قال تعالي:

(وَيَسْأَلُونَكَ عَنِ الرُّوحِ ۖ قُلِ الرُّوحُ مِنْ أَمْرِ رَبِّي وَمَا أُوتِيتُم مِّنَ الْعِلْمِ إِلَّا قَلِيلًا)

صدق الله العظيم

الاسراء(85)

Dedication

To:

My mother who represented the candles that burn to give light to others.

To

My husband who provided the good atmosphere throughout the study.

Last but not least, to my lovely kids who are the goal that I dedicate my life for ……

I dedicate this simple work.

Acknowledgement

My acknowledgements and gratefulness at the beginning and at last is to God who gave us the gift of the mind. Profound thanks and gratitude to everyone who encouraged me to complete this thesis. My gratitude is extended to my supervisor **Dr. Mohammed Mohammed Omer** and co-supervisor **Dr. Ahmed Mostafa Mohammed,** for their helps. Their works have stimulated and fostered my efforts in producing this research. My gratitude is also extended to **Dr. Mohammed Abdelwhab**, and special thanks to Dr. Badereldin Abunaib and Radiology Department in Royal Care Hospital for the continuous help and facilitation. My gratitude extends to my colleagues College of Medical Radiological Sciences, Sudan University of Sciences and Technology Department for their continuous help and support.

Finally I would like to warmly thank of my long-suffering family for never-ending support. May almighty God bless them.

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List of Abbreviations

Abbreviation	Full meaning
AD	Alzheimer’s disease
MRI	Magnetic Resonance Imaging
T1	Time constant for longitudinal relaxation
T2	Time constant for transverse relaxation due to spin-spin energy transfer
CSF	Cerebrospinal fluid
CA	Cornu Ammonis
MCI	Mild cognitive impairment
APP	amyloid precursor protein
Apo E	apolipoprotein E
LOAD	late-onset sporadic Alzheimer’s disease
ADDLs	Amyloid-derived diffusible ligands
DR6	Death receptor 6
Aβ	Amyloid beta
EEG	Electroencephalography
ECG or EKG	Electrocardiogram
PET	Positron Emission Tomography
CT	Computerized Tomography
SPECT	Single Photon Emission Computed Tomography
NMR	nuclear magnetic resonance
CBF	cerebral blood flow
OER	oxygen extraction
CMRO2	Cerebral metabolic rate of oxygen
(MMSE)	Mini-Mental State Examination
ADAS-Cog	Alzheimer’s disease Assessment Scale-Cognitive Subscale
GCA	global cortical atrophy
Sag	Sagittal
TR	Repetition Time
T2w	T2 Weighted
FlAIR	Fluid-attenuated Inversion Recovery
MTA	Medial temporal lobe atrophy
FTLD	Frontotemporal Lobar Degeneration
VaD	Vascular Dementia
DLB	Dementia with Lewy bodies
WMH	white matter hyperintensities

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Abstract

Alzheimer's disease (AD) is a multifaceted disease in which cumulative pathological brain insults result in progressive cognitive decline that ultimately leads to dementia. The aim of this study was to evaluate the structural MRI changes in AD, focusing particularly on atrophy in typical late-onset of AD. Also to identify other promising biomarkers that can set structural loss in the broader context of functional changes at different stages of the disease.

The study was conducted in Sudan in Royal Care Hospital, 302 subjects were enrolled (200 Male and 102 female). All subjects underwent thorough clinical and cognitive assessments at the time of their MRI scans. Each subject's cognitive evaluation included the Mini-Mental State Examination (MMSE) to provide a global measure of mental status; the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog). They have been classified as predementia, early stage of AD, moderate AD and late stage of AD.

MRI studies were performed on 1.5 Tesla Toshiba whole body MR systems using standard imaging head coil. Routine brain MRI was performed in 3 orthogonal planes, including at least T1, T2, and fluid-attenuated inversion recovery (FLAIR) weighted images. Additional sagittal reconstructions will enable the assessment of midline structures as well as parietal atrophy, which may be involved in certain neurodegenerative disorders. FLAIR images are used to assess global cortical atrophy (GCA), vascular white matter hyperintensities and infarctions.

The result of the study revealed that age is the most important risk factor for Alzheimer disease (AD) because it is independently linked to brain atrophy; the common affected age group was (70 – 80) years, particularly more than 80 years. The generalized atrophy has been observed in 78.1% of the cases. Furthermore, ventricular enlargement was seen in 65% of the cases.

Differences in hippocampal volumes between normal, CI and AD subjects were significant for both the left and the right side. Individual trajectories of

hippocampal volume changes as a function of time, the mean change in each group indicates that Alzheimer's disease patients had on average a smaller hippocampus and greater volume loss over time than normal subjects, whereas moderate stage of AD patients had intermediate values between Alzheimer's disease and normal subjects.

Structural MRI markers now support earlier and more-precise diagnosis and measurement of progression. The presences of atrophy as well as ventricular changes are a partially validated marker for early diagnosis of the disease.

المستخلص

مرض الزهايمر هو مرض متعدد الأوجه يؤدي الي تغييرات مرضية في الدماغ متراكمة تؤدي إلى تدهور إدراكي تدريجي يؤدي في النهاية إلى الخرف. كان الهدف من هذه الدراسة هو تقييم التغيرات الهيكلية للدماغ في صورة الرنين المغناطيسي، مع التركيز بشكل خاص على الضمور في وقت متأخر من بداية المرض. أيضا لتحديد المؤشرات الحيوية الواعدة الأخرى التي يمكن أن تحدث تغيرات هيكلية ووظيفية في مراحل مختلفة من المرض.

أجريت الدراسة في السودان في مستشفى رويال كير ، حيث تم تسجيل 302 شخص (200 ذكر و 102 أنثى). خضع جميع المرضي لتقييم سريري شامل في وقت التصوير بالرنين المغناطيسي الخاص بهم. تضمن التقييم فحص الحالة الذهنية البسيطة (MMSE) لتوفير مقياس عالمي للحالة العقلية ؛ مقياس تقييم الإدراك المعرفي لمرض الزهايمر (ADAS-Cog). وقد تم تصنيفها على ثلاث مراحل هي مرحلة ما قبل المرض، والمرحلة المبكرة من المرض و المرحلة المتأخرة من المرض. أجريت دراسات التصوير بالرنين المغناطيسي على جهاز توشيبا بقوة مغناطيس 1.5(تسلا) باستخدام ملف تصوير الرأس القياسي. تم إجراء التصوير بالرنين المغناطيسي الروتيني للدماغ في ثلاثة محاور متعامدة ، بما في ذلك على الأقل زمن الانتظار الأول و الثاني.

كشفت نتائج الدراسة أن العمر هو أهم عامل خطر لمرض الزهايمر لأنه يرتبط بشكل مستقل بضمور الدماغ، و الفئة العمرية المصابة الشائعة (70 - 80) سنة ، ولا سيما أكثر من 80 سنة. وقد لوحظ الضمور المعمم في 78.1 ٪ من الحالات. وعلاوة على ذلك ، لوحظ تضخم بطين الدماغ في 65 ٪ من الحالات. كانت الفروق في أحجام الحصين كبيرة بين الحالة الطبيعية وقصورالإدراك و مرض الزهايمر لكل من الجانب الأيسر والأيمن. الاختلافات في معدلات الحجم بين شق الحصين الأيمن والايسر لم تكن كبيرة، وبالتالي تم أخذ متوسط القيم.

يتغير المسار الفردي لحجم الحصين كدالة للوقت ، ويشير متوسط التغير في كل مجموعة إلى أن مرضى الزهايمر لديهم في المتوسط حصين أصغر حجمًا وفقدان حجم أكبر بمرور الوقت أكثر من الأشخاص العاديين ، في حين كانت المرحلة المعتدلة من مرضى الزهايمر لديهم قيم وسيطة بين مرضي ألزهايمر و الاصحاء.

تدعم الآن علامات التصوير بالرنين المغناطيسي الهيكلية تشخيصًا مبكرًا أكثر دقة وقياسًا في حالة وجود ضمور في حجم الدماغ وكذلك تغييرات البطين مما يعتبرعلامة تحقق للتشخيص المبكر للمرض.

CHAPTER ONE

INTRODUCTION

1.1 Introduction:

Alzheimer's disease (AD) is a multifaceted disease in which cumulative pathological brain insults result in progressive cognitive decline that ultimately leads to dementia. Amyloid plaques, neurofibrillary tangles (NFTs), neurodegeneration, and inflammation are the well-established pathological hallmarks of AD (Prins and van Swieten, 2010). Neuronal and synaptic losses appear to be key determinants of cognitive impairment in AD (Terry et al., 1991). If neuronal loss leads to cerebral atrophy, then it can be expected that cognitive decline and atrophy will be closely associated (Vemuri and Jack, 2010).

Imaging modalities can be thought of as in vivo indicators of specific pathologies. Amyloid labeling PET ligands, such as ^{11}C Pittsburgh compound B (PIB) primarily measure brain amyloid plaque load (Klunk et al., 2004). MRI, on the other hand, is an in vivo indicator of neurodegeneration; Serial multi-modality imaging studies which are sensitive to the different aspects of Alzheimer's disease pathology are an ideal way to answer questions about the temporal sequencing of different pathologic features of the disease (Jack et al., 2008).

MRI measures brain morphometry and therefore can capture gray matter atrophy related to the loss of neurons, synapses, and dendritic de-arborization that occurs on a microscopic level in AD; white matter atrophy related to the loss of structural integrity of white matter tracts, presumably resulting from demyelination and dying back of axonal processes; and *ex vacuo* expansion of cerebrospinal fluid (CSF) spaces (Vemuri and Jack, 2010).

In research, imaging is helping address many of the scientific questions outlined in (Selkoe et al., 2012): providing insights into the effects of AD and its

temporal and spatial evolution. Furthermore, imaging is an established tool in drug discovery, increasingly required in therapeutic trials as part of inclusion criteria, as a safety marker, and as an outcome measure.

MRI-based measures of atrophy are regarded as valid markers of disease state and progression for several reasons. Atrophy seems to be an inevitable, inexorably progressive concomitant of neurodegeneration. The topography of brain tissue loss correlates well with cognitive deficits, both cross-sectionally and longitudinally (Vemuri et al., 2008). The earliest sites of tau deposition and MRI-based atrophic changes typically lie along the perforant (polysynaptic) hippocampal pathway (entorhinal cortex, hippocampus and posterior cingulate cortex), consistent with early memory deficits (Thompson et al., 2003).

The volume of the hippocampus is a commonly used structural MRI measurement in brain research (Giordano et al., 2001). Many studies focus on a decrease in hippocampal volume associated with a wide variety of neurological and psychiatric conditions including depression1, posttraumatic stress disorder (PTSD), borderline personality disorder (BPD), schizophrenia, alcohol abuse and Alzheimer's, Parkinson's and Huntington's diseases (Smeland et al., 2017).

Hippocampal volume is frequently used in the study of Alzheimer's disease (AD) and as such may be developed into a standardized biomarker for dementia and AD (Sforza et al., 2016). The volume of the hippocampus, adjusted for age and gender, has been found to best discriminate controls from early-onset AD cases in comparison to other medial temporal lobe structures. However, a stronger correlation was found between change in hemispheric volume measurements (whole brain and ventricle) and cognitive performance compared to the correlation between medial temporal lobe volume decrease and cognitive performance.

MRI-based hippocampal volume measurement may become a useful diagnostic tool in cases of memory impairment which may indicate early-onset AD, and measurement of whole brain atrophy rates may be preferable for some clinical

trials, especially considering that it can more easily be automated (Cao et al., 2016).

In this study, we aim to evaluate the structural MRI changes in AD, focusing particularly on atrophy in typical late-onset of AD. We also address other promising biomarkers that can set structural loss in the broader context of functional changes at different stages of the disease.

1.2 Problem of the study:

Alzheimer's disease is the most common cause of dementia and a growing health problem globally. There is misunderstanding of age-related brain atrophy; AD manifests itself in the context of aging. While age and AD are independent processes, they concurrently affect the brain.

1.3 Objectives of the study:

1.3.1 General objective:

The main objective of this study was to evaluate the Morphology of the Brain using MRI in Healthy Aging and Alzheimer's in Sudan.

1.3.2 Specific objectives:

- To identify the differences in the degree of white matter changes, specific MR parameters that can be used in Sudanese patients with Dementia and AD.
- To measure regional and global brain atrophy
- To assess the possible etiological factors that can be unique to Sudanese patients like: Environmental cause including infectious diseases, diet, lifestyle and history of disorders that affect the vascular system.
- To assess the hippocampus volume using MRI in Healthy Aging and in Alzheimer's patients.

CHAPTER TWO

LITRETURE REVIEW

2.2 Anatomy and Physiology of the Brain

The brain serves many important functions. It gives meaning to things that happen in the world surrounding us. Through the five senses of sight, smell, hearing, touch and taste, the brain receives messages, often many at the same time (Ribas et al., 2017).

The brain controls thoughts, memory and speech, arm and leg movements, and the function of many organs within the body. It also determines how people respond to stressful situations (i.e. writing of an exam, loss of a job, birth of a child, illness, etc.) by regulating heart and breathing rates. The brain is an organized structure, divided into many components that serve specific and important functions (Pordy, 2016).

The weight of the brain changes from birth through adulthood. At birth, the average brain weighs about one pound, and grows to about two pounds during childhood. The average weight of an adult female brain is about 2.7 pounds, while the brain of an adult male weighs about three pounds (Ratsep et al., 2016).

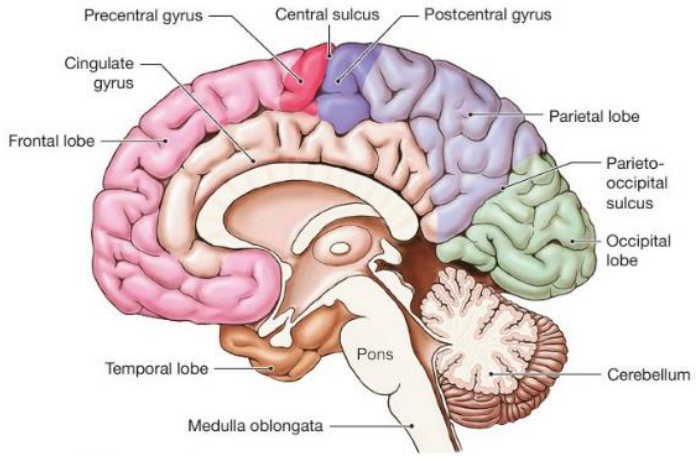

Figure 2.1 Anatomy of the brain

2.2.1 The Cell Structure of the Brain

The brain is made up of two types of cells: neurons and glial cells, also known as neuroglia or glia. The neuron is responsible for sending and receiving nerve impulses or signals. Glial cells are non-neuronal cells that provide support and nutrition, maintain homeostasis, form myelin, and facilitate signal transmission in the nervous system. In the human brain, glial cells outnumber neurons by about 50 to one. Glial cells are the most common cells found in primary brain tumors (Delvecchio et al., 2017).

When a person is diagnosed with a brain tumor, a biopsy may be done, in which tissue is removed from the tumor for identification purposes by a pathologist. Pathologists identify the type of cells that are present in this brain tissue, and brain tumors are named based on this association. The type of brain tumor and cells involved impact patient prognosis and treatment (Tanaka, 2017).

