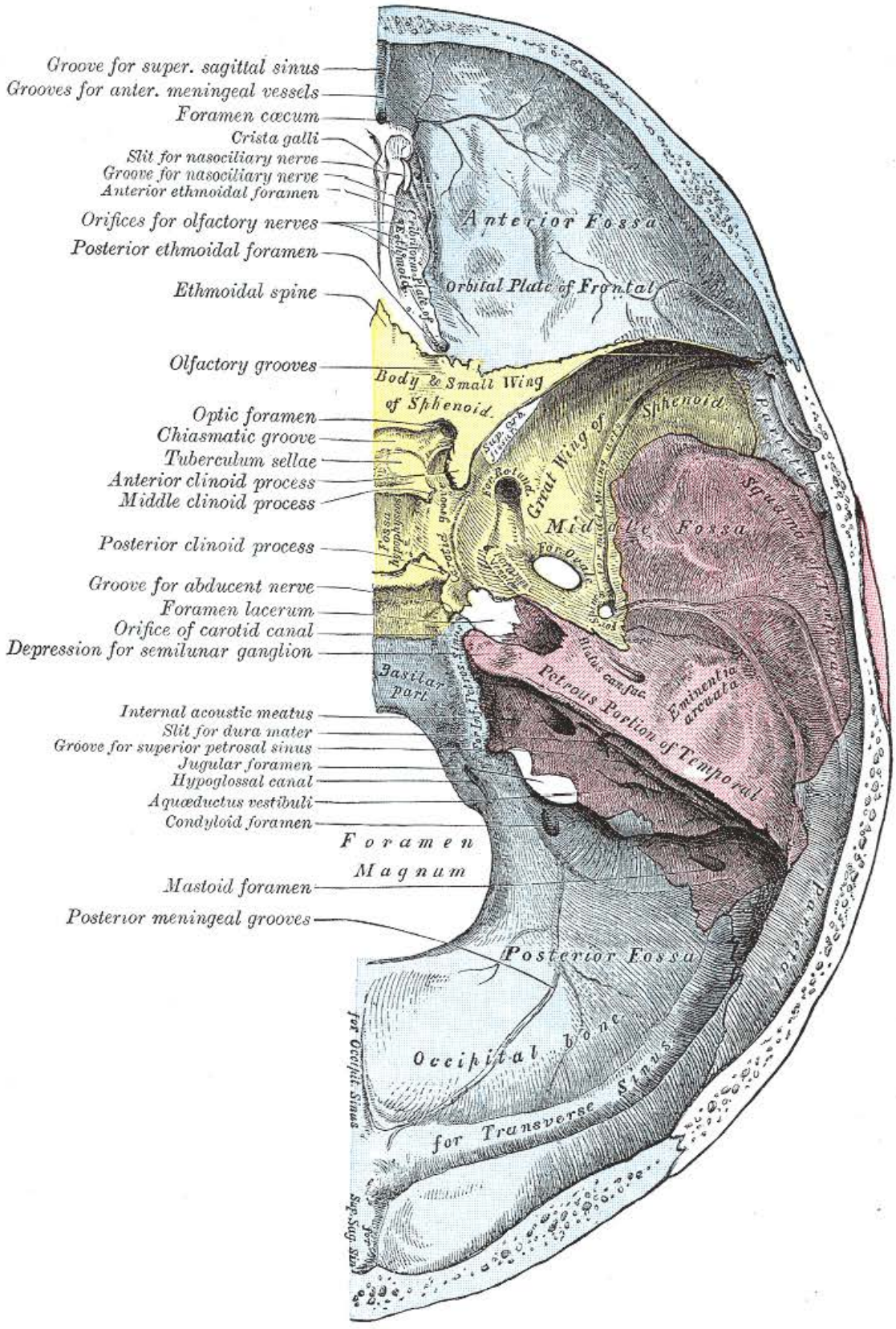

Figure 2.3. Lithograph plate showing the base of the human cranium (Adapted from Gray and Lewis (1924))

The human cranium is consists of neurocranium and viscerocranium. These two different parts are derived from different embryological processes. The viscerocranium is formed by the facial bones while the neurocranium is formed by the skull or cranial vault. These bones are formed and held together by a series of sutures and joints.

Other than containing the brain, the cranium also contains sinus cavities. Sinus cavities are air filled cavities which are lined by the same epithelial cells that lines the airways.

The cranium was developed from endochondral ossification and intramembranous ossification. The bones that support the brain are mostly developed from endochondreal ossification while the skull roof is formed by means of endochondral ossification.

