A STUDY OF CLINICO-NEURORADIOLOGIC CORRELATION IN PATIENTS WITH DEMENTIA

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1. INTRODUCTION

A STUDY OF CLINICO-NEURORADIOLOGIC CORRELATION IN PATIENTS WITH DEMENTIA

1. INTRODUCTION

1.1 DEFINITIONS

Dementia is characterized by decline in the cognitive functioning of an individual that significantly affects the quality of life and intrudes into the activity of daily living. The prevalence of dementia is increasing and is on the rise. This is due to the increased longevity that has resulted in increasing proportions of elderly population in whom the prevalence of dementia is higher. Dementia is defined by the DSM 5 criteria as decline from previously established baseline in the at least one of the cognitive domains: Memory and learning, executive function, language, complex attention, social cognition and perceptual motor function and it affects the activities of daily living. The symptoms in these patients do not occur exclusively during delirium and are not explainable by psychiatric disorder (1).

1.2 PREVALENCE

The global prevalence of dementia was estimated to be 47.47 million in 2015. The prevalence is projected to be 75.63 million and 135.46 million in 2030 and 2050 respectively (2). The prevalence of dementia in elderly in India is estimated to be 0.9 to 4.8% in the urban area and 0.6 to 3.5% in the rural areas respectively. The prevalence of dementia in South India is estimated to be 3.36% in the geriatric population. (3)

1.3 CONNECTOMICS

The approach to cognitive deficits in dementia has evolved substantially. Cognitive deficitsare now localised to domain specific large scale networks called Connectomes, rather than localising it to a specific disease specific anatomic locus, (4).

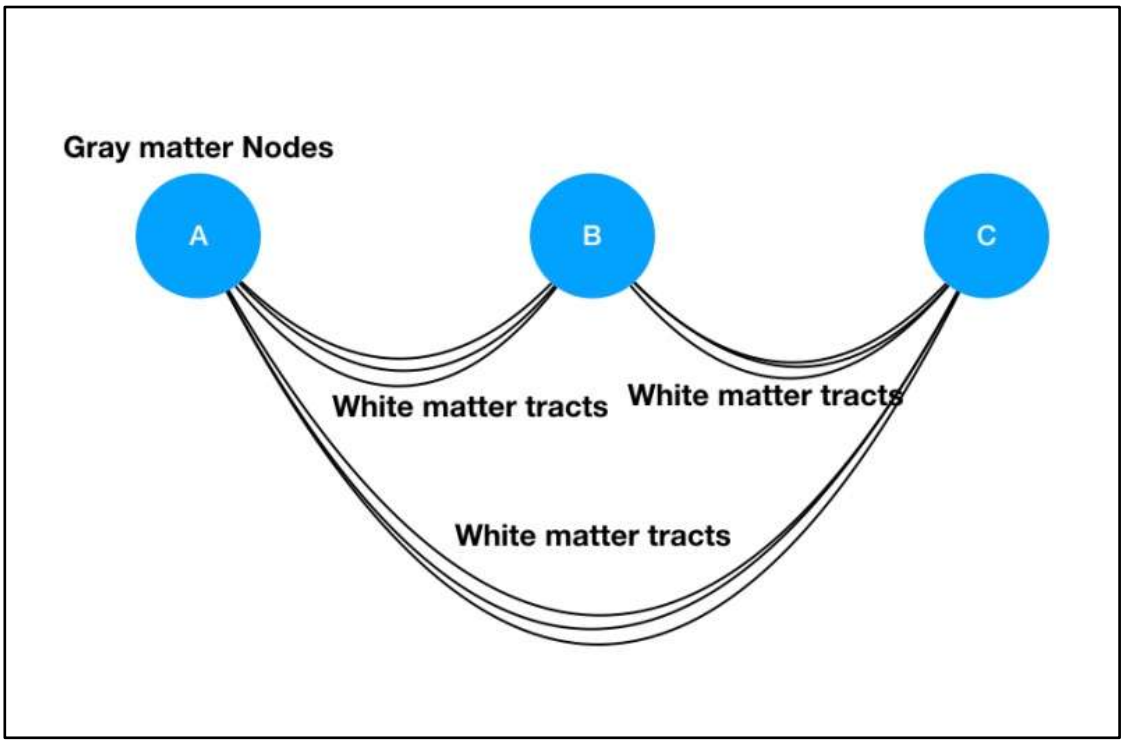


Figure 1 : Connectomes showing grey matter hubs interconnected by white matter tracts