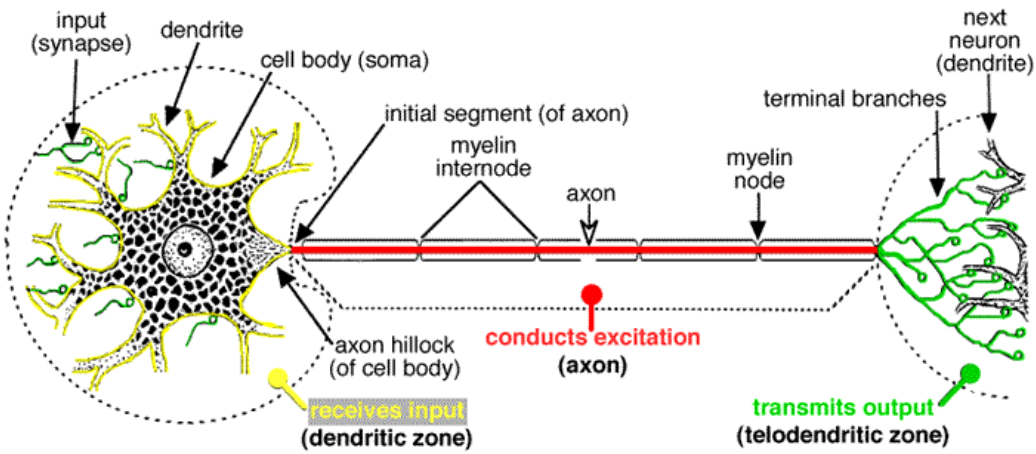

Figure 2.2 structure of Neuron

2.2.2 The Meninges

The brain is housed inside the bony covering called the cranium. The cranium protects the brain from injury. Together, the cranium and bones that protect the face are called the skull. Between the skull and brain is the meninges, which consist of three layers of tissue that cover and protect the brain and spinal cord.

From the outermost layer inward they are: the dura mater, arachnoid and pia mater (Ratsep et al., 2016).

In the brain, the dura mater is made up of two layers of whitish, nonelastic film or membrane. The outer layer is called the periosteum. An inner layer, the dura, lines the inside of the entire skull and creates little folds or compartments in which parts of the brain are protected and secured. The two special folds of the dura in the brain are called the falx and the tentorium. The falx separates the right and left half of the brain and the tentorium separates the upper and lower parts of the brain (Wang et al., 2016).

The second layer of the meninges is the arachnoid. This membrane is thin and delicate and covers the entire brain. There is a space between the dura and the arachnoid membranes that is called the subdural space. The arachnoid is made up of delicate, elastic tissue and blood vessels of varying sizes. The layer of meninges closest to the surface of the brain is called the pia mater. The pia mater has many blood vessels that reach deep into the surface of the brain. The pia, which covers the entire surface of the brain, follows the folds of the brain. The major arteries supplying the brain provide the pia with its blood vessels. The space that separates the arachnoid and the pia is called the subarachnoid space. It is within this area that cerebrospinal fluid flows (Pordy, 2016).

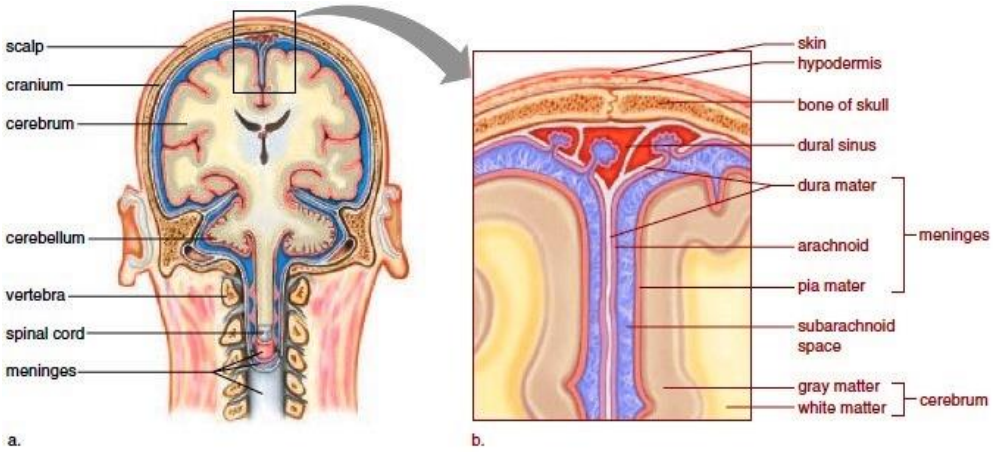

Fig.2-3: The Meninges of the brain

2.2.3 Cerebrospinal Fluid

Cerebrospinal fluid (CSF) is found within the brain and surrounds the brain and the spinal cord. It is a clear, watery substance that helps to cushion the brain and spinal cord from injury. This fluid circulates through channels around the spinal cord and brain, constantly being absorbed and replenished. It is within hollow channels in the brain, called ventricles, that the fluid is produced. A specialized structure within each ventricle, called the choroid plexus, is responsible for the majority of CSF production. The brain normally maintains a balance between the amount of CSF that is absorbed and the amount that is produced. However, disruptions in this system may occur (Delvecchio et al., 2017).

2.2.4 The Ventricular System

The ventricular system is divided into four cavities called ventricles, which are connected by a series of holes called foramen, and tubes. Two ventricles enclosed in the cerebral hemispheres are called the lateral ventricles (first and second). They each communicate with the third ventricle through a separate opening called the Foramen of Munro. The third ventricle is in the center of the brain, and its walls are made up of the thalamus and hypothalamus. The third ventricle connects with the fourth ventricle through a long tube called the Aqueduct of Sylvius. CSF flowing through the fourth ventricle flows around the brain and spinal cord by passing through another series of openings (Tanaka, 2017).

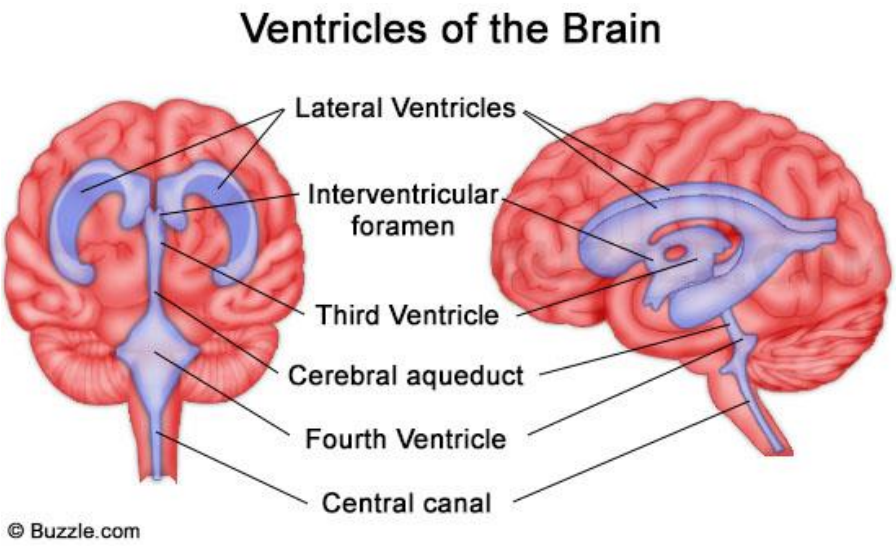

Figure 2-4: The Meninges of the brain

2.2.5 Hippocampus Anatomy

The hippocampus is one of the brain structures making up the limbic system. Although the hippocampus lies beneath the cerebral cortex it is not truly a subcortical structure in that it is really a cortical infolding itself, albeit much older and more primitive than the surrounding neocortex. Hence, it is also referred to as archicortex, or paleocortex. Further, the older and therefore also simpler paleocortex of the hippocampus is composed of only three layers, which can be contrasted to the much more entangled six layers of the neocortex, but more on that later. The hippocampus is so named since early on its appearance was likened to a "seahorse", and thus was dubbed the latin equivalent (Sforza et al., 2016).

A cross-section taken perpendicular to the long axis (septal-temporal) will reveal the internal structure as two interlocking "Cs", one reversed in relation to the other, each with its own principle cell layer. One "C" makes up Ammon's Horn or Cornu Ammonis (CA1-CA3), also known as the "Hippocampus proper". The principle cell layer of Ammon's Horn is the stratum pyramidale, or

the pyramidal cell layer. The other "C" is made up of the Dentate Gyrus, of which the stratum granulosm, or granule cell layer is the principle cell layer. Although the dentate gyrus is commonly included as part of the Hippocampus, it is cytoarchitectonically distinct from the hippocampus proper (Ropireddy et al., 2012). However, sometimes the hilus of the dentate gyrus, the area inside the C created by the granule cells is referred to as CA4, as though it belonged to the hippocampus proper. The hilar region is referred to as CA4 because the pyramidal cell layer of the CA1-CA3 regions begins to breakdown as a tightly packed cell layer and becomes more spread out and sparse, or more of a polymorph layer, in this region (Cao et al., 2016).

Consequently, early neuroanatomists did not distinguish between these areas. Since the dentate gyrus is not truly part of the hippocampus, terms like "Hippocampal formation" are used to discuss Ammon's Horn and the dentate gyrus together. The intrinsic connections between the principle cell layers of the dentate gyrus and CA regions of the hippocampus are very clear. The intrinsic connections were so clear, in fact, that Ramon y Cajal was able to determine the major direction of afferent connections or synaptic flow of the "trisynaptic circuit" through the examination of Golgi stained normal material by itself, as early as (y Cajal, 1954).

Damage to the hippocampus can lead to loss of memory and difficulty in establishing new memories. In Alzheimer's disease, the hippocampus is one of the first regions of the brain to be affected, leading to the confusion and loss of memory so commonly seen in the early stages of the disease (Apostolova et al., 2012). The major functions of the hippocampus include:

2.2.5.1 Memory:

Historically, the link between the hippocampus and long-term memory formation was first described by William Scoville and Brenda Milner who

reported what happened to an epileptic individual who underwent surgery on the organ that was intended to relieve his seizures (Scoville and Milner, 2000).

The patient had severe amnesia after the procedure as well as an inability to form new memories of events such as when or where a situation occurred (termed episodic memory). The only memories he did retain were those from many years earlier, as far back as childhood (Scoville and Milner, 2000).

Experts generally agree that the hippocampus plays a role in the formation of new memories and in the detection of new surroundings, occurrences and stimuli. Some also believe the organ is involved in declarative memory; that is memories that can be stated verbally such as facts and figures. However, studies have shown that damage to the hippocampus does not affect a person's ability to learn a new skill such as playing a musical instrument or solving certain types of puzzles which suggests that the memories involved in learning a procedure are governed by brain areas other than the hippocampus (Reess et al., 2018).

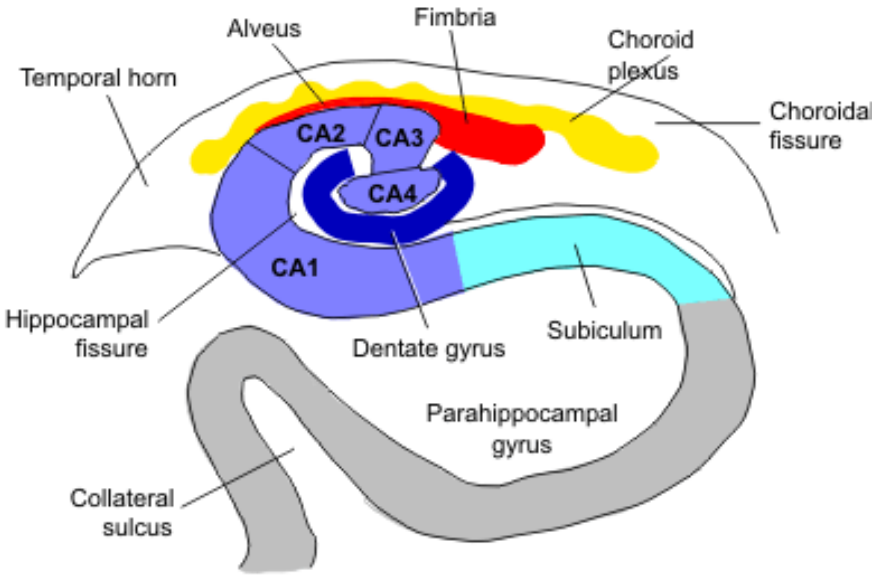

Figure 2-5: The structure of Hippocampus

2.2.5.2 Behavioral inhibition:

Animal experiments investigating the effects of hippocampal damage have previously suggested that, firstly, the damage causes hyperactivity and, secondly, that it affects the ability to inhibit responses that have previously been learnt (Cao et al., 2016).

2.1.5 Brainstem:

The brainstem is the lower extension of the brain, located in front of the cerebellum and connected to the spinal cord. It consists of three structures: the midbrain, pons and medulla oblongata. It serves as a relay station, passing messages back and forth between various parts of the body and the cerebral cortex. Many simple or primitive functions that are essential for survival are located here (Smith and DeMyer, 2003).

The midbrain is an important center for ocular motion while the pons is involved with coordinating eye and facial movements, facial sensation, hearing and balance. The medulla oblongata controls breathing, blood pressure, heart rhythms and swallowing. Messages from the cortex to the spinal cord and nerves that branch from the spinal cord are sent through the pons and the brainstem. Destruction of these regions of the brain will cause "brain death." Without these key functions, humans cannot survive (Hurley et al., 2010).

The reticular activating system is found in the midbrain, pons, medulla and part of the thalamus. It controls levels of wakefulness, enables people to pay attention to their environments, and is involved in sleep patterns. Originating in the brainstem are 10 of the 12 cranial nerves that control hearing, eye movement, facial sensations, taste, swallowing and movements of the face, neck, shoulder and tongue muscles. The cranial nerves for smell and vision originate in the cerebrum. Four pairs of cranial nerves originate from the pons: nerves 5 through 8 (Iwanaga et al., 2017).

2.1.6 Cerebellum:

The cerebellum is located at the back of the brain beneath the occipital lobes. It is separated from the cerebrum by the tentorium (fold of dura). The cerebellum fine tunes motor activity or movement, e.g. the fine movements of fingers as they perform surgery or paint a picture. It helps one maintain posture, sense of balance or equilibrium, by controlling the tone of muscles and the position of limbs. The cerebellum is important in one's ability to perform rapid and repetitive actions such as playing a video game. In the cerebellum, right-sided abnormalities produce symptoms on the same side of the body (Ribas et al., 2017).

2.1.7 Cerebrum:

The cerebrum, which forms the major portion of the brain, is divided into two major parts: the right and left cerebral hemispheres. The cerebrum is a term often used to describe the entire brain. A fissure or groove that separates the two hemispheres is called the great longitudinal fissure. The two sides of the brain are joined at the bottom by the corpus callosum. The corpus callosum connects the two halves of the brain and delivers messages from one half of the brain to the other. The surface of the cerebrum contains billions of neurons and glia that together form the cerebral cortex (Yagmurlu et al., 2015).

Research has determined that touching one side of the brain sends electrical signals to the other side of the body. Touching the motor region on the right side of the brain, would cause the opposite side or the left side of the body to move. Stimulating the left primary motor cortex would cause the right side of the body to move. The messages for movement and sensation cross to the other side of the brain and cause the opposite limb to move or feel a sensation (Rhoton, 2007).