During pregnancy, especially during the first trimester, the geometry of the cranium and its fossae are rapidly changing, thus it is the most important phase for development of any congenital skull defects.

At birth, the bones of the cranium are separated by fontanelles. Fontanelles are regions containing dense connective tissue which are replaced by bone as the child grows older. There are six fontanelles which are frontal, occipital, sphenoid and mastoid.

Cranial cavity is divided into three cranial fossae which are anterior, middle and posterior cranial fossae. Anterior cranial fossa houses the frontal lobes of the brain. Anteriorly, it is bounded by the posterior wall of frontal sinuses. Posteriorly it is bounded by the anterior clinoid process and planum sphenoidale. Bilateral frontal bones form the lateral bounderies. Ethmoid bone

forms the central part of the floor. Cribriform plate is located central to this, in which the olfactory nerve passes. Crista galli is a sharp upward projection of the ethmoid bone in the midline, where the falx cerebri is attached. Foramen cecum lies between the frontal crest and crista galli. This is the site of communication between the draining veins of the nasal cavity and superior sagittal sinus. Sulcus chiasmaticus which houses the optic chiasm sits posteriorly in the midline.

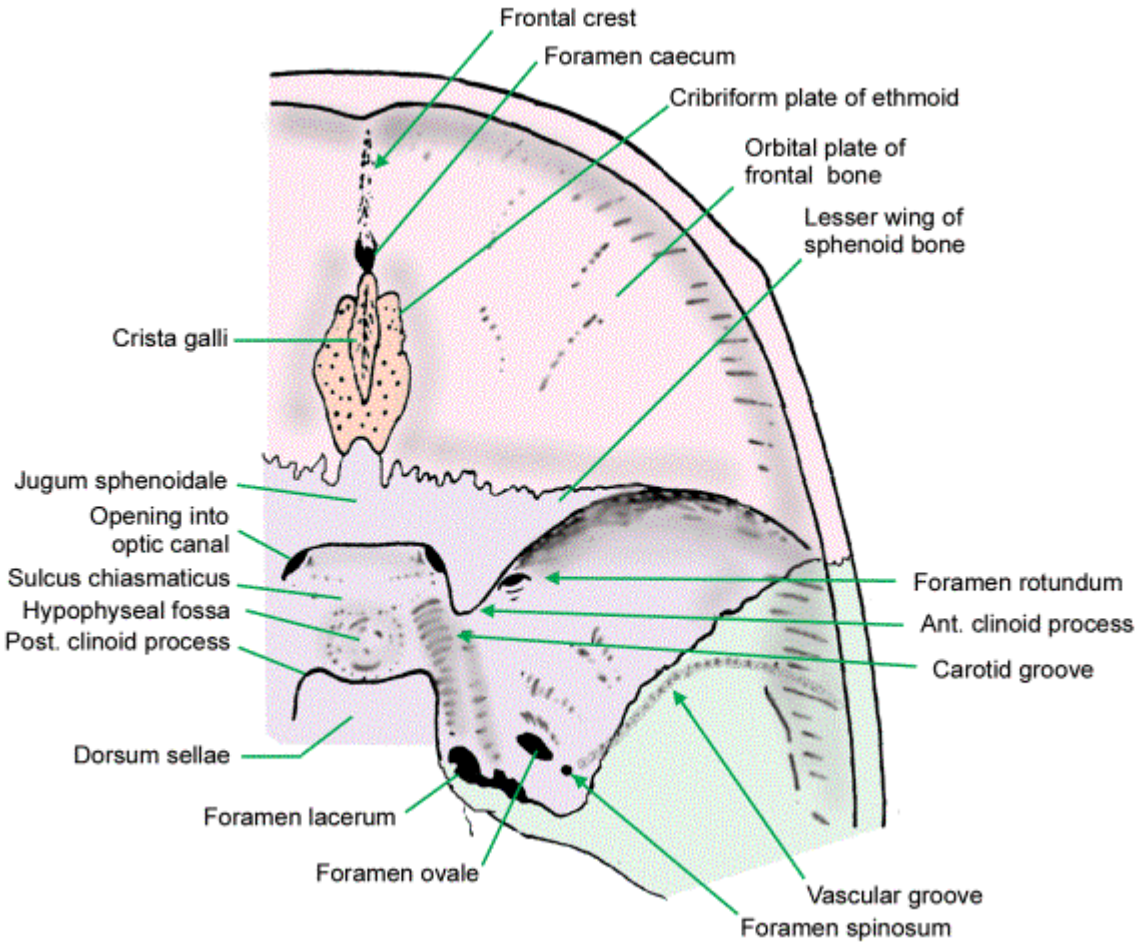

Figure 2.4. Anterior cranial fossa and part of middle cranial fossa (Adapted from Singh (2004))