These Connectomes consist of different grey matter nodes connected to each other with reciprocal connections by white matter tracts that convey the processes and information, Figure 1(5). The components of these networks are categorised as critical and contributory. The studies based on lesion which affect the particular cognitive domain helps identify the critical components and those areas identified by functional studies during the activity of the particular cognitive domain are categorised as contributory components.

2. AIMS & OBJECTIVES

2. AIMS & OBJECTIVES

2.1 AIM:

To study the association between clinical deficits in cognitive domains of attention, memory and language in subjects with dementia and the neuroimaging correlates of the corresponding networks.

2.2 OBJECTIVES:

To evaluate clinical deficits in cognitive domains of attention, memory and language in subjects with dementia

To study the neuroimaging findings in subjects of Dementia on MR voxel based morphometry, MR diffusion tensor imaging and 18-Fluorodeoxyglucose Positron Emission Tomography in corresponding networks of attention, language and memory respectively.

To determine neuroimaging correlates of deficits in attention, language and memory in subjects with dementia in corresponding networks of attention, language and memory respectively.

3. NEED FOR THE STUDY

3. NEED FOR THE STUDY

The anatomy of the network and the cortical grey matter hubs are evolving with the increased capability of the in vivo imaging of these tracts and cortices. The precise mapping of each connectome is required for accurate knowledge of its function and the deficit that would arise from its lesion. The mapping of the connectome would also play an important role in the intervention during neurosurgery. These newer techniques will also plan and enable the neurosurgeon to decide the approach, trajectory and extent. Individual, regional and racial variability in the connectome are possible as the genes play crucial in the development of these circuits. The nature of these connectomes in health and disease will also vary depending upon the etiology especially dementia. Hence, this study is aimed at studying the association between clinical deficits in cognitive domains of attention, memory and language in subjects with dementia and the neuroimaging correlates of the corresponding networks.

4. REVIEW OF LITERATURE

4. REVIEW OF LITERATURE

4.1 Evolution from Functional cortical areas to functional connectomics:

4.1.1 Historical evolution of Disconnection syndromes and Unfolding of connectomics:

The nineteenth and the twentieth century has seen several path breaking findings in the field of cognitive neurosciences. The work on cognitive function predates the 19th century. However, it was Frank Joseph Gall in the late 19th century, who distinguished between gray matter cortical areas and white matter tracts. His description in phrenology in which he describes the use of extra cranial metrics for the calculation of cortical dimensions has fallen out of favour (6). Later in 19th century, Theodore Meynert, in his work performed detailed description of the white matter tracts. He classified the white matter tracts into projection fibres, commissural fibres and association fibres. Projection fibres consist of ascending and descending white matter tracts to and from the cortex. Commisural fibres connect the cortical areas between hemispheres. Association fibres connect cortical areas within the same hemisphere. (7)