2.1.8 Cranial Nerves:

There are 12 pairs of nerves that originate from the brain itself. These nerves are responsible for very specific activities and are named and numbered as follows:

- Olfactory: Smell
- Optic: Visual fields and ability to see
- Oculomotor: Eye movements; eyelid opening
- Trochlear: Eye movements
- Trigeminal: Facial sensation
- Abducens: Eye movements
- Facial: Eyelid closing; facial expression; taste sensation
- Auditory/vestibular: Hearing; sense of balance
- Glossopharyngeal: Taste sensation; swallowing
- Vagus: Swallowing; taste sensation
- Accessory: Control of neck and shoulder muscles
- Hypoglossal: Tongue movement

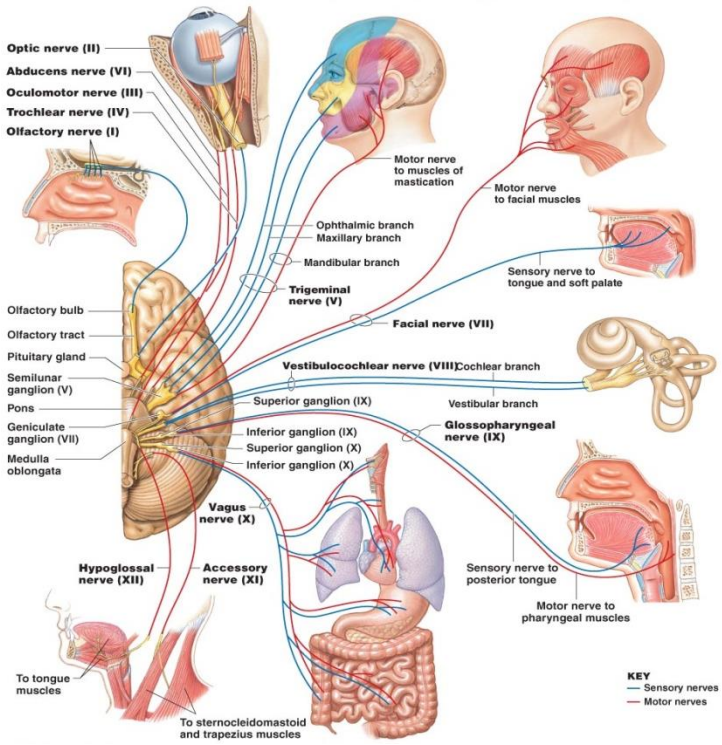

Figure 2-6: The branches of the 12 cranial nerves and their function

2.1.9 Hypothalamus:

The hypothalamus is a small structure that contains nerve connections that send messages to the pituitary gland. The hypothalamus handles information that comes from the autonomic nervous system. It plays a role in controlling functions such as eating, sexual behavior and sleeping; and regulates body temperature, emotions, secretion of hormones and movement. The pituitary gland develops from an extension of the hypothalamus downwards and from a second component extending upward from the roof of the mouth (Telford and Vattoth, 2014).

2.1.10 The Lobes:

2.1.10.1 Frontal Lobes:

The frontal lobes are the largest of the four lobes responsible for many different functions. These include motor skills such as voluntary movement, speech, intellectual and behavioral functions. The areas that produce movement in parts of the body are found in the primary motor cortex or precentral gyrus. The prefrontal cortex plays an important part in memory, intelligence, concentration, temper and personality. The premotor cortex is a region found beside the primary motor cortex. It guides eye and head movements and a person’s sense of orientation. Broca's area, important in language production, is found in the frontal lobe, usually on the left side (Anderson and Ylvisaker, 2009).

2.1.10.2 Occipital Lobes:

These lobes are located at the back of the brain and enable humans to receive and process visual information. They influence how humans process colors and shapes. The occipital lobe on the right interprets visual signals from the left visual space, while the left occipital lobe performs the same function for the right visual space (Pordy, 2016).

2.1.10.3 Parietal Lobes:

These lobes interpret simultaneously, signals received from other areas of the brain such as vision, hearing, motor, sensory and memory. A person's memory and the new sensory information received, give meaning to objects (Pordy, 2016).

2.1.10.4 Temporal Lobes:

These lobes are located on each side of the brain at about ear level, and can be divided into two parts. One part is on the bottom (ventral) of each hemisphere, and the other part is on the side (lateral) of each hemisphere. An area on the right side is involved in visual memory and helps humans recognize objects and peoples' faces. An area on the left side is involved in verbal memory and helps humans remember and understand language. The rear of the temporal lobe enables humans to interpret other people's emotions and reactions (Pordy, 2016).

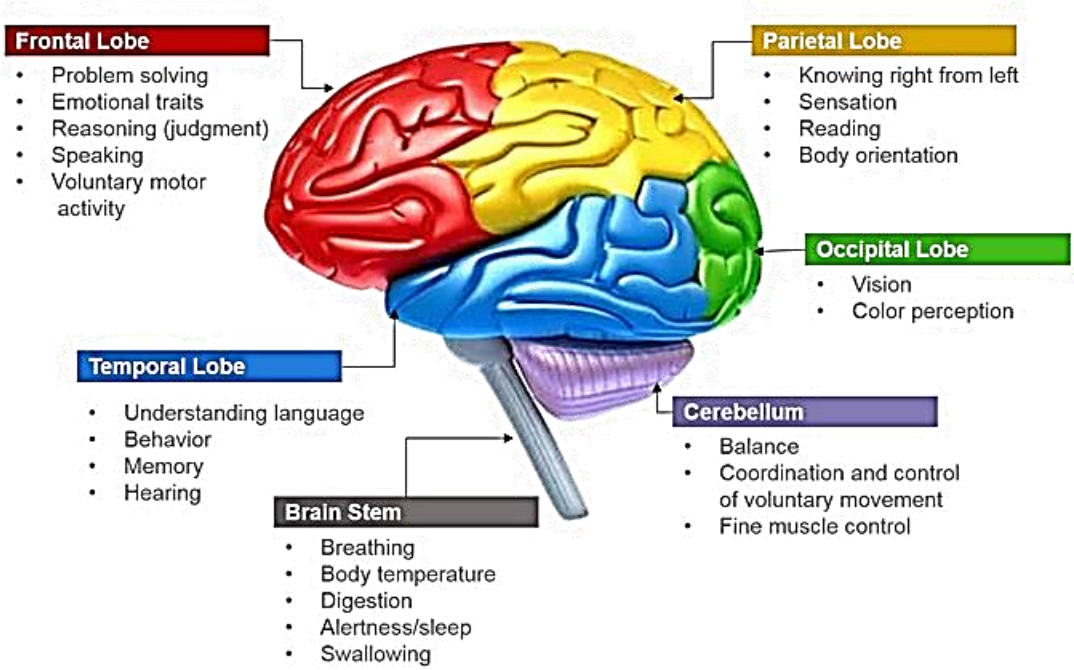

Figure 2-7: The functional lobes of the brain

2.1.11 Limbic System:

This system is involved in emotions. Included in this system are the hypothalamus, part of the thalamus, amygdala (active in producing aggressive behavior) and hippocampus (plays a role in the ability to remember new information) (Tanaka, 2017).

2.1.12 Pineal Gland:

This gland is an outgrowth from the posterior or back portion of the third ventricle. In some mammals, it controls the response to darkness and light. In humans, it has some role in sexual maturation, although the exact function of the pineal gland in humans is unclear (Tanaka, 2017).

2.1.13 Pituitary Gland:

The pituitary is a small gland attached to the base of the brain (behind the nose) in an area called the pituitary fossa or sella turcica. The pituitary is often called the "master gland" because it controls the secretion of hormones (Musumeci et al., 2015). The pituitary is responsible for controlling and coordinating the following:

2.1.14 Growth and development:

The function of various body organs (kidneys, breasts and uterus). The function of other glands (thyroid, gonads, and adrenal glands) Posterior Fossa – This is a cavity in the back part of the skull which contains the cerebellum, brainstem, and cranial nerves (Musumeci et al., 2015).

Thalamus – The thalamus serves as a relay station for almost all information that comes and goes to the cortex. It plays a role in pain sensation, attention and alertness. It consists of four parts: the hypothalamus, the epythalamus, the ventral thalamus, and the dorsal thalamus. The basal ganglia are clusters of nerve cells surrounding the thalamus (Hurcombe, 2011).

2.1.15 Language and Speech Functions:

In general, the left hemisphere or side of the brain is responsible for language and speech. Because of this, it has been called the "dominant" hemisphere. The right hemisphere plays a large part in interpreting visual information and spatial processing. In about one third of individuals who are left-handed, speech function may be located on the right side of the brain. Left-handed individuals may need specialized testing to determine if their speech center is on the left or right side prior to any surgery in that area (Cooper et al., 2017).

Many neuroscientists believe that the left hemisphere and perhaps other portions of the brain are important in language. Aphasia is simply a disturbance of language. Certain parts of the brain are responsible for specific functions in language production. There are many types of aphasias, each depending upon the brain area that is affected, and the role that area plays in language production (Tanaka et al., 2013).

There is an area in the frontal lobe of the left hemisphere called Broca's area. It is next to the region that controls the movement of facial muscles, tongue, jaw and throat. If this area is destroyed, a person will have difficulty producing the sounds of speech, because of the inability to move the tongue or facial muscles to form words. A person with Broca's aphasia can still read and understand spoken language, but has difficulty speaking and writing. There is a region in the left temporal lobe called Wernicke's area. Damage to this area causes Wernicke's aphasia. An individual can make speech sounds, but they are meaningless (receptive aphasia) because they do not make any sense (Cooper et al., 2017).

2.2 Pathology of the Brain:

2.2.1 Alzheimer's disease:

AD is a degenerative brain disease and the most common cause of dementia. Dementia is also caused by other diseases and conditions. It is characterized by

a decline in memory, language, problem-solving and other cognitive skills that affect a person's ability to perform everyday activities. This decline occurs because nerve cells (neurons) in parts of the brain involved in cognitive function have been damaged and no longer function normally. In Alzheimer's disease, neuronal damage eventually affects parts of the brain that enable a person to carry out basic bodily functions such as walking and swallowing. People in the final stages of the disease are bed-bound and require around-the-clockcare. Alzheimer's disease is ultimately fatal (Grundman M, et al2004).

Alzheimer's disease was first identified more than 100 years ago, but 70 years passed before it was recognized as the most common cause of dementia and a "major killer. Although research has revealed a great deal about Alzheimer's, much is yet to be discovered about the precise biologic changes that cause Alzheimer's, why it progresses more quickly in some than in others, and how the disease can be prevented, slowed or stopped.

Researchers believe that early detection will be key to preventing, slowing and stopping Alzheimer's disease. The last 10 years have seen a tremendous growth in research on early detection. This research spurred the 2011 publication of proposed new diagnostic criteria and guidelines for Alzheimer's disease. Under the proposed criteria, the disease begins before symptoms such as memory loss appear, while earlier criteria require memory loss and a declinein thinking abilities for an Alzheimer's diagnosis to be made. Because scientific evaluation of the proposed criteria is ongoing, "Alzheimer's disease" in this report refers to the disease as defined by the earlier criteria. The disease course is divided into four stages, with a progressive pattern of cognitive and functional impairment (Prins and van Swieten, 2010).

2.2.1.1 Signs and symptoms of Alzheimer’s disease:

- Forgetting things occasionally
- Misplacing items sometimes
- Minor short-term memory loss
- Not remembering exact details

2.2.1.2 Early stage Alzheimer's

- Not remembering episodes of forgetfulness
- Forgets names of family or friends
- Changes may only be noticed by close friends or relatives
- Some confusion in situations outside the familiar

2.2.1.3 Middle stage Alzheimer's

- Greater difficulty remembering recently learned information
- Deepening confusion in many circumstances
- Problems with sleep
- Trouble knowing where they are

2.2.1.4 Late stage Alzheimer's

- Poor ability to think
- Problems speaking
- Repeats same conversations
- More abusive, anxious, or paranoid

2.2.1.5 Stages of Alzheimer’s disease

The first symptoms are often mistakenly attributed to ageing or stress. Detailed neuropsychological testing can reveal mild cognitive difficulties up to eight years before a person fulfills the clinical criteria for diagnosis of AD. These early symptoms can affect the most complex activities of daily living. The most

noticeable deficit is short term memory loss, which shows up as difficulty in remembering recently learned facts and inability to acquire new information (Malpass, 2011a).

Subtle problems with the executive functions of attentiveness, planning, flexibility, and abstract thinking, or impairments insemantic memory (memory of meanings, and concept relationships) can also be symptomatic of the early stages of AD. Apathy can be observed at this stage, and remains the most persistent neuropsychiatric symptom throughout the course of the disease Depressive symptoms, irritability and reduced awareness of subtle memory difficulties are also common. The preclinical stage of the disease has also been termed mild cognitive impairment (MCI). This is often found to be a transitional stage between normal ageing and dementia. MCI can present with a variety of symptoms, and when memory loss is the predominant symptom, it is termed "amnestic MCI" and is frequently seen as a prodromal stage of Alzheimer's disease (Guo et al., 2014).

2.2.1.5.1 Early stage of Alzheimer’s disease:

In people with AD, the increasing impairment of learning and memory eventually leads to a definitive diagnosis. In a small percentage, difficulties with language, executive functions, perception (agnosia), or execution of movements (apraxia) are more prominent than memory problems. AD does not affect all memory capacities equally. Older memories of the person's life (episodic memory), facts learned (semantic memory), and implicit memory (the memory of the body on how to do things, such as using a fork to eat or how to drink from a glass) are affected to a lesser degree than new facts or memories.

Language problems are mainly characterized by a shrinking vocabulary and decreased word fluency, leading to a general impoverishment of oral and written language.[26][29] In this stage, the person with Alzheimer's is usually capable of communicating basic ideas adequately. While performing fine motor

tasks such as writing, drawing or dressing, certain movement coordination and planning difficulties (apraxia) may be present, but they are commonly unnoticed. As the disease progresses, people with AD can often continue to perform many tasks independently, but may need assistance or supervision with the most cognitively demanding activities (Malpass, 2011b).

2.2.1.5.2 Moderate stage of Alzheimer's disease:

A photograph of a patient at West Riding Lunatic Asylum with dementia Progressive deterioration eventually hinders independence, with subjects being unable to perform most common activities of daily living. Speech difficulties become evident due to an inability to recall vocabulary, which leads to frequent incorrect word substitutions (paraphasias). Reading and writing skills are also progressively lost. Complex motor sequences become less coordinated as time passes and AD progresses, so the risk of falling increases. During this phase, memory problems worsen, and the person may fail to recognise close relatives.

Long-term memory, which was previously intact, becomes impaired (Jones et al., 2006).

Behavioural and neuropsychiatric changes become more prevalent. Common manifestations are wandering, irritability and labile affect, leading to crying, outbursts of unpremeditated aggression, or resistance to caregiving. Approximately 30% of people with AD develop illusionary misidentifications and other delusional symptoms. Subjects also lose insight of their disease process and limitations (anosognosia). These symptoms create stress for relatives and carers, which can be reduced by moving the person from home care to other long-term care facilities (Malpass, 2011a).

2.2.1.5.3 Advanced Stage of Alzheimer's Disease:

During the final stages, the patient is completely dependent upon caregivers. Language is reduced to simple phrases or even single words,

eventually leading to complete loss of speech. Despite the loss of verbal language abilities, people can often understand and return emotional signals. Although aggressiveness can still be present, extreme apathy and exhaustion are much more common symptoms. People with Alzheimer's disease will ultimately not be able to perform even the simplest tasks independently; muscle mass and mobility deteriorate to the point where they are bedridden and unable to feed themselves. The cause of death is usually an external factor, such as infection of pressure ulcers or pneumonia, not the disease itself (Stoub et al., 2005).

2.2.1.6 Risk of Alzheimer's disease:

Although aging per se causes neither dementia nor Alzheimer's disease, it is the most strongly associated risk factor for AD. Family history, or genetic predisposition, is another important risk factor; a history of AD in a first-degree relative (parent or sibling) increases the odds of developing AD three- to fourfold. A history of severe head injury that leads to brief loss of consciousness doubles the risk of developing AD (Saarelainen et al., 2018).

These three risk factors age, genetic predisposition, and head trauma meet the accepted epidemiological criteria for causal factors; they provide a plausible biological explanation and their effects are strong and consistent. Other risk factors that have been investigated such as maternal age, hypothyroidism, and exposure to environmental, LLC toxins such as aluminum or to chemicals such as benzene and toluene have not been shown to meet the above criteria. Factors that apparently decrease a person's risk for AD have also been identified. Among these, the most important appears to be educational and occupational attainment (Saarelainen et al., 2018).

People who achieve only a low level of education have double the risk of developing AD compared with those who have had 6 to 8 or more years of schooling. Education presumably increases the brain's reserve capacity such that the clinical manifestations of AD are delayed or become more difficult to

detect. Other factors that have been implicated as having a protective effect but need to be confirmed by further and more careful studies include postmenopausal estrogen replacement therapy, long-term use of anti-inflammatory drugs, and cigarette smoking. As an increasing proportion of the population survives beyond the age of 85 years, more people will be at risk for developing a dementing disorder. Recent well-designed epidemiological studies have assessed the prevalence of all dementias (including Alzheimer's disease) in diverse communities around the world (Ansai et al., 2017).