Middle cranial fossa is located posterior to the anterior cranial fossa and is deeper than the anterior cranial fossa. It is narrow in the middle and widens at the lateral aspects of the skull. Anteriorly it is bounded by the posterior margins of the lesser wing of sphenoid, anterior clinoid process and anterior margin of the chiasmatic groove. Posteriorly it is bounded by superior angles of petrous part of temporal bone and dorsum sellae. Laterally it is bounded by the squamous temporal, sphenoid angle of the temporal bone and greater wing of sphenoid. It houses the temporal lobes of the brain and part of the brainstem.

Posterior cranial fossa is the deepest and the largest of the three cranial fossae. It is formed by the dorsum sellae and clivus of the sphenoid; occipital, petrous and mastoid part of the temporal bone and the mastoid angle of the parietal bone. Posterior cranial fossa houses the cerebellum, pons and medulla oblangata. Foramen magnum is situated on the floor of the posterior cranial fossa.

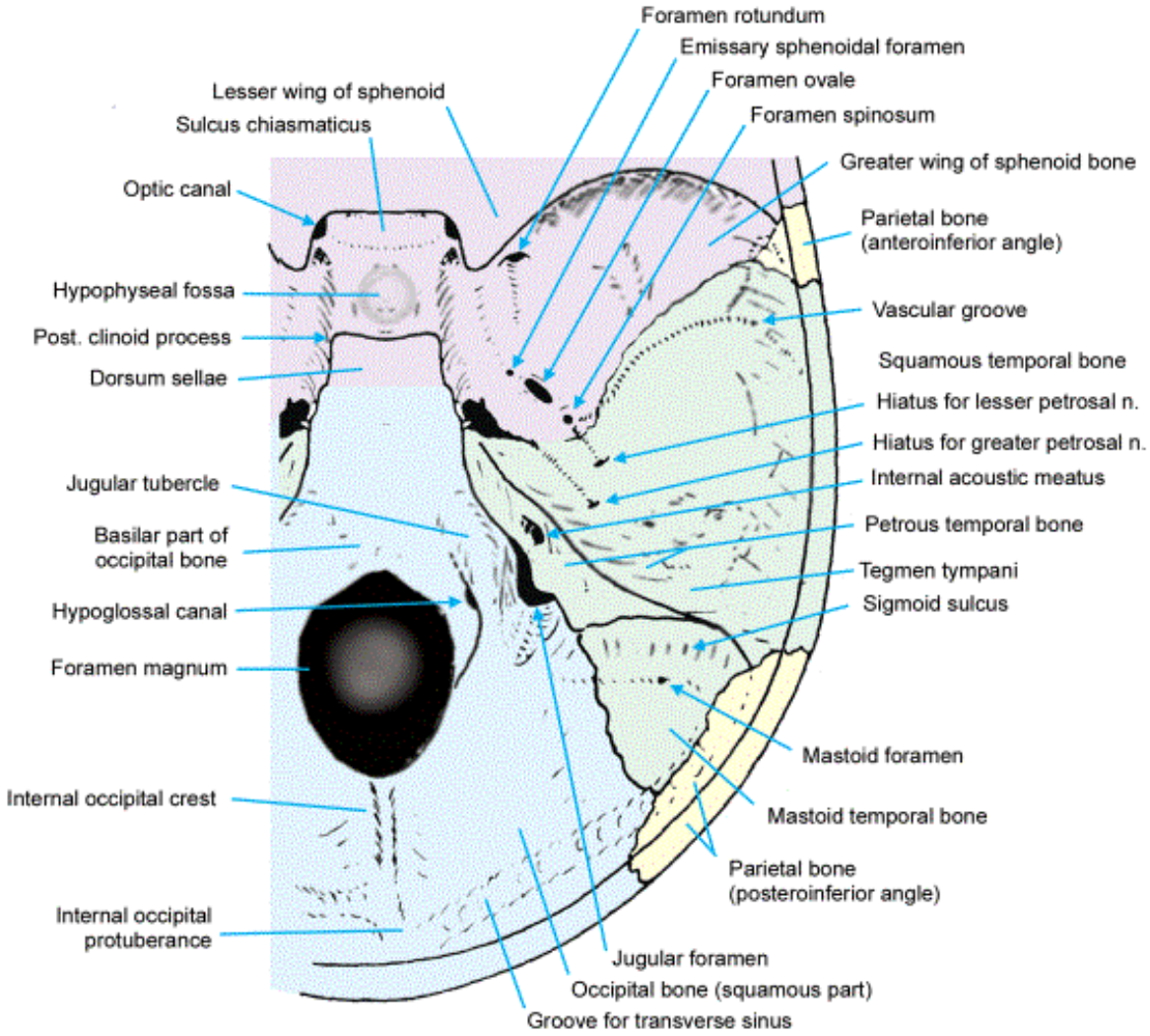

Figure 2.5. Middle and posterior cranial fossa (Adapted from Singh (2004))

2.2 Brain anatomy and function

The brain is an organ suspended in cerebrospinal fluid with average weight of approximately 1.5 kilograms. Human brain shares similar basic general structures as to other mammals although the ratio of human brain to the body is larger compared to other mammals. The organ is suspended in the cerebrospinal fluid and protected from external elements by skull vault. It is isolated from the rest of the circulation by the blood-brain barrier.

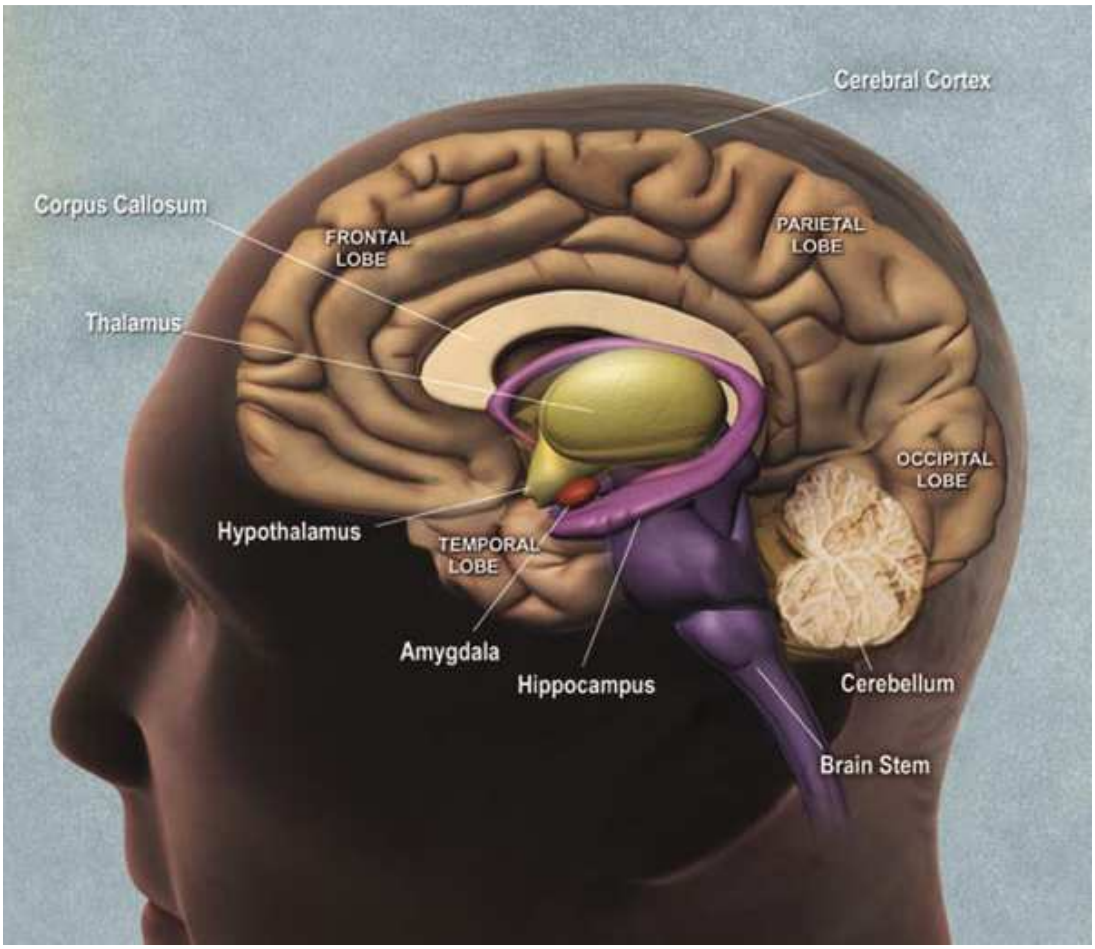

Figure 2.6. Drawing of the human brain (Adapted from Rodgers (2008))