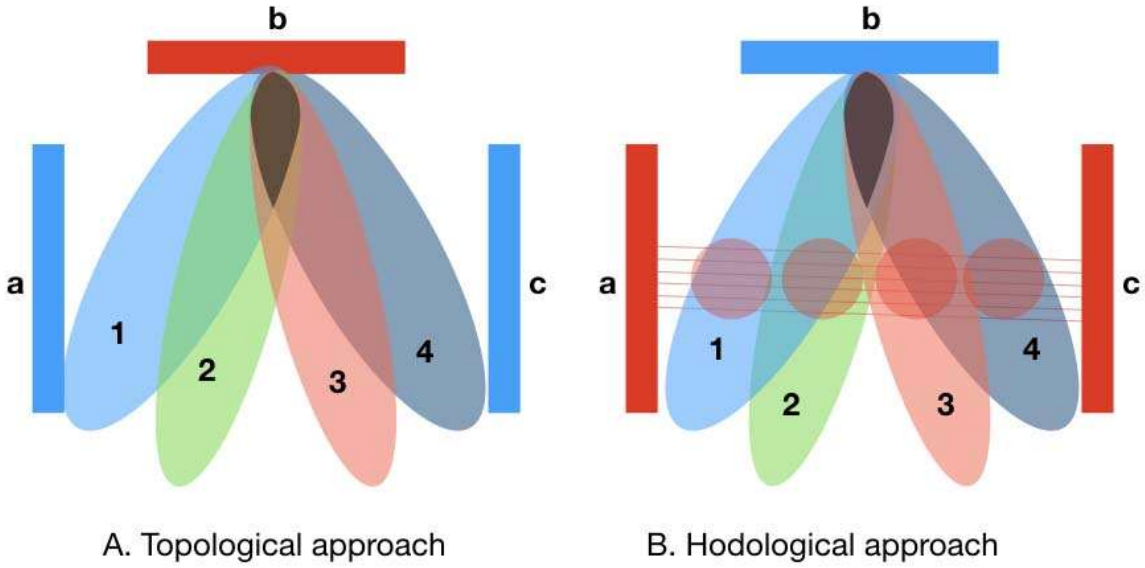
It was Karl Wernicke who is considered Father of disconnection theory, whose major work in the 19th century produced several advancements in the field of cortical network. According to Wernicke's associationist school, higher specialised function was not localised to a particular cortical area, but however was due to interaction between the motor and sensory image areas. His exceptional contribution is exemplified by his work on "The aphasia symptom-complex" in which he described conduction aphasia due to lesion in the arcuate fasciculus. This formed the prototype for the study of disconnection syndromes (8, 9). His assistants in his clinic from the associationist school, Heinrich

Lissauer and Hugo Liepmann performed work and described cases of agnosia and apraxia respectively (10, 11). Liepmann in his work on apraxia, described that the lesions of left parietal lobe produced bilateral apraxia, whereas lesion of the anterior part of the corpus callosum produced unilateral left sided apraxia (11). Jules Dejerine in the late 19th century described Alexia. He described alexia with agraphia due to lesion in the left angular gyrus in the inferior parietal lobe and alexia without agraphia due to lesion in the central white matter of the occipital cortex on the left side. Dejerine differed from Wernicke in the consideration of specialised function for cortical regions (12, 13).

However, the early 20th century witnessed the fall of the disconnection era. The higher specialised functions were considered to be localised to specialised cortical areas. And the principles of disconnection fell out of favour. This view of cortical localisation of specialised functions rather than to networks was bolstered by Campbell's work on the development of neuroanatomy and Broadmann who described division of cortical areas in to individual cytoarchitectonic areas. Paradoxically Kleist, Wernicke's successor described elaborate on cortical maps with specialised function attributed to these areas. These views were further supported by works of Von Monakow (Switzerland), Henry Head (England), Karl Lashley (America), Henry Head (England). By 1965, the disconnections were considered notes of the past (6, 14, 15).

However, the associationist model was revived by Norman Geschwind in his work "Brain" in the year 1965. He described the 'Fleschig's rule' and the phylogenetic evolution of sensory and association cortices. According to the Fleschig's rule, there are no long white matter tracts that connect primordial zones. The primordial zones are the cortical areas which are myelinated at birth. These tracts relay through the surrounding rim of association cortex and are connected to other primordial zones. Geschwind