These surveys indicate that 25 to 35% of those 85 and over are affected by some form of dementia. In one such study conducted in East Boston the prevalence of AD alone in the 85-and-over age group was found to be 47%. The variations in prevalence rates are due primarily to differences in the criteria used by investigators to identify individuals with dementia and, more specifically, with AD. One of the major problems in all such community surveys of dementia is that 15 to 30% of the sample population may be unwilling, unable, or unavailable to participate. Because it is possible that dementia might be more frequent among those who do not participate, the reported prevalence rates may actually underestimate the true prevalence. Regardless of these problems in methodology and the differences in the estimates, two important facts have emerged from the epidemiological studies conducted during the past several decades (Patel, 2017).

The prevalence of dementia increases in an exponential fashion with increasing age; that is, the percentage of the population affected doubles for every decade people live beyond the age of 65. Thus, if 10% of all people 65 and older have AD, 20% of the over-75 population will be affected and 40% of all those over age 85. Since the Industrial Revolution, but particularly starting at the turn of the last century, life expectancy has been increasing. During the past 3 decades, improvements in public health measures, diet, and health behavior have brought about dramatic demographic changes, including a lower birthrate. Thus, today

in most industrialized countries, the 85-and-older age group is the fastest-growing segment of population. These two facts, the growing number of older people and the increasing incidence of dementia with age, point to an ever larger group of those at risk for Alzheimer's disease (Fyfe, 2018).

2.2.1.7 Cause of Alzheimer's disease:

The cause for most Alzheimer's cases is still mostly unknown except for 1% to 5% of cases where genetic differences have been identified. Several competing hypotheses exist trying to explain the cause of the disease:

2.2.1.7.1 Genetics:

The genetic heritability of Alzheimer's disease (and memory components thereof), based on reviews of twin and family studies, range from 49% to 79%. Around 0.1% of the cases are familial forms of autosomal (not sex-linked) dominant inheritance, which have an onset before age .This form of the disease is known as early onset familial Alzheimer's disease (Li et al., 2017).

Most of autosomal dominant familial AD can be attributed to mutations in one of three genes: those encoding amyloid precursor protein (APP) and presenilins 1 and 2. Most mutations in the APP and presenilin genes increase the production of a small protein called Aβ42, which is the main component of senile plaques. Some of the mutations merely alter the ratio between Aβ42 and the other major forms—particularly Aβ40—without increasing Aβ42 levels. This suggests that presenilin mutations can cause disease even if they lower the total amount of Aβ produced and may point to other roles of presenilin or a role for alterations in the function of APP and/or its fragments other than Aβ. There exist variants of the APP gene which are protective (Tosto et al., 2017).

Most cases of Alzheimer's disease do not exhibit autosomal-dominant inheritance and are termed sporadic AD, in which environmental and genetic

differences may act as risk factors. The best known genetic risk factor is the inheritance of the ε4 allele of the apolipoprotein E (APOE). Between 40 and 80% of people with AD possess at least one APOEε4 allele. The APOEε4 allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes. Like many human diseases, environmental effects and genetic modifiers result in incomplete penetrance. For example, certain Nigerian populations do not show the relationship between dose of APOEε4 and incidence or age-of-onset for Alzheimer's disease seen in other human populations. Early attempts to screen up to 400 candidate genes for association with late-onset sporadic AD (LOAD) resulted in a low yield (Prins and van Swieten, 2010).

Mutations in the TREM2 gene have been associated with a 3 to 5 time's higher risk of developing Alzheimer's disease. A suggested mechanism of action is that when TREM2 is mutated, white blood cells in the brain are no longer able to control the amount of beta amyloid present (Prins and van Swieten, 2010).

The oldest, on which most currently available drug therapies are based, is the cholinergic hypothesis, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective. Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid, leading to generalized neuroinflammation (Fyfe, 2018).

2.2.1.7.2 Amyloid hypothesis:

In 1991, the amyloid hypothesis postulated that extracellular amyloid beta (Aβ) deposits are the fundamental cause of the disease. Support for this postulate comes from the location of the gene for the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit at least the

earliest symptoms of AD by 40 years of age (Wang et al., 2017c).

Also, a specific isoform of a polipoprotein, APOE4, is a major genetic risk factor for AD. Whilst a polipoproteins enhance the breakdown of beta amyloid, some isoforms are not very effective at this task (such as APOE4), leading to excess amyloid buildup in the brain.[58] Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology with spatial learning deficits (Wang et al., 2017b).

An experimental vaccine was found to clear the amyloid plaques in early human trials, but it did not have any significant effect on dementia. Researchers have been led to suspect non-plaque Aβ oligomers (aggregates of many monomers) as the primary pathogenic form of Aβ. These toxic oligomers, also referred to as amyloid-derived diffusible ligands (ADDLs), bind to a surface receptor on neurons and change the structure of the synapse, thereby disrupting neuronal communication. One receptor for Aβ oligomers may be the prion protein, the same protein that has been linked to mad cow disease and the related human condition, Creutzfeldt–Jakob disease, thus potentially linking the underlying mechanism of these neurodegenerative disorders with that of Alzheimer's disease (Hunter and Brayne, 2018).

In 2009, this theory was updated, suggesting that a close relative of the beta-amyloid protein, and not necessarily the beta-amyloid itself, may be a major culprit in the disease. The theory holds that an amyloid-related mechanism that prunes neuronal connections in the brain in the fast-growth phase of early life may be triggered by ageing-related processes in later life to cause the neuronal withering of Alzheimer's disease. N-APP, a fragment of APP from the peptide's N-terminus, is adjacent to beta-amyloid and is cleaved from APP by one of the same enzymes. N-APP triggers the self-destruct pathway by binding to a neuronal receptor called death receptor 6 (DR6, also known

as TNFRSF21). DR6 is highly expressed in the human brain regions most affected by Alzheimer's, so it is possible that the N-APP/DR6 pathway might be hijacked in the ageing brain to cause damage. In this model, beta-amyloid plays a complementary role, by depressing synaptic function (Hunter and Brayne, 2018).

2.2.1.7.3 Tau hypothesis:

In Alzheimer's disease, changes in tau protein lead to the disintegration of microtubules in brain cells. The tau hypothesis proposes that tau protein abnormalities initiate the disease cascade.

In this model, hyperphosphorylated tau begins to pair with other threads of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies. When this occurs, the microtubules disintegrate, destroying the structure of the cell's cytoskeleton which collapses the neuron's transport system. This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells (Wang et al., 2017c).

2.2.1.7.4 Other hypotheses:

A neurovascular hypothesis has been proposed which state that poor functioning of the blood brain barrier may be involved.

The cellular homeostasis of biometals such as ionic copper, iron, and zinc is disrupted in AD, though it remains unclear whether this is produced by or causes the changes in proteins. These ions affect and are affected by tau, APP, and APOE, and their dysregulation may cause oxidative stress that may contribute to the pathology. The quality of some of these studies has been criticised, and the link remains controversial. The majority of researchers do not support a causal connection with aluminium (Wang et al., 2017a).

Smoking is a significant AD risk factor. Systemic markers of the innate immune system are risk factors for late-onset AD. There is tentative evidence that

exposure to air pollution may be a contributing factor to the development of Alzheimer's disease. An infection with Spirochetes (a bacterium) in gum disease may cause dementia and may be involved in the pathogenesis of Alzheimer's disease.

The hypothesis is that just as the fetus goes through a process of neurodevelopment beginning with neurulation and ending with myelination, the brains of people with AD go through a reverse neurodegeneration process starting with demyelination and death of axons (white matter) and ending with the death of grey matter. Likewise the hypothesis is, that as infants go through states of cognitive development, people with AD go through the reverse process of progressive cognitive impairment (Wang et al., 2017a).

2.2.1.7.5 Neuropathology of Alzheimer’s disease:

Alzheimer's disease is characterized by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus. Degeneration is also present in brainstem nuclei like the locus coeruleus. Studies using MRI and PET have documented reductions in the size of specific brain regions in people with AD as they progressed from mild cognitive impairment to Alzheimer's disease, and in comparison with similar images from healthy older adults (Wang et al., 2017c).

Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD. Plaques are dense, mostly insoluble deposits of beta-amyloid peptide and cellular material outside and around neurons. Tangles (neurofibrillary tangles) are aggregates of the microtubule-associated protein tau which has become hyperphosphorylated and accumulate inside the cells themselves. Although many older individuals develop some plaques and tangles as a consequence of ageing, the brains of

people with AD have a greater number of them in specific brain regions such as the temporal lobe. Lewy bodies are not rare in the brains of people with AD (Wang et al., 2017c).

2.2.1.7.6 Biochemistry:

Enzymes act on the APP (amyloid precursor protein) and cut it into fragments. The beta-amyloid fragment is crucial in the formation of senile plaques in AD.

Alzheimer's disease has been identified as a protein misfolding disease (proteopathy), caused by plaque accumulation of abnormally foldedamyloid beta protein, and tau protein in the brain. Plaques are made up of small peptides, 39–43 amino acids in length, called amyloid beta (Aβ). Aβ is a fragment from the larger amyloid precursor protein (APP). APP is a transmembrane protein that penetrates through the neuron's membrane. APP is critical to neuron growth, survival, and post-injury repair. In Alzheimer's disease, gamma secretase and beta secretase act together in a proteolytic process which causes APP to be divided into smaller fragments. One of these fragments gives rise to fibrils of amyloid beta, which then form clumps that deposit outside neurons in dense formations known as senile plaques (Hunter and Brayne, 2018).

AD is also considered a tauopathy due to abnormal aggregation of the tau protein. Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubules. These microtubules act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back. A protein called tau stabilises the microtubules when phosphorylated, and is therefore called a microtubule-associated protein. In AD, tau undergoes chemical changes, becoming hyperphosphorylated; it then begins to pair with other threads, creating neurofibrillary and disintegrating the neuron's transport system (Tosto et al., 2017).

2.2.1.7.7 Disease mechanism:

Exactly how disturbances of production and aggregation of the beta-amyloid peptide give rise to the pathology of AD is not known. The amyloid hypothesis traditionally points to the accumulation of beta-amyloid peptides as the central event triggering neuron degeneration (Patel, 2017).

Accumulation of aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell's calcium ion homeostasis, induces programmed cell death (apoptosis). It is also known that Aβ selectively builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilisation ofglucose by neurons.

Various inflammatory processes and cytokines may also have a role in the pathology of Alzheimer's disease. Inflammation is a general marker of tissue damage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response. There is increasing evidence of a strong interaction between the neurons and the immunological mechanisms in the brain. Obesity and systemic inflammation may interfere with immunological processes which promote disease progression (Patel, 2017).

2.2.1.8 Diagnosis of Alzheimer’s disease:

2.2.1.8.1 Patient history:

A patient history helps the doctor assess an individual's past and current health situation. It also helps the doctor evaluate any medical problems, develop a plan of treatment, and monitor the patient's health over time. During this evaluation, the doctor asks the patient a series of questions. A thorough patient history includes Patient age and sex, Chief complaint, History of current illness, Past medical history, Current health status, Psychosocial history (marital status, living conditions, employment, sexual history, significant life events), Mental status (memory, language, driving, judgment), Family history (including any

illnesses that seem to run in the family) and Review of systems (questions about current symptoms not included in the client complaint (Ansai et al., 2017).

2.2.1.8.2 Physical Exam:

The physical examination is part of the patient care process. The exam enables the doctor to assess the overall physical condition of the patient. If the patient has a medical complaint, the physical exam provides the doctor with more information about the problem, which helps the doctor determine an appropriate plan of treatment. The physical exam may include an examination of the following depending on relevant patient history:

- Vital signs (temperature, blood pressure, pulse)
- Height and weight
- Skin
- Head, eyes, ears, nose
- Throat/neck
- Chest, including lungs and heart
- Breasts
- Abdomen
- Bones and muscles
- Nerves
- Rectal/genital area

2.2.1.8.3 Laboratory tests:

When a doctor is diagnosing a disorder, he or she often orders laboratory tests on certain fluids and tissue samples from the body. These tests can help identify problems and diseases. There are hundreds of laboratory tests available to help a doctor make a diagnosis. The most common are blood tests and urinalysis. Blood tests involve a series of tests routinely done on blood to look for

abnormalities associated with various diseases and disorders that can contribute to memory problems. These tests might be used by the doctor to help rule out other disorders that might be causing symptoms similar to those of Alzheimer's disease (Ansai et al., 2017).

2.2.1.8.4 Lumbar Puncture/Spinal Tap:

A lumbar puncture, also called a spinal tap, is a procedure in which the fluid surrounding the spinal cord (called the cerebrospinal fluid or CSF) is withdrawn through a needle and examined in a laboratory. Testing the CSF can help your doctor diagnose disorders of the central nervous system) that may involve the brain, spinal cord, or their coverings (meninges). CSF testing for protein related to Alzheimer’s disease is often done in the appropriate clinical situations to diagnose Alzheimer’s disease (Fyfe, 2018).

2.2.1.8.5 Electroencephalography (EEG):

Electroencephalography (EEG) is a medical imaging technique that measures brain function by analyzing the electrical activity generated by the brain. This activity is measured through special electrodes applied to the scalp. EEG is a completely non-invasive procedure—meaning that nothing is inserted into the body. EEGs can be used repeatedly in adults and children with virtually no risks or limitations, and is helpful in the diagnosis of brain disorders. The EEG procedure is non-invasive and painless. It is often helpful in identifying some disorders that can mimic Alzheimer's disease in specific clinical contexts (Tosto et al., 2017).

2.2.1.8.6 Electrocardiogram (ECG or EKG):

An electrocardiogram (EKG or ECG) is a recording of the heart's electrical activity. This activity is registered as a graph or series of wavy lines on a moving strip of paper. This gives the doctor important information about the

heart. For example, it can show the heart's rate and rhythm. It also can help show decreased blood flow, enlargement of the heart, or the presence of damage due to a current or past heart attack. EKGs are non-invasive, quick, safe, and painless, and are routinely done if a heart condition is suspected.

2.2.1.8.7 Neuropsychological Testing:

Neuropsychological testing studies the relationship between the brain and behavior. It is used when the patient is having serious problems with short- and long-term memory, attention and concentration, word and name association, language understanding, and other symptoms that persist or worsen over time. These tests help in the diagnosis and treatment of conditions that affect thinking, emotion, and behavior. These include Alzheimer's disease, various psychiatric problems (depression, anxiety disorders), medication-related conditions, substance abuse, strokes, and tumors. Neuropsychological tests accompany a comprehensive interview with the patient, and might include tests to assess attention, memory, language, the ability to plan and reason, and the ability to modify behavior, as well as assessments of personality and emotional stability. Neuropsychological testing also can help the doctor and family better understand the impact of a disorder on a patient's everyday functioning.In addition, the following tests also might be done to help diagnose and monitor the progression of Alzheimer's disease (Ritter et al., 2017).

2.2.1.8.8 Positron Emission Tomography (PET) Scan:

PET scanning is a three-dimensional imaging technique, utilizing the injection of a radioactive tracer that allows a doctor to examine the heart, brain, or other internal organs. PET scans can also show how the organs are functioning; unlike X-ray, CT, or MRI, which show only body structure. PET is particularly useful for the detection of cancer and coronary artery disease, and can provide information to pinpoint and evaluate diseases of the brain. PET imaging can

show the region of the brain that is causing a patient to have seizures, and is useful in evaluating degenerative brain diseases such as Alzheimer's, Huntington's, and Parkinson's. PET scans can show the difference in brain activity between a normal brain and one affected by Alzheimer's disease. It can also help differentiate Alzheimer's disease from other forms of dementia. Amyloid imaging is a special type of PET scanning which shows deposits of amyloid, a protein, in the brain and provides a high degree of confidence in the diagnosis (Nordberg, 2004).