The brain is divided into four lobes which are the frontal, parietal, temporal and occipital lobes. Each of this lobes consist of numerous cortical folds, each control various functions such as memory, motor, sensory, language and vision. The lobes names are derived from the skull bones that overlies them rather than being an actual lobe by itself. The frontal lobe controls behaviour, attention and other executive functions. The parietal lobe controls somatosensation, hearing, language and spatial cognition. The temporal lobe controls auditory and visual memories, language and some speech and hearing. The occipital lobe controls visual, visual-spatial cognition, colour and movement.

The largest part of the brain is the cerebrum which is located superior to the brain stem. It contains and covered by numerous convoluted cortical layers. The brainstem is located inferior to the cerebrum while the cerebellum is located posterior to the brainstem.

Cerebral cortex is a dominant feature of the human brain. It is essentially a sheet of neural tissue, folded allowing large surface area to fit inside a cranium. Total surface area of each cerebral hemisphere is estimated to approximately 1.3 square feet (Toro *et al.*, 2008).

The brain is firmly surrounded by three layers of membranes or meninges, which protects the brain from injury and infection. The three layers are dura mater, arachnoid mater and pia mater.

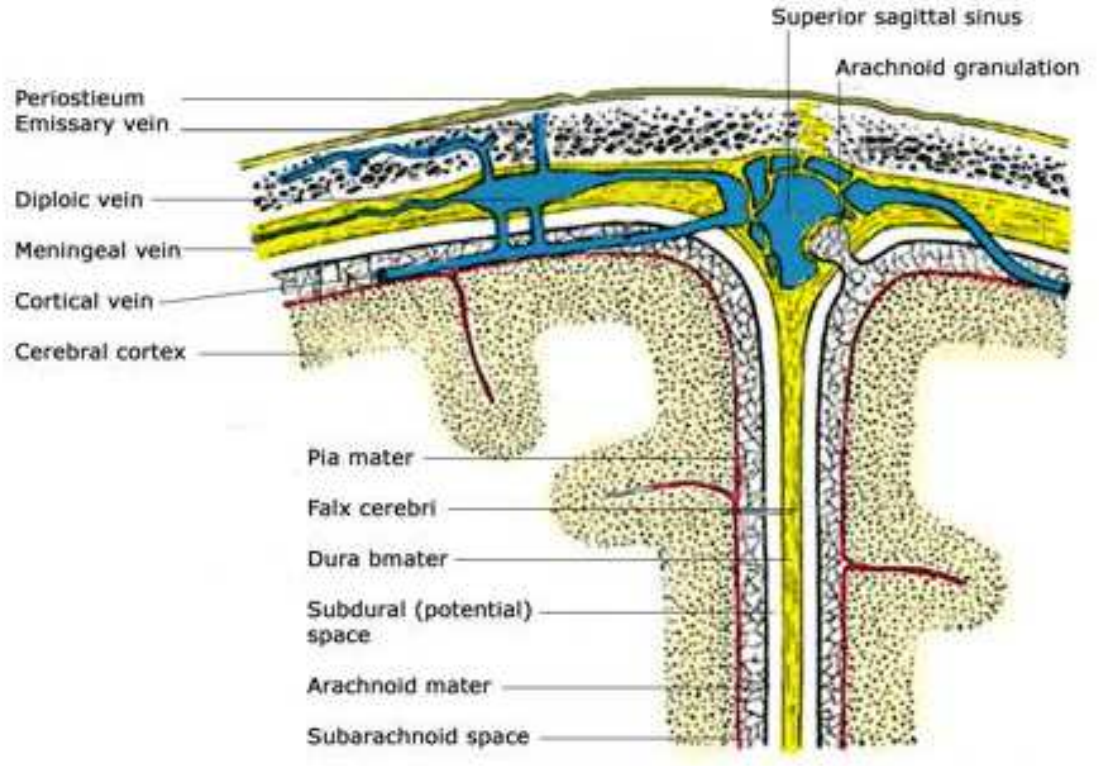

Figure 2.7. Meningeal layers of the brain (Adapted from Knipe (2013))

Dura mater is also known as pachymeninx while the arachnoid mater and pia mater are collectively referred to as lepromeninges. Dura mater is a thick membrane derived from the mesoderm. It surrounds the brain and spinal cord, keeping the cerebrospinal fluid within. It is pierced by the cranial nerves, the internal carotid arteries and vertebral arteries. Intracranially it is formed two layers which are the outer endosteal layer that is continuous via the sutures and foraminae with the periosteum; and inner meningeal layer, which continuous inferiorly the theca of the spinal cord.