extrapolated the Fleschig's rule to the motor cortex and to inter hemispheric connections. His work on phylogenetic evolution of the cortices revealed that in lower mammals, the primary sensory and motor cortices were interconnected. As we move above the evolution scale, in higher mammals, the primary sensory and motor cortices relay through the surrounding rim of association cortex. However, the intermodal connections between somesthesia, auditory and visual are weak and these primary cortices have a strong limbic connections. In humans, these various sensory cortices for visual, auditory and somesthesia are relayed through the association cortices to the inferior parietal lobe. In the inferior parietal lobe, the sensory inputs are multi modally integrated and provides multimodal non-limbic associations between sensory information. Geschwind's work in disconnection syndromes included description of disconnection between sensory and limbic areas, disconnection between Wernicke's area and sensory areas, disconnection between motor areas and sensory areas, disconnection between hemispheres. Disconnection between the sensory and the limbic areas resulted in pain asymbolia and verbal learning impairment. Disconnection between the sensory areas and Wernicke's area resulted in tactile aphasia (known as tactile anomia in the current day cognitive neurosciences), pure word deafness, pure alexia and modality specific agnosias. Disconnection between motor and sensory areas results in apraxia. Disconnection between motor and sensory speech area produces conduction aphasia (16, 17). The work by Geschwind was carried over by Antonio Damasio and Marsel Mesulam. Damasio carried over the work in cognitive neurosciences with the use of emerging imaging modalities such as computerised tomography, PET, SPECT and expanded the understanding in perception, language and emotion (18, 19, 20). Mesulam performed work on emerging methods to unearth the neural connections, neurophysiology in primates and computational theory. This provided important understanding in attention,



A. Topological approach

B. Hodological approach

Figure 2. (A) According to topological approach, when the cortical lesion from four patients with the same neurological deficit are overlapped onto the same cortical map, the critical area for the neurological deficit is the area with the maximum over lap and the four lesions are mere extensions of this critical area, b . (B) According to hodological approach, when the cortical lesion from four patients with the same neurological deficit are overlapped onto the same cortical map, the neurological deficit is due to the involvement of networks that pass from 'a' to 'c' through the lesion area in these patients. a, b, c are three different cortical areas. 1, 2, 3 and 4 are lesion locations of four different patients.

language, memory, aphasia and neglect. There have been recent shifts in the concept of localisation of the cognitive function between cortical areas and functional network connectomics (4, 21, 22, 23).

4.1.2 Topological Approach vs Hodological approach:

In Topological approach the lesion is localised to cortical areas, whereas in hodological approach the lesion is localised to the network. This can be better understood by the studying lesion overlap study as depicted in figure 2. In lesion overlap study, the cortical lesions from multiple patients with the same neurological deficit are overlapped onto a single cortical map. The neural substrate derived from the lesion overlap depends on the approach applied: topological or hodological. In topological approach, when the cortical lesion from four patients with the same neurological deficit are overlapped onto the same cortical map, the critical area for the neurological deficit is the area with the maximum over lap and the four lesions are mere extensions of this critical area, Figure 2. In the figure 2A, according to the topological approach the lesion is located in area ‘b’. In hodological approach, when the cortical lesion from four patients with the same neurological deficit are overlapped onto the same cortical map, the neurological deficit is due to the involvement of networks that pass through the lesion area in these patients. In the figure 2B, according to the hodological approach the lesion is located in the network that connects the areas ‘a’ and ‘c’. (24) Figure 2.

4.2 NEURAL NETWORKS

Networks are divided into local networks and large scale networks. Local networks connect areas within single architectonic field to areas within or in the immediate contiguous field. Large scale networks are widely separated and forms the pillar for complex cognitive domains (4).

4. 2.1 ATTENTION:

The components of the attention network are perceptual, motor and limbic. Areas involved in attention include Frontal Eye Field (FEF), Posterior parietal gyrus (PPG), areas 23 and 24 of the cingulate gyrus. They have extensive reciprocal monosynaptic connections between the three areas. The subcortical areas involved in attention are superior colliculus, striatum, pulvinar nucleus of the thalamus. The cortical areas are reciprocally connected to the subcortical structures. (21, 25, 26)