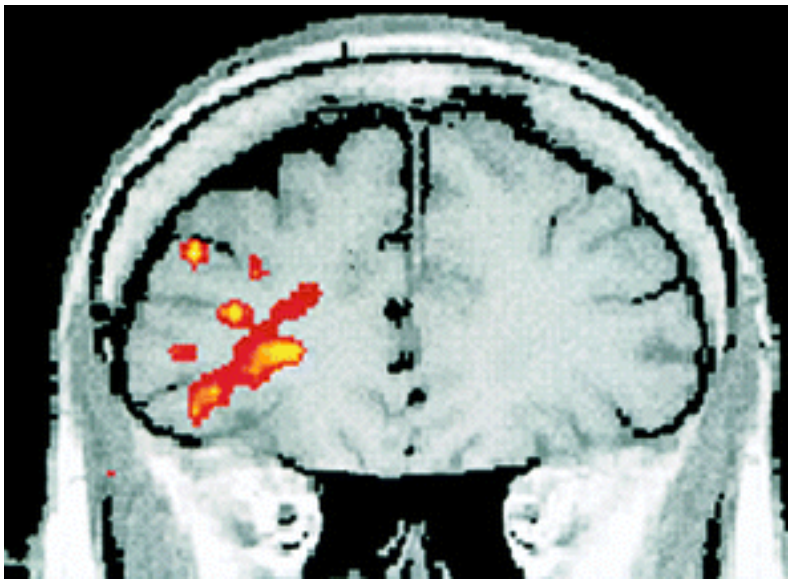

Figure 2.8: Differences in sites and sizes of regions of brain activation after memory task of patient with mild cognitive impairment and control subject. 67-year-old man shown in B was one of group of subjects with mild cognitive impairment who were found to have statistically less activation than control subjects in five of seven brain regions studied; similar trend that was not statistically significant was seen in other two brain regions. Brain activation studies in both groups were obtained in identical fashion and were analyzed using same statistical threshold, smoothing and clustering. (Courtesy of Petrella J, Durham, NC) Brain activation functional imaging performed during memory task in 71-year-old man with normal cognitive functioning, on no medication, shows robust activation (depicted in colored voxels) in right frontal lobe.

2.2.1.8.9 Single Photon Emission Computed Tomography (SPECT) Scan:

SPECT is a non-invasive technique for creating very clear, three-dimensional pictures of a major organ, such as the brain or heart. SPECT scans use radionuclide imaging – a technique that involves the injection of a very small amount of a radioactive substance, called a tracer. Energy from the tracer in the body is detected by a special camera, which then takes the pictures. SPECT can map blood flow in certain regions of the brain, and is useful in evaluating specific brain functions. This might reveal abnormalities that are characteristic of Alzheimer's disease. Dopamine transporter SPECT is a special type of SPECT used in Parkinson's disease and Lewy body dementia (Nordberg, 2004).

2.2.1.8.10 Measurement and imaging of cerebral function in ageing and dementia:

There has been considerable interest in the measurement of cerebral energy metabolism in the dementing diseases since such measurements became possible in man in the 1940’s. The original interest was due to the prevalent pathogenic theories relating to chronic cerebrovascular insufficiency as a cause of dementia, not fully revised until the seminal work of the Newcastle pathologists in the late 1960’s (Tomlinson et al., 1970). Concomitant with the change in pathological emphasis from chronic ischaemic to degenerative processes, techniques became available for the regional mapping of cerebral blood flow in man (Lassen and Ingvar, 1963). It had been shown that flow and energy consumption in the cerebral hemisphere were coupled in normal man under resting conditions and so regional flow information was taken to reflect regional cerebral metabolism, albeit indirectly (Wang et al., 2017c).

The search for diagnostic patterns of flow abnormalities and for structural-pathophysiological correlations in ageing and the various types of dementia became a principal goal of research. As patterns of metabolic dysfunction were

identified, the relationship of changes in normal ageing to pathological processes became a field of primary interest. This was paralleled by the elaboration of sophisticated techniques for measuring cerebral flow and glucose metabolism in animals with a very high degree of regional precision, using autoradiographic techniques (Sokoloff, 1984).

Anatomical localisation in human studies advanced dramatically with the application of tomographic reconstruction techniques to imaging by transmitted (X-ray) or emitted (pray) radiation. With X-ray computed tomography (CT) the main thrust of research has been clinical and oriented diagnostically. The differentiation between the degenerative and vascular dementias has occupied the majority of workers and, as a result, much effort has also been expended on defining structural changes in the brain that accompany normal as well as abnormal ageing (Wang et al., 2017b).

Positron-emission tomography (PET) has developed into a technique for applying quantitative tracer methodology to investigate cerebral function regionally in man. In terms of dementia and ageing, studies have to-date concentrated on reexamining the significance of disturbed energy metabolism, though more recently investigations of specific neurotransmitter pathways in certain dementing diseases have also commenced. The eventual aim of research with these functional imaging tools must be the elucidation of pathophysiological mechanisms and to some degree this has been a feature of some studies already (Nordberg, 2004).

There are also diagnostic and predictive features in functional images which are becoming identified in certain specific dementing illnesses. Most recently, the techniques of nuclear magnetic resonance (NMR) imaging and, hopefully in the near future, NMR spectroscopy are being applied to investigations of the dementias (Bessonet al., 1985). The former represents an apparently safe technique sensitive to structural changes which involve alterations in cerebral water or fat content. NMR imaging appears to be providing new information

concerning the extent of white matter disease in certain varieties of dementing illness (Bradley et al., 1984). The application of NMR spectroscopy to topical measurements in the human brain in vivo is in its infancy (Pritchard et al., 1983). In the near future it seems unlikely that information on more than high energy phosphates and pH will be readily available. However, the possibility of recognizing changes in amino acid concentrations of possible significance for neurotransmission using proton, as opposed to phosphorus spectroscopy is conceivable (Nordberg, 2004).

In summary it can be said that imaging and measurement of cerebral metabolism and blood flow continues to occupy clinical research for the following reasons. It allows the localization of areas of dysfunction in vivo with increasing precision, which permits a study of the natural history of the diseases in functional terms which can then be correlated to specific structures. This localisation of in vivo pathophysiology may have clinical implications in terms of prognosis and in pointing towards new, possibly fruitful areas of investigation. However, it seems reasonable to suggest that the thrust of new research must now progress beyond isolated studies of energy metabolism towards more fundamental questions concerning the delineation of possible specific neuronal populations affected in dementia. The measurement of physiological, biochemical and pharmacological variables in absolute units also presents a unique opportunity to monitor the effects of therapeutic intervention objectively. Disturbances of other aspects of metabolism, e.g. amino acid turnover and protein metabolism, analysis of receptor function, transmitter storage and release and the selective marking and function of glial as well as neuronal elements in the brain are further areas which may become amenable to study. Metabolic imaging and measurement with PET will be at the forefront of such clinically oriented research in man. It is also clear that many of the insights into the mechanisms underlying the degenerative dementias are, and will continue to come from in vitro metabolic studies, molecular biology and

genetics and in work with animal models, testing infective and other theories of pathogenesis. The remainder of this chapter will review the work of the last 40 years into the changes of cerebral energy metabolism and blood flow that accompany human ageing and dementia (Weiner et al., 2009).

2.2.1.8.11 Normal Ageing:

Hemispheric measurements Studies of cerebral blood flow in the brain of man Began with Kety and Schmidt who developed a technique for measuring the mean flow per hemisphere. Extension of the method to include arteriovenous substrate or metabolite differences permits the measurement of mean uptake or release rates into or from the brain. The initial studies dating from the late 1940's showed a mean cerebral blood flow (CBF) of 52 m1/100 g/min with an oxygen consumption (CMRO2) of 3.5 m1/100 g/min and an arteriovenous oxygen difference (A-VO2) of 6.6 vol% corresponding to a fractional oxygen extraction (OER) of 0.37. The effects of hyperoxia and hypoxia as well as hyper- and hypocapnia were studied (Kety and Schmidt, 1946, 1948b). Relative anoxia caused by inhalation of 10% oxygen gas led to a significant fall in arterial oxygen content, compensating hyperventilation and hypocapnia. Under these circumstances, CBF rose with evidence of peripheral vasodilation but CMRO2 remained constant. Hyperoxia caused by inhalation of 100% oxygen gas resulted in a rise in oxygen content of arterial blood, no change in Pco,, a fall in CBF with again no change in CMR,,. There was evidence of vasoconstriction in the cerebral vasculature with an increase in vascular resistance. Hypercapnia under normoxic conditions resulted in respiratory acidosis, an increase in CBF, a marked fall in OER to 0.29 but no change in CMR,,. The increase in CBF was accompanied by a marked fall in cerebrovascular resistance. Thus in these early experiments, the evidence was clear that homeostatic mechanisms served to maintain a constant cerebral oxygen consumption. In the case of altered oxygen content, blood flow rose or

fell to maintain a constant oxygen delivery (CBF x arterial oxygen content). However, if oxygen delivery was compromised, by interference with blood flow homeostasis, oxygen extraction rose or fell appropriately, thus maintaining energy metabolism and, hence, function. One of the observations made by Kety and Schmidt in their paper relating to the effects of hyperventilation and anoxia (1 948b) remains pertinent to all subsequent studies. They noted that despite constant CMRO2 mental changes were observed in their subjects. They speculated that "derangement of higher functions may occur from subtle or complex biochemical changes" and that their description in terms of CMR,, alone was as inadequate as predicting the fidelity of a radio by its power requirements. Investigation of changes in CBF and CMR,, associated with increasing age has occupied many subsequent researchers. Kennedy investigated children with the nitrous oxide (Kety-Schmidt) technique and showed in nine normal children with a mean age of 6 years that CBF averaged 106 m1/100 mg/min - twice that of normal young men. CMR,, averaged 5.2 ml O,/IOO ml/min, an increase of 50%. The fractional oxygen extraction was therefore considerably lower than in early adulthood (0.3 1 cf. 0.37).This finding raises important questions. What is the nature of the CBF: CMR, couple and what determines its setting, as measured with the OER? Why is the metabolism of children's brains higher than that of young adults - is this a finding of physiological significance, or an artifact (Fleisher et al., 2008).

In terms of ageing, Kety reviewed in 1956 the 16 studies employing the nitrous oxygen technique to that date that had produced information on this subject. The studies quoted gave data from groups of subjects numbering 4 to 19, of mean ages ranging from 6 to 93. CBF seemed to decline with age; the largest decrease occurring in children and teenagers in who average CBF in four groups of increasing age was 104, 90, 68 and 60 m1/100 g/min. By the twenties, CBF stabilised out at between 52 and 65 m1/100 g/min, remaining in the fifties until subjects of mean age 68 and 93 were reported with mean CBF of 43 and 39

m1/100 g/min, respectively. Kety commented that from young adulthood to old age there appeared to be a 25% reduction in CBF. The decline in CMRO2 was less pronounced and of the order of 20%. However, this latter figure was greatly biased by very low values in the groups of mean age 68 and 93. Finally, Kety demonstrated that these pooled results suggested a small increase of A-Vo, with age. The problem with these data is that the nitrous oxide technique had undergone modifications so that not all the results were strictly comparable and the various age groups were represented by a greater or lesser number of subjects. Nevertheless there was a hint that the process of ageing was associated with some decline in metabolic and flow parameters, which were not exactly parallel and were associated with a gradual resetting of the flow: metabolism couple such that the proportion of oxygen extracted by the brain gradually increased. A major problem with these studies was that the ageing populations were not adequately selected for normality and a disease-free state. Indeed some subjects had hypertension and various other diseases since many subjects were drawn from hospitalized populations.

As a result of this, with thorough testing and a "process of clinical evaluation and elimination," doctors today can diagnose Alzheimer's disease with over 90% probability. The disease is present when tests specific to Alzheimer’s disease are positive, i.e., 90% to 100% positive predictive value. The following diagnostic tools might be used to help make a diagnosis of Alzheimer's disease:

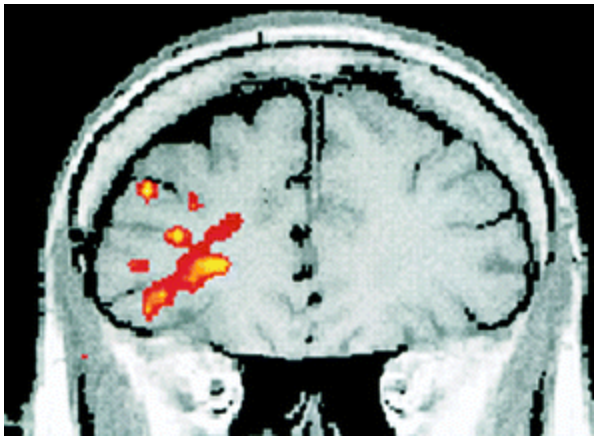

Figure 2-9. —Differences in sites and sizes of regions of brain activation after memory task of patient with mild cognitive impairment and control subject. 67-year-old man shown in B was one of group of subjects with mild cognitive impairment who were found to have statistically less activation than control subjects in five of seven brain regions studied; similar trend that was not statistically significant was seen in other two brain regions. Brain activation studies in both groups were obtained in identical fashion and were analyzed using same statistical threshold, smoothing and clustering. (Courtesy of Petrella J, Durham, NC) Brain activation functional imaging performed during memory task in 71-year-old man with normal cognitive functioning, on no medication, shows robust activation (depicted in colored voxels) in right frontal lobe.

2.2.1.8.12 Computed tomography (CT) scan:

A computed tomography (CT) scan is a technique in which multiple X-rays of the body are taken from different angles in a very short period of time. These images are then fed into a computer, which creates a series of cross-sectional "slices" of the body. Contrast material could be given if needed depending on the patient's clinical history to help differentiate abnormal regions of the brain. CT imaging creates the images by measuring how quickly the body and organs absorb the X-rays. CT scans often can reveal certain changes that are characteristic of Alzheimer's disease in its later stages. These changes include a reduction in the size of the brain (atrophy), widened indentations in the tissues, and enlargement of the fluid-filled chambers called cerebral ventricles (Johnson et al., 2012).

The uncertainty inherent in a clinical diagnosis of AD has driven a search for diagnostic imaging markers. A definitive diagnosis still requires

histopathological confirmation and the inaccessibility of the brain means imaging has a key role as a window on the brain. Historically, imaging—first computed tomography (CT) and then MRI—was used only to exclude potentially surgically treatable causes of cognitive decline. Now its position in diagnosis also includes providing positive support for a clinical diagnosis of AD in symptomatic individuals by identifying characteristic patterns (signatures) of structural and functional cerebral alterations. We can now also visualize the specific molecular pathology of the disease—amyloid deposits—with amyloid imaging. Alongside this increasing specificity for AD, imaging also contributes to differential diagnosis in practice by identifying alternative and/or contributory pathologies. Imaging is central to identifying vascular and non-AD degenerative pathologies and has helped in the recognition of the prevalence of mixed pathology in dementia (Fleisher et al., 2008).

In the setting of mild cognitive impairment (MCI), the determination of underlying pathology carries immediate prognostic importance. Only a fraction of patients with MCI progress to clinical AD over 5–10 years (Ganguli et al., 2004) and a recent meta-analysis concluded that most people with MCI will not progress to dementia even after 10 years of follow-up Two community-based studies have shown over one-third of patients diagnosed with MCI at baseline may eventually return to normal cognition. Obviously, it would be of great value to be able to predict which MCI subjects were destined to progress to a clinical diagnosis of AD. This is true even in the absence of disease-modifying treatments, but will be especially critical when disease-modifying treatments become available (Ritchie et al., 2017).

Looking to the future, imaging has helped establish that there is a long preclinical and presymptomatic period where the pathological effects of AD are detectable. Although more data are needed, imaging is starting to provide prognostic information at this early preclinical stage. The need for an earlier and

more certain diagnosis will only increase as disease-modifying therapies are identified. This will be particularly true if, as expected, these therapies work best (or only) when initiated at the preclinical stage (Ritchie et al., 2017).

2.2.1.8.13 Specialized Tests:

The doctor may call for a blood test in cases where there's a family history of early-onset Alzheimer's. To date, genetic testing offers diagnostic value only in cases of early-onset familial Alzheimer's disease. Searching for genetic mutations in individuals who do not have a strong family history of Alzheimer's and who did not show symptoms before age 65 is fruitless (Van Straaten et al., 2004).