Arachnoid mater is the second layer of the meninges, interposed between the more superficial dura mater and deeper pia mater. It is separated from the pia mater by subarachnoid space in which the cerebrospinal fluid

flows. Arachnoid mater loosely surrounds the brain and extends to the superior surface of pituitary fossa but does not envelope the pituitary itself.

Pia mater is a thin fibrous tissue, impermeable to fluid and extends into the sulci. It is a translucent, mesh like meningeal cover, spanning nearly the entire surface of the brain. It is highly vascular layer with blood vessels supplying the brain as well as protecting the blood vessels and encloses the venous sinuses.

2.3 Brain Development

During gastrulation cells will migrate into the interior part of the embryo and later forms three germinal layers. These germinal layers are endoderm, mesoderm and ectoderm in which endoderm giving rise to skin and nervous system, endoderm gives rise to gastrointestinal system while mesoderm gives rise to the rest of the organs.

Post gastrulation, mesoderm forms the notochord in which during the third week of gestation, notochord send signals to the ectoderm and becoming neuroectoderm. This forms the neural plate which is the origin of the central nervous system. Neural plate then folds to form neural groove and later folds to form neural tube. The ventral part of this tube is called the basal plate while dorsal part is called the alar plate.

Later in fourth week of gestation, superior part of the neural tube flexes at the level of mesencephalon. Procencephalon forms superior to the mesencephalon while rhombocephalon forms inferior to mesencephalon. At the basal plate of procencephalon, the optical vessels form.

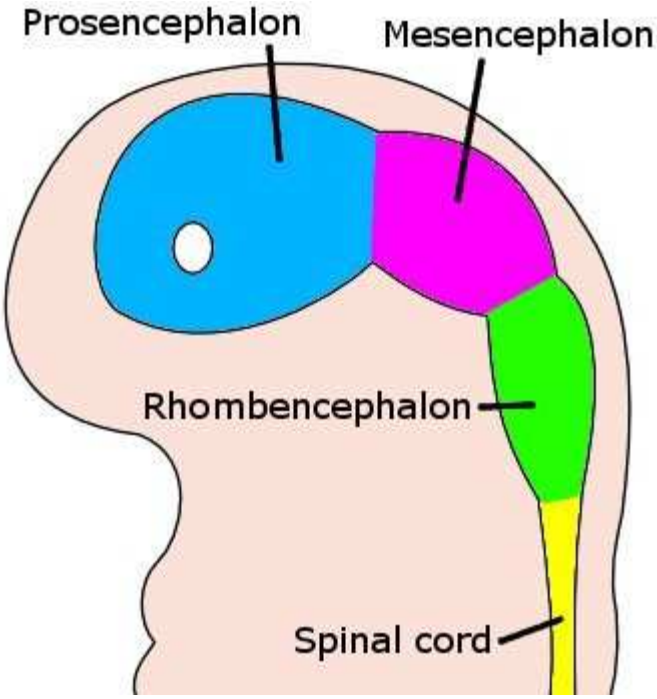

Figure 2.8. The human embryo's brain at four weeks gestation (Adapted from Wikipedia (2013))

During the fifth week of gestation, the basal plate of procencephalon becomes the diencephalon. The alar plate of procencephalon then extends to form the telencephalon. Brain stem of the embryo consists of diencephalon, rhombocephalon and mesencephalon and continues to flex during this time.

Rhombocephalon then folds posteriorly causing flaring of the alar plate forming the fourth ventricle. Upper part of the rhombocephalon forms pons and cerebellum while lower part of rhombocephalon forms the medulla oblongata.

At nine weeks and later, there is expansion of cerebral hemispheres due to formation and differentiation of neurons and glials, and later forming brain lobes, sulci and gyri (Shiota, 2008).

2.4 Brain volume in normal aging process

Aging has shown to have effects on the cells, vasculature, molecules, gross morphology and cognition (Peters, 2006). Therefore, aging process is shown to have similar effects to the brain as well as the rest of the body. Many recent studies show age related decrease in brain size as well as expansion of the cerebral ventricles that being shown to expand as a function of age. Although regional volume decrease is not uniform throughout the whole brain (Trollor and Valenzuela, 2001), it is estimated that the brain shows decline in volume and/or weight around 2-5% per decade after the age of 40 years old (Peters, 2006).