Each cortical area is connected to at least two of the three subcortical areas and vice versa. FEF provides a map for orientation and exploratory movements. Cingulate provides motivation and value to the spatial coordinates. Superior colliculus is the motor component. PPG is concerned with sensory perception of extra personal space. Multimodal sensory specific multi-synaptic downstream projection to posterior parietal gyrus conveys relevant information in an orderly manner. This information from PPG is transferred in a grid like manner (not in the convergence distillate pattern). PPG provides access to extra personal space, spatial location of the extra personal events, decides the attention worthiness of the event or location. Superior colliculus and FEF are both directors of saccades. The neurons in the FEF, fire prior to the saccade directed towards the relevant object. The neurons in the subcortical structures concerned with attention including superior colliculus, caudate and medial pulvinar also fire prior to the onset of saccade. Brain stem reticular activating system also plays a role in attention. (27, 28, 29)

The cortical neurons in the FEF mediate fine control of saccades while the subcortical neurons in the superior colliculus, caudate and medial pulvinar mediate gross control of saccades. These enable exploration of the far space component of the extra personal space. The exploration of the near space using limb movements is mediated by

cortical neurons in the area 6 of the premotor cortex. Posterior parietal gyrus sculpts the attention landscape. FEF and the subcortical structures plans strategy to navigate through the landscape. Further, a value system is assigned to the attention landscape by the cingulate cortex. All the three core cortical components namely - FEF, Area 23 and 24 in cingulate cortex and FEF, all are engaged simultaneously without temporal hierarchy and the output is the emergent quality of the whole network. In object addressed attention, visual association areas in the temporal cortex also play a role. (29, 30, 31, 32)

Three local networks are concerned with attention. Local network 1 is exploratory network and includes: Frontal eye field, adjacent Broadmann Area 6 concerned with for exploratory limb movement, Broadmann Area 45D (dorsal component of Broadmann Area 45), Broadmann Area 46P (ventral component of Broadmann Area 46). Local Network 2 is the perceptual local network and includes PPG, adjacent rim of intra-parietal sulcus, medial parietal cortex, posterior portion of the superior temporal sulcus, superior parietal lobule. Local network 3 is the motivational network and includes retrosplenial cingulate cortex. The firing of the reticular formation projects to exploratory, perceptual and motivational local network and influences the level of attention. The reticular formation in turn receives input from the ascending pathways. (4, 33)

Cortico striatal pathways integrate the neural computations in both FEF and PPG. They compare and synchronise with them. Similar organisation also happens in cortico-cortical networks including comparison and synchronisation. (34)

Attention is the result of emergent quality of the three hubs namely PPG for perception, area 23 and 24 cingulate for motivation, Frontal eye field for exploratory movements and not merely a sum of the three hubs. There are three levels of schematic

relationship in this network: First level is anatomic site, second level includes neural computation, third level is behavioural component which includes cognition and comportment. Each behaviour is sub served by multiple hubs and each hub sub serves multiple behaviours. (4, 33)

4.2.2 LANGUAGE

4.2.2.1 The evolution of Hubs in Language:

Johan Christian Reil identified in 1812, unnamed white matter fibres around the sylvian fissure. In 1822, Carl Burdach named the perisylvian tracts as fasciculus arcuatus. Paul Broca (1861), identified the motor speech area concerned with speech production. Wernicke (1874) identified the sensory area for speech concerned with speech comprehension. Wernicke also described the psychic arc connecting the temporal and frontal areas. It was Dejerinein 1895, who believed that arcuate fasciculus consisting of short Ufibres in neighbouring perisylvian regions connected the sensory and motor speech areas. Dejerine was also responsible for naming Superior Longitudinal Fasciculus. Broca's area is for speech production. Norman Geschwind in 1965-70, emphasised the role of angular gyrus in the inferior parietal lobule in language network and proposed the Wernicke - Geschwind model. Marco Catani and Ffytche demonstrated an indirect pathway running parallel to the arcuate fasciculus through inferior parietal lobule. It has two parts: The anterior part connects the Broca's area to the inferior parietal lobule and the posterior part connecting the Wernicke's area to the inferior parietal lobule. (6, 9, 24)

The anatomic core of spoken language includes Wernicke's area in the Temporo-parietal junction and Broca's area in the frontal operculum. The two areas and the interconnections between the two are sufficient only for the process of speech repetition.