The test for the ApoE genotype can increase diagnostic confidence somewhat, but it isn't recommended for screening purposes. The role of neuroimaging in dementia nowadays extends beyond its traditional role of excluding neurosurgical lesions. Radiological findings may support the diagnosis of specific neurodegenerative disorders and sometimes radiological findings are necessary to confirm the diagnosis. It is a challenge for neuroimaging to contribute to the early diagnosis of neurodegenerative diseases such as Alzheimer's disease (Van Straaten et al., 2004).

Early diagnosis includes recognition of pre-dementia conditions, such as mild cognitive impairment (MCI). In addition, early diagnosis allows early treatment using currently available therapies or new therapies in the future. Neuroimaging may also be used to assess disease progression and is adopted in current trials investigating MCI and AD (Johnson et al., 2012).

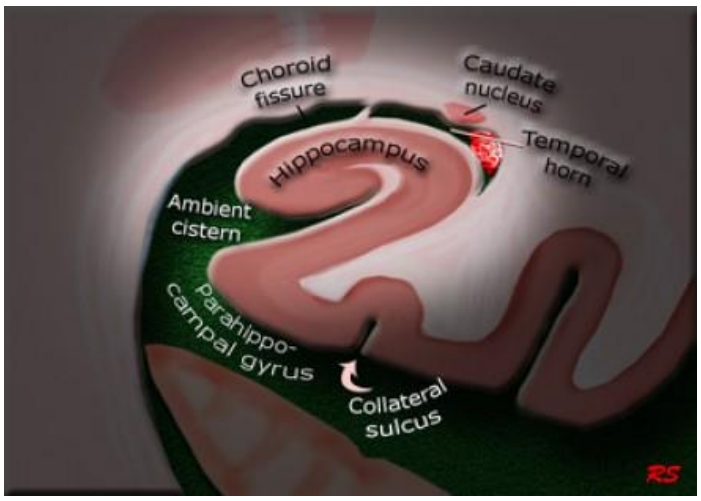

Figure 2-10: The coronal image shows the hippocampus, the main structure involved in many forms of dementia.

2.2.1.8.14 Diagnosis of the Alzheimer Diseases by MRI:

The initial criteria for CT scan diagnosis of Alzheimer disease includes diffuse cerebral atrophy with enlargement of the cortical sulci and increased size of the ventricles. A multitude of studies indicated that cerebral atrophy is significantly greater in patients with Alzheimer disease than in patients who are aging without Alzheimer disease (Van Straaten et al., 2004).

This concept was soon challenged, however, because cerebral atrophy can be present in elderly and healthy persons, and some patients with dementia may have no cerebral atrophy, at least in the early stages. The extent of cerebral atrophy was determined by using linear measurements; in particular, bifrontal and bicaudate diameters and the diameters of the third and lateral ventricles. Various measurements were adjusted according to the diameter of the skull to account for normal variation (Van Straaten et al., 2004).

To complement this modification, volumetric studies of the ventricles were done. Despite these efforts, it is still difficult to distinguish between findings in a healthy elderly patient and those in a patient with dementia. In addition, a review of serial CT scans obtained over several months was not clinically useful

in the primary diagnosis of the disease (Ritter et al., 2017).

2.2.1.8.14.1 Rate of change of brain atrophy:

Changes in the rate of atrophy progression can be useful in diagnosing Alzheimer disease. Longitudinal changes in brain size are associated with longitudinal progression of cognitive loss and enlargement of the third and lateral ventricles is greater in patients with Alzheimer disease than in control subjects (Frisoni et al., 2010).

2.2.1.8.14.2 Changes in brain structure:

Diffuse cerebral atrophy with widened sulci and dilatation of the lateral ventricles can be observed. Disproportionate atrophy of the medial temporal lobe, particularly of the volume of the hippocampal formations (< 50%), can be seen. Dilatation of the perihippocampal fissure is a useful radiologic marker for the initial diagnosis of Alzheimer disease, with a predictive accuracy of 91%. The hippocampal fissure is surrounded laterally by the hippocampus, superiorly by the dentate gyrus, and inferiorly by the subiculum. These structures are all involved in the early development of Alzheimer disease and explain the enlargement in the early stages (Frisoni et al., 2010).

At the medial aspect, the fissure communicates with the ambient cistern, and its enlargement on CT scans is often seen as hippocampal lucency or hypoattenuation in the temporal area medial to the temporal horn. The temporal horns of the lateral ventricles may be enlarged. Prominence of the choroid and hippocampal fissures and enlargement of the sylvian fissure may be noted. White matter attenuation is not a feature of Alzheimer disease (Frisoni et al., 2010).

2.2.1.8.14.3 Degree of Confidence:

CT scan indices of hippocampal atrophy are highly associated with Alzheimer disease, but the specificity is not well established. Use of a no quantitative

rating scale showed a sensitivity of 81% and a specificity of 67% in differentiating 21 patients with Alzheimer disease with moderate dementia from 21 age-matched control subjects. Hippocampal volumes in a sample of similar size permitted correct classification of 85% of control subjects (Farid et al., 2012).

2.2.1.8.14.4 False positives/negatives:

Hippocampal atrophy appears to be a feature of vascular disease (multi-infarct dementia) and Parkinson disease, even in patients with Parkinson disease without dementia. Hippocampal and entorhinal cortical atrophy are features offrontotemporal dementia, but they do not appear to be as profound as atrophy is in Alzheimer disease (Farid et al., 2012).

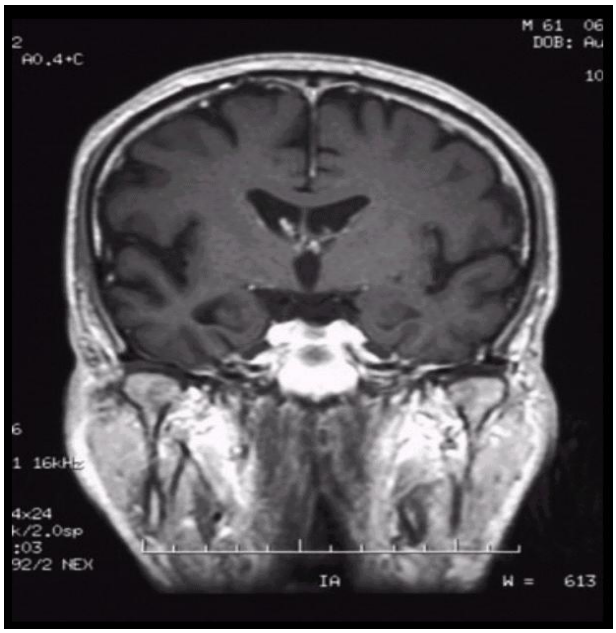

Figure 2.11: Coronal, T1-weighted magnetic resonance imaging (MRI) scan in a patient with moderate Alzheimer disease. Brain image reveals hippocampal atrophy, especially on the right side.

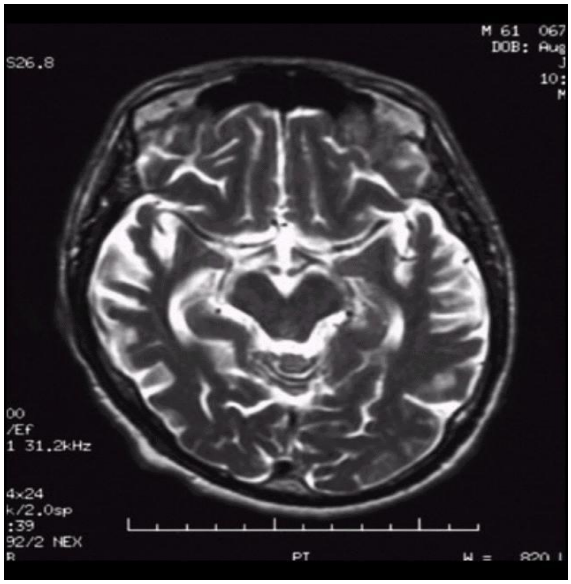

Figure 2.12: Axial, T2-weighted magnetic resonance imaging (MRI) scan of the brain reveals atrophic changes in the temporal lobes.

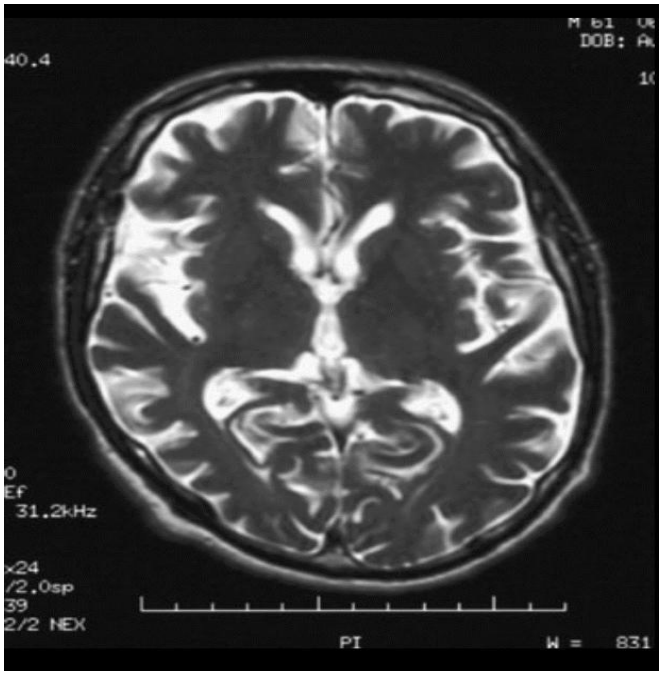

Figure 2.13: Axial, T2-weighted magnetic resonance imaging (MRI) scan shows dilated sylvian fissure resulting from adjacent cortical atrophy, especially on the right side.

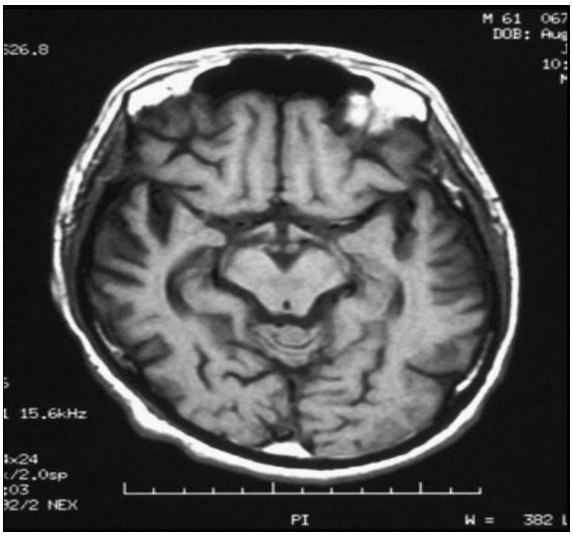

Figure 2.14 Axial, T1-weighted magnetic resonance imaging (MRI) scan shows a dilated sylvian fissure caused by adjacent cortical atrophy.

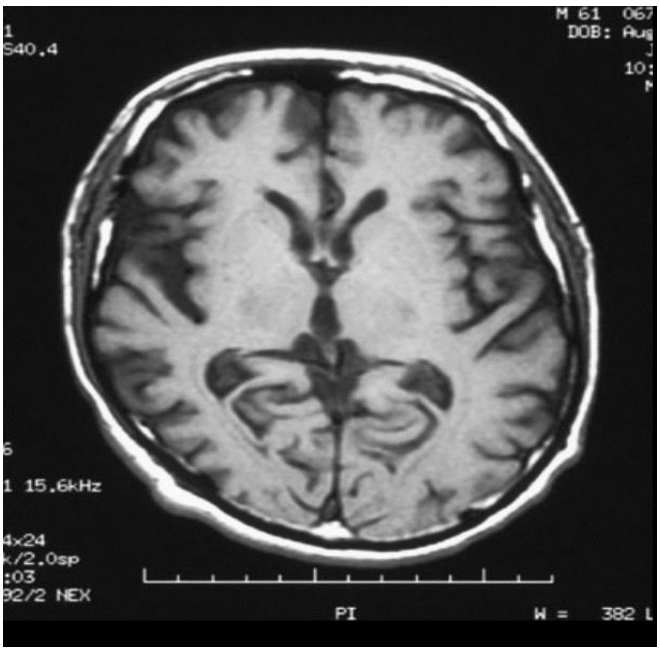

Figure 2.15. Axial, T1-weighted magnetic resonance imaging (MRI) scan shows bilateral cortical atrophy with accentuated cortical sulci; there is decreased involvement in the posterior aspect.

2.2.1.8.14.5 Basics of Structural MRI as Applied to AD:

MRI utilizes the fact that protons have angular momentum which is polarized in a magnetic field. This means that a pulse of radiofrequency can alter the energy state of protons and, when the pulse is turned off, the protons will, on returning to their energy stage, emit a radiofrequency signal. By a combination of different gradients and pulses, "sequences" can be designed to be sensitive to

different tissue characteristics. In broad terms structural MRI in AD can be divided into assessing atrophy (or volumes) and changes in tissue characteristics which cause signal alterations on certain sequences such as white matter hyperintensities on T2-weighted MRI as a result of vascular damage. A number of MR sequences that are sensitive to microstructural change (e.g., magnetization transfer or diffusion) have shown alterations in AD. These sequences are already important research tools; however, they have not yet found a place in routine clinical practice in AD and they will not be considered further here (Stoub et al., 2005).

2.2.1.8.14.6 Utility of Structural MRI in Atrophy of AD:

Progressive cerebral atrophy is a characteristic feature of neurodegeneration that can be visualized in life with MRI (best with T1-weighted volumetric sequences). The major contributors to atrophy are thought to be dendritic and neuronal losses. Studies of regional (e.g., hippocampal) MRI volumes have shown these are closely related to neuronal counts at autopsy (Bobinski et al., 1999). The pattern of loss differs between diseases reflecting selective neuronal vulnerability and/or regional disease expression. AD is characterized by an insidious onset and inexorable progression of atrophy that is first manifest in the medial temporal lobe (Shanks et al., 2007).

The entorhinal cortex is typically the earliest site of atrophy, closely followed by the hippocampus, amygdala, and parahippocampus (Lenzi et al., 2011). Other structures within the limbic lobe such as the posterior cingulate are also affected early on. These losses then spread to involve the temporal neocortex and then all neocortical association areas usually in a symmetrical fashion. This sequence of progression of atrophy on MRI most closely fits histopathological studies that have derived stages for the spread of neurofibrillary tangles Nonetheless, a significant minority of AD cases have atypical presentations and in these cases the pattern of atrophy accords with clinical phenotype (Lenzi et al., 2011).

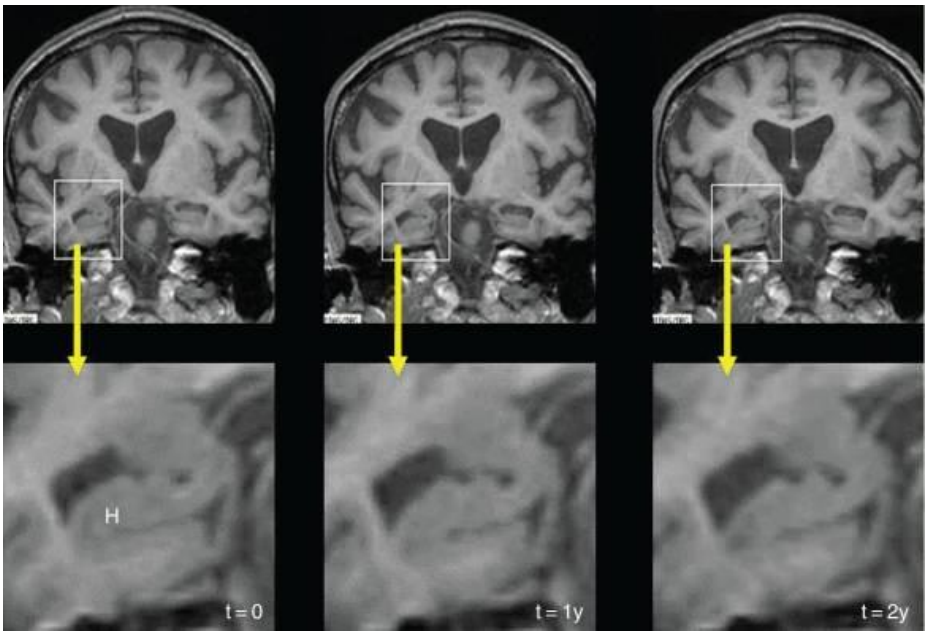

Figure 2.16 This series of three coronal T1-weighted studies, from an individual with autopsy-proven Alzheimer disease (AD), were each acquired 1 yr apart and show progressive hippocampal (H) atrophy as the individual progressed from memory complaints (*left* column, t = 0) to MCI (*center*, t = 1y) and on to fulfill criteria for AD.