Some studies also had shown almost similar findings, showing that the brain shrinks at rates up to 1% each year. Literature described that the shrinking of grey matter is reported to be originated from neuronal cell death as well as decline in neuronal volume. Rate of reduction of brain volume also showed marked increase in age more than 70 years old (Scahill *et al.*, 2003).

Aging brain also widely seen as a cause for reduced or impaired memory and other cognitive function. For example impairment in episodic and semantic memory which is commonly seen in Alzheimer's disease (Parkin, 1983). Memory impairment and aging are closely related to two neurotransmitters – dopamine and serotonin as well as other hormonal influence. These two factors are related not only to memory but to aging process as well.

Post mortem and in vivo imaging studies have suggested that prefrontal, entorlinal and temporal cortex are the most severely affected regions of the brain in regards to aging (Haug, 1985). While these changes are physiologic

and age related, studies suggested that patients with Alzheimer's disease have shown to have great significant difference in morphology of the brain (Ohnishi *et al.*, 2001). This indicated that not only there are differences in brain morphology, but also there are changes in brain volume as well as a whole.

2.5 Disorders affecting the brain volume

There are a few diseases which affects the brain and its morphology. Among these, Alzheimer's disease, schizophrenia and bipolar disorder has become the subject for research of brain morphology. Many of the studies looked into the general brain morphology changes while some looked into the possibility of using findings from studies of brain morphology of these patients to predict future treatment strategies as well as creating new disease altering drugs.

Alzheimer's disease (ICD 10:G30) (Alzheimer, 1991) is a disease which affects memory and is a common form of dementia. Named after a German neuropathologist Alois Alzheimer in 1906, the disease natural history is that it progresses and worsens, eventually leading to death.

Alzheimer's disease usually affects people with age more than 60 years old. However, the presentation may vary in different patients. Most patients with early Alzheimer's disease showed impairment in recalling recent events. Diagnosis of Alzheimer's disease usually confirmed with certain memory related tests that evaluate behaviour and thinking skills. On imaging, MRI is the most preferred method to exclude any other organic causes as well as to see the progression or changes in brain morphology. Untreated, patients with Alzheimer's disease could lead to confusion, irritability, aggression, mood swings and long term memory loss.

Studies have been conducted in imaging of patients with Alzheimer's disease. A study by Fox and Freeborough (1997) showed significant differences in rate of atrophy in patients with Alzheimer's disease compared to healthy

control. The authors found that in patients with Alzheimer's disease, the rate of atrophy ranged from 10 to 40 times faster than healthy control subjects, which showed aggressive and degenerative nature of Alzheimer's disease. Another study by Silbert *et al.* (2003) was conducted to assess whether MRI brain volume measurements are valid predictors of Alzheimer's disease pathology. He found that rate of ventricular volume increase is significant over healthy control and concluded that MRI volume measured over time are valid biomarkers of progression of Alzheimer's disease.

Patients with cognitive impairment are also at risk of developing Alzheimer's disease. A study by a group of researchers from University of California San Diego (McEvoy *et al.*, 2011) was done to see whether a single MRI measurement can provide a predictive prognostic information in patients with mild cognitive impairment. This study involved 164 patients with Alzheimer's disease and 203 healthy control subjects in which the data gathered from the MRI were used to discriminate patients with mild cognitive impairment and evaluate their risk scores. They found that MRI measurement showed more informative patient specific risk estimates in predicting the change from mild cognitive impairment to Alzheimer's disease.

Another study by Chiang *et al.* (2011) was done to determine whether temporoparietal brain volumes could be used to predict future memory decline in healthy individuals. The study involved 149 cognitively healthy individuals whom underwent MRI of the brain at the initial phase of the study and at 2 years follow up. The patients were also underwent neuropsychological assessment at the start of the study and at 2 years follow up. The study result showed that the

temporoparietal brain volume can be used to identify with high accuracy healthy individuals who are at risk for future memory decline.

Schizophrenia (ICD 10:F20) is a mental disorder with severely impaired thinking, emotions and behaviour. Commonly patients with schizophrenia have common symptoms such as auditory hallucinations; paranoid or bizarre delusions with disorganize speech and thinking. It affects approximately 7 per 1000 adult population mostly in 15 to 35 years old age group. It is a treatable disease if recognized and treated early.