The input modality for language is auditory and the output is based on the articulatory movements of the speech apparatus. Phonetics, syntax and semantics are components of language produced by different cognitive operations. (4, 35)

4.2.2.2 Neuro-linguistic Models

Wernicke in 1874 described the first language network model. He described the first frontal convolution, which is the inferior frontal gyrus in the current day cognitive neurology that contains the motor imagery that contains representations of speech. The rearousal of these imagery will produce the pattern of sound which is controlled by the distant cortices and is monitored the sensory cortex. The first temporal gyrus is the sensory and contains acoustic images that match with heard words. The sensory and motor areas are connected by the fibrae propriae that converge through the insular cortex. According to Wernicke, the disruption of this pathway resulted in aphasia and the impairment in the monitoring of the broca's area by the sensory area results in paraphasias. (9)

Lichtheim expanded the wernicke's concepts in the Wernicke-Lichtheim model. According to Lichtheim, the broca's and the wernicke's area are also connected to each other through a hypothetical 'concept centre' which acted as thought centre for the motor and sensory speech centres. The thought centre aids in the understanding of words from the sensory centre and it transfers inputs to the Broca's area for verbalisation. However, it was supported only by minimal evidence with theoretical description to fit in the clinical observation without anatomical correlation. He also described the transcortical motor aphasia and transcortical sensory aphasia. Geschwind described the presence of multimodal association cortex in the angular gyrus of the inferior parietal lobe, where information from the auditory, visual and somesthetic association areas converge. The

disconnection syndrome according to Geschwind may result from lesion of the white matter pathways and the association cortices. (16, 17, 36)

According to the dual stream model of language processing, the processing for language begins in the auditory cortex with the auditory signal being deciphered spectroscopically. The processed information is transferred to the phonological network situated around the posterior part of superior temporal sulcus. Subsequently dorsal stream and ventral stream plays an important role. The dorsal stream which is predominantly left sided transfers the information for speech processing and motor integration. The ventral stream functions bilaterally with a left preponderance, that aids in comprehension. The white matter tracts concerned with dorsal and ventral stream are discussed further. (37, 38, 39)

4.2.2.3 Cortical Hubs in Language Areas:

Broca's area and Wernickes area are without strict cytoarchitectonic borders. Wernicke's area is essentially restricted to posterior one third of the superior temporal gyrus but the core also includes the adjacent parts of heteromodal area 37, 39 and 40 within the limits along with auditory association cortex of the posterior superior temporal cortex. Wernicke's aphasia is characterised by intact fluency, normal melody and good articulation but severe paraphasia. Circumlocutions, neologisms, reduction in nouns are features seen in Wernicke's aphasia. Inability to repeat the spoken sentences is also a cardinal feature. To summarise Wernicke's aphasia has receptive and expressive components. It is multimodal affecting both spoken and written language. Wernicke's area provides an entry point of breaking down the auditory sequences into word components. They trigger the lexicon for meaning and thought. The lexicon is probably a multidimensional matrix containing a lot of information. Wernicke's area acts as a nodal

bottle neck for access to the multidimensional information grid. It is a final common pathway for converting thoughts into meaningful words. (40, 41)

Broca's Area includes BA 44 as its core, rim area of BA 6 from the premotor cortex as well as the rim areas of BA 45, 47 and 12 which are part of prefrontal heteromodal cortex. Broca's aphasia is characterised by non fluent, effortful, paraphasic speech. It is also characterised by features such as agrammatism with preserved comprehension for content words and abnormal repetition. The comprehension component of Broca's aphasia include difficulty in understanding sentences that are syntactically complex with the use of prepositions and word orders. The language network has two poles: the syntactically articulatory pole is occupied by Broca's area and the semantic lexicon pole is occupied by the Wernicke's area. Broca's area acts as a bottle neck converting the neural word representations into corresponding articulatory sequences. The function of the Broca's area is to arrange morphemes, phonemes and inflections of words sequentially in a way that would form a word and sentences influencing the syntax and thereby ascribing meaning. Similar to Wernicke's aphasia, Broca's aphasia also has receptive and expressive components but of a different nature. The language network is a cerebral representation of dichotomies like expression / reception, sensory / motor, syntax / semantics which are relative and not obsolete. (42, 43, 44, 45)