This series of three coronal T1-weighted studies, from an individual with autopsy-proven Alzheimer disease (AD), were each acquired 1 yr apart and show progressive hippocampal (H) atrophy as the individual progressed from memory complaints (It is increasingly clear that by the time a typical AD patient comes to diagnosis atrophy is well established. Even in mildly affected individuals (e.g., mean MMSE of 24/30) entorhinal volumes are already reduced by 20–30% and hippocampal volumes by, 15–25%. Because rates of hippocampal atrophy in mild AD are 3–5% per year this suggests that there must have been a period of several years before diagnosis where medial temporal lobe atrophy was already in process (Schuff et al., 2009).

Longitudinal MRI studies of individuals who are initially asymptomatic but who subsequently develop AD support this suggestion and find that hippocampal volumes are already reduced by about 10% 3 years before receiving a diagnosis of dementia due to AD and that rates of hippocampal atrophy increase gradually some 5 years before diagnosis. By the time a clinical diagnosis is made, atrophy is also quite widespread with whole brain volumes

down by 6%; rates of loss having gradually accelerated (at 0.3% per year) in the 2–4 years up to a diagnosis (Chen et al., 2010).

Assessment of medial temporal atrophy on MRI has been shown to have positive predictive value for AD. Visual assessment differentiates mild AD from normal aging with a sensitivity and specificity of 80–85%. Differentiating MCI subjects who will progress to AD in the near future from those who will not is a more difficult task: Medial temporal atrophy on MRI is still a very significant predictor of progression with sensitivity and specificity of 50–70% for distinguishing individuals who will progress to AD from those who will not. For these reasons medial temporal lobe atrophy now forms one of the biomarkers of AD included in proposed criteria for diagnosing (prodromal) AD at a pre-dementia stage (Dubois et al., 2007). The severity of hippocampal atrophy tends to be greater in AD than in dementia with Lewy bodies (DLB) or vascular dementia (VaD)—when matched for clinical severity. Nonetheless, hippocampal atrophy is a feature of DLB and VaD, and in frontotemporal dementia (FTD) can be more severe anteriorly than in AD (Scheltens et al., 2002).

The differential diagnosis of AD therefore needs to take into account the overall pattern of imaging (and other) features of these dementias: for instance, focal frontal/temporal lobar atrophy on MRI would point to a diagnosis of FTD, whereas marked signal changes in white matter may suggest VaD. The overall pattern of atrophy is used in clinical practice and there is interest in automated pattern classification of MRI to predict AD at an early stage and to distinguish it from other dementias (Chen et al., 2010).

2.2.1.8.14.7 Measuring Progression in AD with Structural MRI:

The fact that pathologically increased cerebral atrophy starts early (even presymptomatically), continues relentlessly, at least until individuals are severely affected, and correlates with clinical decline has led to atrophy on MRI being suggested as a marker of disease progression and a potential outcome measure in trials. The amount, distribution, and rate of cerebral atrophy are all

closely correlated with cognitive deficits. In the absence of an intervention cerebral volume loss in AD has clear, direct, and profound negative clinical consequences. Epidemiological-autopsy studies of individuals with and without dementia showed that, whereas plaques, tangles, and atrophy are all associated with dementia, atrophy was the factor that most strongly correlated with dementia at all ages (Hua et al., 2008).

It appears that histopathological hallmarks of AD are markers of disease process whereas the clinical state is captured by the extent of neurodegeneration—for which atrophy may be considered an in vivo measure. Rates of regional and/or global atrophy on MRI have as a result been proposed as outcome measures in trials seeking to show a disease-modification effect in AD; the motivation for this is the potentially increased power to detect a disease-slowing effect. Sample size calculations based on natural history studies would support this with only 20% as many patients being expected to be needed for the same effect using MRI measures than if clinical scales were used (Schuff et al., 2009).

Rates of hippocampal and whole brain atrophy on MRI have to date been the most widely included imaging measures in trials; however, other MRI measures show promise, including cortical thickness or composites of change. The validation of this approach, however, awaits the discovery of disease-modifying therapies particularly as therapies may have an effect on progression of volume loss through mechanisms other than reduced rates of neuronal loss (e.g., hydration, inflammatory, and anti-inflammatory effects). It is likely that multiple imaging and fluid biomarkers will be included in trials that seek to understand as well as measure effects on disease progression (Fox et al., 2005).

2.2.1.8.14.8 Availability and Utility of Structural MRI:

An obvious strength of MRI is its availability. A testament to its value in diagnosis in dementia is the fact that European and U.S. guidelines recommend that all subjects with cognitive decline undergo structural imaging (MRI or CT) and that it is part of proposed diagnostic criteria for AD and for other dementias.

In most centers, MRI is regarded as an essential investigation in dementia—a marker of its utility. Although not as rapid as CT, a typical high-resolution volumetric sequence can be acquired in 5–10 min and more basic sequences in considerably less time. MRI is safe and as it does not involve ionizing radiation individuals can be imaged serially without concerns about carcinogenicity. MRI offers a range of different sequences that can probe different tissue characteristics providing multiple clinical and research measures in the same session. Atrophy as an outcome measure has strengths over clinical measures because it is not subject to practice effects or (realistically) to floor or ceiling effects, and it theoretically has a greater ability to detect disease slowing. MRI measures of atrophy reflect cumulative neuronal damage which in turn is directly responsible for clinical state. When compared with other imaging markers (and other biomarkers) cerebral atrophy has, as strength, its strong correlation with cognitive decline (Dubois et al., 2007).

2.2.1.8.14.9 Limitations of Structural MRI in AD:

Structural MRI lacks molecular specificity. It cannot directly detect the histopathological hallmarks of AD (amyloid plaques or neurofibrillary tangles) and as such it is downstream from the molecular pathology. Cerebral atrophy is a nonspecific result of neuronal damage and, whereas certain patterns of loss are characteristic of different diseases, they are not entirely specific. Atrophy patterns overlap with other diseases and unusual forms of AD have atypical patterns of atrophy too. In more severely affected individuals and those with claustrophobia, MRI may not be tolerated whereas a rapid CT scan may be more feasible. In terms of measuring progression, volume changes on MRI may be produced by factors other than the progression of neuronal loss and as such assessment of disease modification may be obscured, at least in the short term, by such spurious effects. As the name implies, structural MRI cannot assess function; this is provided with increasing sophistication by functional MRI and PET (Dubois et al., 2007).

Overall the availability, ease of use, and multiple applications of structural MRI in AD mean it will play a central role in research and practice for some years to come. Increasingly, the other (complementary) modalities described in this article will address the weaknesses of MRI (Frisoni et al., 2010).

CHAPTER THREE

MATERIALS AND METHOD

3.1 Area of the study:

The study was conducted in Khartoum – Sudan at Royal Care Hospital during 2015 – 2018.

3.2 Subjects:

The study included two groups. Group (A) were 100 healthy individuals (66 males, 34 females), Group (B) 302 patients (200 male and 102 female) with high probability of AD. The mean age of all patients was 45 years. All subjects underwent thorough clinical and cognitive assessments at the time of their MRI scans. Each subject's cognitive evaluation included: (i) the Mini-Mental State Examination (MMSE) to provide a global measure of mental status; (ii) the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog). They have been classified as predementia, early stage of AD, moderate AD and late stage of AD. Consent was obtained and the Ethical Committees of the Hospital in which the work was performed approved the study.

3.3 Machine used:

MRI studies were performed on 1.5 Tesla Toshiba whole body MR systems using standard imaging head coil.

3.4 Technique used:

Routine brain MRI was performed in 3 orthogonal planes, including at least T1, T2, and fluid-attenuated inversion recovery (FLAIR) weighted images. T1-weighted images after intravenous gadolinium-based contrast material administration were obtained in at least 2 planes.

Coronal-oblique T1-weighted images are used for the assessment of medial temporal lobe and hippocampal atrophy. They are obtained in a plane orthogonal to the long axis of the hippocampus; this plane is orientated parallel to the brainstem. These should be thin-section images and are ideally obtained by reformatting a sagittal 3D T1 sequence through the entire brain. Additional

sagittal reconstructions will enable the assessment of midline structures as well as parietal atrophy, which may be involved in certain neurodegenerative disorders. FLAIR images are used to assess global cortical atrophy (GCA), vascular white matter hyperintensities and infarctions.

Table 3.1: MRI Protocol Dementia	
Sag T1W	3D MPRAGE isotropic voxels coronal reformat perpendicular to hippocampi
Tra FlAIR	3mm slices, 1mm isotropic voxels
Tra T2W	3mm slices, 1mm isotropic voxels
Tra T2*	Gradient –echo, 3mm slices, TE>20ms, small flip angle

3.5 Image interpretation:

3.5.1 Assessment of MR in Dementia:

MR-study of a patient suspected of having dementia was assessed in a standardized way. First of all, treatable diseases like subdural hematomas, tumors and hydrocephalus need to be excluded. Next we should look for signs of specific dementias such as:

- Alzheimer's disease (AD): medial temporal lobe atrophy (MTA) and parietal atrophy.
- Frontotemporal Lobar Degeneration (FTLD): (asymmetric) frontal lobe atrophy and atrophy of the temporal pole.
- Vascular Dementia (VaD): global atrophy, diffuse white matter lesions, lacunes and 'strategic infarcts' (infarcts in regions that are involved in cognitive function).
- Dementia with Lewy bodies (DLB): in contrast to other forms of dementia usually no specific abnormalities

Then MR images was scored in a systematic way for global atrophy, focal atrophy and for vascular disease (i.e. infarcts, white matter lesions, lacunes) as

illustrated in the table below:

Table 3.2: MR Findings in Dementia				
	AD	**VaD**	**FTLD**	**Lewi**
Hippocapal atrophy	+++	++	++	_
Temporal Atrophy	++	_	+++	_
Frontal Atrophy	_	_	_	_
Parietal Atrophy	++	+	_	_
Lacunes	_	+++	_	_
WML'S	_	+++	_	_
Strategic Infarcts	_	+++	_	_

MRI findings in a patient with cognitive disorder was assessed using the following standardized method:

1. GCA-scale for Global Cortical Atrophy
2. MTA-scale for Medial Temporal lobe Atrophy
3. Koedam score for parietal atrophy
4. Fazekas scale for WM lesions
5. Looking for strategic infarcts

Table 3.3: MR Assessment in Dementia	
Global Atrophy	Vascular Dementia Normal aging
Med Temp Atrophy	AD,FTLD,(asymmetric)
Frontal Atrophy	FTLD
WML'S	Vascular Dementia Normal Aging
Strategic Infarcts	Vascular Dementia

3.5.1.1 GCA-scale for Global Cortical Atrophy:

GCA scale is the mean score for cortical atrophy throughout the complete cerebrum:

- 0: no cortical atrophy
- 1: mild atrophy: opening of sulci
- 2: moderate atrophy: volume loss of gyri
- 3: severe (end-stage) atrophy: 'knife blade' atrophy.

3.5.1.2 MTA-scale for Medial Temporal lobe Atrophy:

The MTA-score should be rated on coronal T1-weighted images at a consistent slice position. Select a slice through the corpus of the hippocampus, at the level of the anterior pons.

Table 3.4: MTA visual rating scale

Score	Width of choroid fissure	Width of Temporal horn	Height of hippocampal formation
0	N	N	N
1	↑	N	N
2	↑↑	↑↑	↓
3	↑↑↑	↑↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓

3.5.1.3 Fazekas scale for WM lesions:

On MR, white matter hyperintensities (WMH) and lacunes – both of which were frequently observed in the elderly – are generally viewed as evidence of small vessel disease. The Fazekas-scale provides an overall impression of the presence of WMH in the entire brain. It is best scored on transverse FLAIR or

T2-weighted images, score were rated as follows:

- Fazekas 0: None or a single 59unctuate WMH lesion
- Fazekas 1: Multiple 59unctuate lesions
- Fazekas 2: Beginning confluence of lesions (bridging)
- Fazekas 3: Large confluent lesions

3.5.1.4 Assessment of normal ageing:

The findings in a normally aging brain can overlap with findings in dementia. As implicated earlier, there may be some degree of atrophy, though mainly of the white matter with increasing prominence of the perivascular spaces and non-specific fronto-parietal sulcal widening. There may also be some degree of medial temporal lobe atrophy. A MTA-score of 2 for individuals older than 75 years of age may be normal. As the brain ages, there is an increasing deposition of iron in specific areas of the brain: mainly the basal ganglia, nucleus ruber and pars reticluaris of the substantia nigra. There also may develop a rim of high signal intensity on T2W and FLAIR images around the ventricles, known as caps and bands.

3.5.1.5 Strategic infarctions:

Strategic infarctions are infarctions in areas that are crucial for normal cognitive functioning of the brain. These areas are summarized in the table.

Table 3.5: Strategic Infarctions

Med Cerebral Artery	Parieto-temporal or temp-occip association areas Angular Gyurs
Post Cerebral Artery	Paramedian thalamic, inferior medial temporal lobe
Watershed infarctions	Superior Frontal or Parietal
Lacunar Infection	Bilateral Thalamic

3.5.1.6 Koedam score for Parietal Atrophy:

In addition to medial temporal lobe atrophy, parietal atrophy also has a positive predictive value in the diagnosis of AD. Atrophy of the precuneus is particularly characteristic of AD. This is particularly the case in young patients with AD (presenile AD), who may have normal MTA-scores. The Koedam scale rates parietal atrophy - assessed in sagittal, coronal and axial planes. In these planes, widening of the posterior cingulate and parieto-occipital sulci as well as parietal atrophy (including the precuneus) was rated as shown below:

Table 3.6: Koedom score for Parietal Atrophy		
Grade 0	No cortical atrophy	Close sulci of parietal lobes and cuneus
Grade 1	Mild parietal cortical atrophy	Mild widening of posterior cingulate and parito –occipital sulci
Grade 2	Substantial parietal atrophy	Substantial widening of thw sulci
Grade 3	End- stage ‘knife blade’ atrophy	Extreme widening of the posterior cingulate and parieto-occipital sulci

3.6 Data Collection:

Standardized forms were used to collect data on mores variables divided into main categories, namely age, sex, Signs the (AD), Types the (AD), and causes (AD) and Diagnostic Imaging Factors the (AD).

3.7 Data Analysis:

Data analysis was performed using SPSS version 20. Descriptive statistic and cross-tabulation as well as correlation were obtained. Statistical significant was considered if ($p<0.05$).