The diagnosis of schizophrenia is made according to a pre-set criterion. For a person to be diagnosed with schizophrenia, the person must have at least one major criterion two minor criteria present for one month duration within six months. The major criteria are:

i. Thought echo, thought insertion or withdrawal, or thought broadcasting.
ii. Delusions of control, influence or passivity; or delusion of perception.
iii. Hallucination.
iv. Neologisms or break in train of thoughts, resulting in incoherent or irrelevant speech.
v. Catatonic behaviour.
vi. Negative symptoms such as marked apathy, paucity of speech and blunting of emotional response.

Treatment of schizophrenia are mainly by antipsychotic drugs in which if started early in the initial stage of the disease, will prevent further decline in brain volume.

Brain volume loss in patients with schizophrenia has been extensively studied in previous years. van Haren *et al.* (2008) conducted a study looking into the loss of brain volume in patients with schizophrenia over the course of the illness. MRI scans of the brain were performed over a period of 5 years involving 96 schizophrenia patients and 113 healthy control subjects ranging from 16 years old to 56 years old of age. His study showed that over the course of 5 years, there was excessive brain volume loss concomitant with increase in ventricular size in patients with schizophrenia compared to healthy individuals. The study further showed that patients with poor disease outcome developed more excessive brain volume loss than patients with good disease outcome and he concluded that the brain volume changes are clinically relevant in patients with schizophrenia.

Another study involving brain volume changes in patients with first episode of schizophrenia was done by Cahn *et al.* (2002). Imaging studies in patients with schizophrenia usually involved grey matter volume loss. The author reasoned that previously, there was no study done to determine brain volume loss in patients with first episode of schizophrenia. The study stated that clinical deterioration in schizophrenia is greatest in early stages of the disease and assumed that imaging of the brain would show significant brain volume changes. This study involved 34 patients with first episode of schizophrenia and 36 healthy control subjects. MRI scan of the brain were performed at the beginning of the study and 1 year after the first MRI brain. The disease outcomes of the patients were measured 2 years after the start of the study. This study showed that there were significant losses of brain volume and grey matter volume with increase of ventricle size at the early stages of the disease.

Study by McDonald *et al.* (2006) also showed that patients with schizophrenia exhibited morphologic distinctions in ventricular and hippocampal regional volumes.

Bipolar disorder (ICD 10:F31) or bipolar affective disorder is a disorder that causes alternating mood swings of alternating mania and depression. It is also known as manic disorder or manic-depressive disorder. Patients have different levels of mania or depressive symptoms, depending on severity. Diagnosis is usually by excluding other organic causes by clinical assessment or imaging. Recent years have showed few studies that were done to see whether there are changes in brain volume in patients with bipolar disorder as opposed to patients with schizophrenia. Study by Arnone *et al.* (2009) showed that patients with bipolar disorder have robust changes in brain volume compared to healthy adults. His study showed whole brain and prefrontal lobe volume reduction with increased lateral ventricle size.

Several meta-analysis (Hoge *et al.*, 1999; McDonald *et al.*, 2004) suggest that brain volume loss in patients with bipolar disorder were not as significant as in patients with schizophrenia. However, these authors suggested the need of further studies to establish a consistent brain volume deviation in patients with bipolar disorder.

2.6 Volumetry method

Volumetric measurements are significantly more sensitive and definitive than visual inspection alone. With the MRI, volumetry techniques have been more optimized and more new techniques have been developed for accurate measurement and volumetry of the brain. This is especially critical in patients who are at risk of developing Alzheimer's disease, or patients with newly diagnosed schizophrenia and bipolar disorder. Several techniques in brain volumetry measurement are manual, semi-automated and automated measurement techniques. Manual volumetry technique once considered the gold standard of brain volumetry. This technique involved manual slice by slice tracing of the brain structures and anatomy and measurement. It is also useful as a correction method of local miscalculation as part of the processing chain in semi-automated volumetry technique (Klauschen *et al.*, 2009). However, manual volumetry is very time consuming and operator dependant, thus each measurement need to be done by a trained and skilled observer.

Semi-automated volumetry technique also used input and feedback from the operator or observer. This has made semi-automated volumetry measurement to be as time consuming as manual volumetry technique and at times can be expensive.

Comparison of manual and automated brain volumetry technique was done by Ambarki *et al.* (2011). The purpose of the study was to evaluate commercially available fully automated software for MRI brain volume assessment. The study was conducted in 41 healthy subjects and 20 patients with hydrocephalus. Both manual and automated volumetry techniques were used in the study with manual technique as the reference standard. The study