CHAPTER FOUR

RESULTS

4.1 Result:

Table 4-1: Gender distribution

	Frequency	Percent
Male	202	66.9
Female	100	33.1
Total	302	100.0

Table 4-2: Age distribution

	Frequency	Percent
50 - 59	11	3.6
60 - 69	4	1.3
70 - 79	75	24.8
> 80	212	70.2
Total	302	100.0

Table 4-3: Subject classification

	Frequency	Percent
Pre-dementia	107	35.4
Early stage of AD	33	10.9
Moderate stage of AD	96	31.8
Late stage of AD	66	21.9
Total	302	100.0

Table 4-4 clinical signs (Anomia)

	Frequency	Percent	Valid Percent	Cumulative Percent
NON	96	31.8	31.8	31.8
YES	206	68.2	68.2	100.0
Total	302	100.0	100.0	

Table 4-5 clinical signs (Apraxia)

	Frequency	Percent	Valid Percent	Cumulative Percent
NON	70	23.2	23.2	23.2
YES	232	76.8	76.8	100.0
Total	302	100.0	100.0	

Table 4-6 clinical signs (Agnosia)					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NON	102	33.8	33.8	33.8
	YES	200	66.2	66.2	100.0
	Total	302	100.0	100.0	

Table 4-7 clinical signs (Amnesia)					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NON	71	23.5	23.5	23.5
	YES	231	76.5	76.5	100.0
	Total	302	100.0	100.0	

Table 4-8 clinical signs (Aphasia)					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NON	83	27.5	27.5	27.5
	YES	219	72.5	72.5	100.0
	Total	302	100.0	100.0	

Table 4-9 Age * Anomia Crosstabulation				
		Anomia		
		NON	YES	Total
Age	50 - 59	3	8	11
	60 - 69	2	2	4
	70 - 79	19	56	75
	> 80	72	140	212
Total		96	206	302

Table 4-10 Age * Apraxia Crosstabulation				
		Apraxia		
		NON	YES	Total
Age	50 - 59	3	8	11
	60 - 69	0	4	4
	70 - 79	35	40	75
	> 80	32	180	212
Total		70	232	302

Table 4-11 Age * Agnosia Crosstabulation				
		Agnosia		
		NON	YES	Total
Age	50 - 59	9	2	11
	60 - 69	0	4	4
	70 - 79	23	52	75
	> 80	70	142	212
Total		102	200	302

Table 4-12 Age * Amnesia Crosstabulation				
		Amnesia		
		NON	YES	Total
Age	50 - 59	1	10	11
	60 - 69	1	3	4
	70 - 79	12	63	75
	> 80	57	155	212
Total		71	231	302

Table 4-13 Age * Aphasia Crosstabulation				
		Aphasia		Total
		NON	YES	
Age	50 - 59	1	10	11
	60 - 69	0	4	4
	70 - 79	27	48	75
	> 80	55	157	212
Total		83	219	302

Table 4-14 Causes of AD				
	Frequency	Percent	Valid Percent	Cumulative Percent
Genetic	132	43.7	43.7	43.7
Cholinergic Hypothesis	115	38.1	38.1	81.8
Amyloid Hypothesis	34	11.3	11.3	93.0
Tau Hypothesis	21	7.0	7.0	100.0
Total	302	100.0	100.0	

Table 4-15 MRI Findings				
	Frequency	Percent	Valid Percent	Cumulative Percent
Brain Atrophy	169	56.0	56.0	56.0
Enlarged Sulci	133	44.0	44.0	100.0
Total	302	100.0	100.0	

Table 4-16 Increased Ventricles				
	Frequency	Percent	Valid Percent	Cumulative Percent
NON	102	33.8	33.8	33.8
YES	200	66.2	66.2	100.0
Total	302	100.0	100.0	

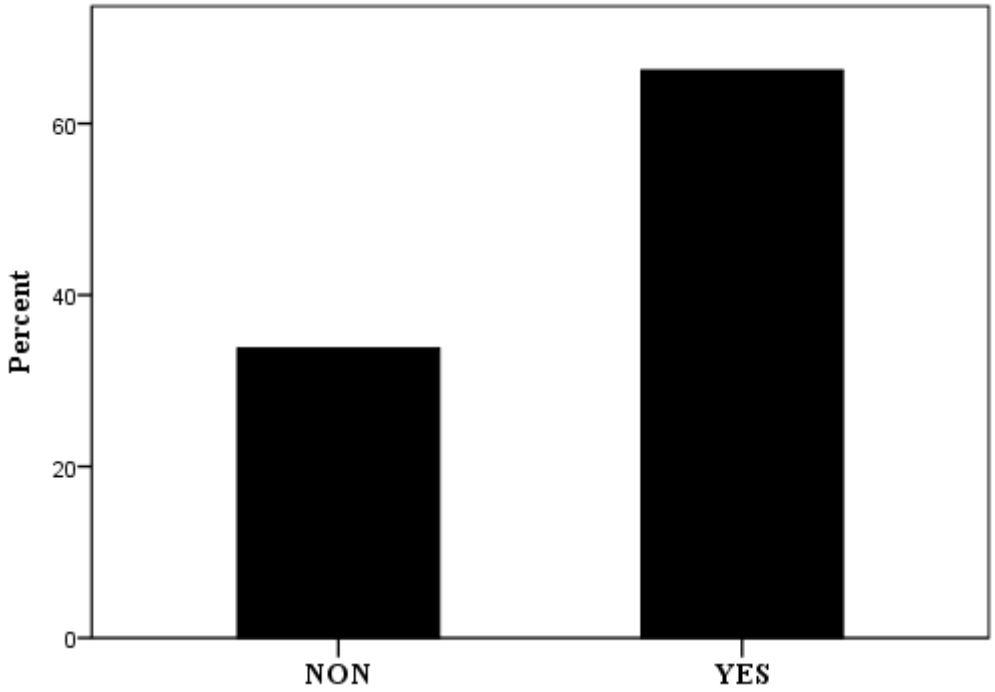

Figure 4-1: Ventricular size enlargement

Table 4-17 White Matter Lesions (Fazekas Scales)				
	Frequency	Percent	Valid Percent	Cumulative Percent
NON	113	37.4	37.4	37.4
YES	189	62.6	62.6	100.0
Total	302	100.0	100.0	

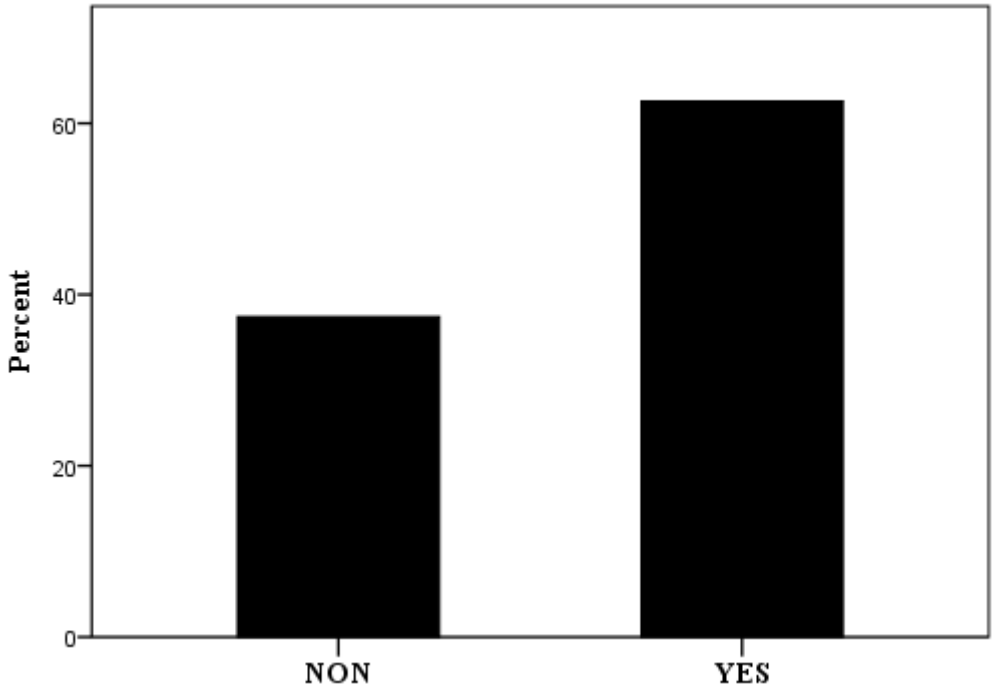

Figure 4-2: White Matter Lesions (Fazekas Scales)

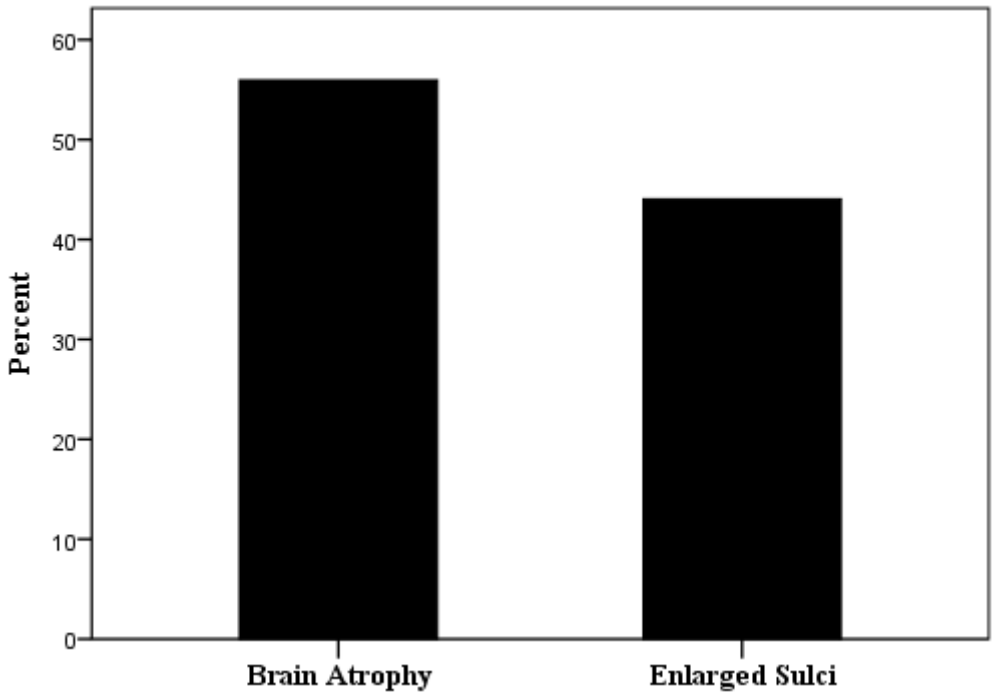

Figure 4-3: MRI findings

Table 4-18: Site of Brain Atrophy

	Frequency	Percent
Hippocampus	46	15.2
Temporal	20	6.6
Generalized Brain Atrophy	236	78.1
Total	302	100.0

Table 4-19: Correlation between Stage of AD and MRI Finding

		MRI Findings		Total
		Brain Atrophy	Enlarged Sulci	
Types	Pre-dementia	49	58	107
	Early stage of AD	11	22	33
	Moderate stage of AD	70	26	96
	Late stage of AD	39	27	66
Total		169	133	302

Table 4-20 hippocampal volume

Hippocampal Volume	**Normal**	**CI**	**Moderate stage of AD**	**Late stage of AD**
Left	2223±302	2019±206	1885±176	1725±126
Right	2175±226	1933±187	1867±119	1702±123

Volume in mm

CHAPTER FIVE

DISCUSSION, CONCLUSION and RECOMMENDATION

5.1 Discussion:

The aim of this study was to evaluate the structural MRI changes in AD, focusing particularly on atrophy in typical late-onset of AD. It is also addressed other changes that can set structural loss in the broader context of functional changes at different stages of the disease.

Age is the most important risk factor for Alzheimer disease (AD), with the prevalence rising substantially between ages 65 and 85. AD develops in the context of normal aging, and the brains of elderly adults without dementia have lower brain weight, reduced tissue volume, and expansion of both the cerebral ventricles and sulci. The result of this study showed that the common affected age group (70 – 80) years, particularly more than 80 years. This result was in line with the previous studies (Raji et al., 2009), this is might be due to the fact that the in older age, there is loss of neuronal cells in neocortical, hippocampal, and cerebellar areas, shrinkage of neurons, and suboptimal DNA repair, leading to compromised neuronal integrity and reduction in synaptic density. As a consequence, age is believed to increase risk for AD because it is independently linked to brain atrophy.

Monitoring structural changes in the brain over time is important in observing the progression of the AD. Tracking the disease progression is especially important since atrophy rates can predict subsequent clinical progression of AD. In this study the generalized atrophy has been observed in 78.1% of the cases, because most of the subjects were in different stages of AD rather than Pre-dementia stage. This result was in line the previous studies which revealed that Rates of whole-brain and hippocampal atrophy are sensitive and powerful markers of progression of neurodegeneration and, as a result, are increasingly used, along with clinical metrics, as outcomes in clinical trials of potential

disease-modifying therapies (Ridha et al., 2006).

Ventricular enlargement is a highly reproducible measure of disease progression, owing to the high contrast between the CSF and the surrounding brain tissue on T1-weighted images. In this study ventricular enlargement was seen in 65% of the cases, the result was in line with the study of (Nestor et al., 2008) where the ventricular enlargement has been noticed in 60% of subject with AD. This is might be due to the fact that the cortical regions associated with dynamic changes in ventricular volume are among those that are regarded as most susceptible to AD-related pathologies, including accumulation of amyloid plaques and tau neurofibrillary tangles, metabolic disruption, functional and connectivity alterations (Apostolova et al., 2012). Ventricular enlargement also demonstrated sensitivity to disease progression by way of discriminating between subjects with stable MCI and those that progressed to AD. Furthermore, ventricular enlargement measures would significantly reduce the number of subjects required to demonstrate a change from the natural history of Alzheimer's disease progression.

Differences in rates between the left and right hippocampus were not significant ($P>0.2$) and therefore the values were averaged. Individual trajectories of hippocampal volume changes as a function of time, the mean change in each group indicates that Alzheimer's disease patients had on average a smaller hippocampus and greater volume loss over time than normal subjects, whereas moderate stage of AD patients had intermediate values between Alzheimer's disease and normal. This result was in line with previous study (Schuff et al., 2009).

Structural imaging based on MRI is an integral component of the clinical assessment of patients with suspected AD. Structural MRI markers now support earlier and more-precise diagnosis and measurement of progression. The presences of atrophy as well as ventricular changes are a partially validated marker for early diagnosis of the disease at the MCI stage. Rates of whole-brain

and hippocampal atrophy are sensitive and powerful markers of progression of neurodegeneration and, as a result, are increasingly used, along with clinical metrics, as outcomes in clinical trials of potential disease-modifying therapies.

5.2 Conclusion:

The aim of this study was to evaluate the structural MRI changes in AD, focusing particularly on atrophy in typical late-onset of AD. It is also addressed other changes that can set structural loss in the broader context of functional changes at different stages of the disease.

The study showed that the most common sign of AD is Apraxia (77%), followed by Amnesia (76%). Predemntia is most type affected patients (35%). The majority of patients diagnosed in moderate stage of AD. Early stage of Alzheimer's disease (AD) is rarely affected patients or rarely diagnosed because with hidden signs and symptoms. The most cause of AD was Genetic factor 44%. The Hippocampal Atrophy imaging factor is most predictive factors as well as Temporal lobe atrophy (MTA). Cognitive impairment in patients with Alzheimer’s disease (AD) is associated with reduction in hippocampal volume in magnetic resonance imaging (MRI).

The combined use of MRI and CSF diagnostic measures for AD have the promise to improve the early and specific diagnosis of AD as well as to improve our understanding of the course of AD on both brain and behavior. It is evident that there are other sources of information to extract from structural MRI in addition to volume or atrophy, such as the hippocampal texture studied in this work, which may produce complementary imaging biomarkers of AD. This was exemplified by the variety of markers applied in a recent grand challenge in medical bimage analysis on differential diagnosis of CTRL, MCI and AD using structural MRI.

5.3 Recommendation:

- Using qualitative techniques by MRI to show that the hippocampal size reduction is found in MCI is a predictor of future.
- Using both neuropathology and neuroimaging studies converge on observations that hippocampal formation pathology is an early feature of AD.
- Further future studies to explain the temporal relationships between EC and hippocampal changes as well as the optimal image acquisition and image measurement strategies to use.
- The combined use of MRI and CSF diagnostic measures for AD have the promise to improve the early and specific diagnosis of AD as well as to improve our understanding of the course of AD on both brain and behavior.
- To investigate potential relation to the metabolic rate of glucose in
- It is evident that there are other ources of information to extract from structural MRI in addition to volume or atrophy, such as the hippocampal texture studied in this work, which may produce complementary imaging biomarkers of AD. This was exemplified by the variety of markers applied in a recent grand challenge in medical bimage analysis on differential diagnosis of CTRL, MCI and AD using structural MRI

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