4.2.2.4 White matter networks in Language:

Language is a higher cognitive function that brings together comprehension and production. Language network consists of Dorsal and Ventral Stream. The dorsal stream of language consists of arcuate fasciculus and Superior longitudinal fasciculus. The ventral stream of language includes extreme capsule, uncinate fasciculus, middle

longitudinal fasciculus, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. (37)

1) Extreme capsule is located between the insula and the claustrum and separated by a thin layer of grey matter from the external capsule. Major portion of the extreme capsule is between the inferior frontal gyrus and posterior portion of the superior temporal gyrus and it is not always discernible by even the DTI atlas. This difficulty has been confirmed by Oishi K et al. (46, 47, 48)
2) Uncinate fasciculus connects the anterior temporal lobe with orbito-frontal cortex. It is implicated in affective responses to emotional auditory input and its role in language is not clear. (49, 50, 51)
3) Human middle longitudinal fasciculus is a cortico cortical fibre pathway. It connects the superior temporal gyrus (STG) (BA 22, 42) and dorsal temporal pole (BA 38) principally angular gyrus (BA 39), superior parietal lobule (BA 6) and its functionality is related to language processing following the dual stream of language processing (52, 53).
4) ILF connects occipital lobe with temporal lobe. Inferior fronto-occipital fasciculus is very close association fibre tract. ILF runs laterally and inferiorly to lateral wall of temporal horn of lateral ventricle under the optic pathway. IFOF runs medially and above the optic pathway. Lesion of left ILF causes visual recognition difficulty and reading disturbances but no difficulty in picture naming. IFOF involvement causes no difficulty in visual recognition but causes difficulty in picture naming. The landmark in ILF and IFOF are roof of the ventricle. Impaired functioning of ILF is associated with alexia, nominal aphasia and reduced verbal fluency. ILF takes support from uncinate to travel from temporal to frontal. (54, 55)

5) IFOF is a long association fibre connects occipital and frontal lobes with posterior parietal and temporal lobes. In language, it is considered to be direct ventral route for language, ILF is considered as indirect ventral route for language. IFOF is involved in semantics, reading and writing. (24, 56, 57)

The fasciculus in the dorsal stream including Arcuate and SLF support repetition, phonology, syntax to morphology, reading and articulation. The fasciculus in the ventral stream support semantics and syntax (37)

Connectivity patterns in language dysfunction have become interesting in view of novel DTI and fMRI. The new Diffusion tensor imaging has modified the classical language models with newer hubs, ancillary nodes and their connections. In addition to the dorsal and ventral pathways for language a visual language stream, a striato-control stream and a motor stream. Broca SFG, Broca lateral SFG and Frontal aslant tract (FAT) also contributes to language. (58, 59, 60)

Two new fasciculus were described namely Operculo - premotor fasciculus connects BA 44 to pre motor region and Triangulo-orbitalis system connects BA 45 and BA 47. Frontal intralobar tracts and associative fibre tract BA 44, 45 with lateral SFG named as Broca lateral SFG tract. Frontal aslant tract (FAT) connects BA 6 and BA 44 in the inferior frontal gyrus with BA 8 and 6 in SFG. Catani et al stated that FAT connects anterior supplementary and pre-supplementary areas. (61, 62)

4.2.3 Memory Network

The areas in memory involve limbic and para-limbic areas. The core limbic areas are amygdala, hippocampus and basal forebrain which include septal nuclei and nucleus of basalis of meynert. The para-limbic areas include orbito frontal, temporo polar, insula,

cingulate and para hippocampal regions. Fornix, mamillothalamic tract, ansa peduncularis and stria terminalis are the connecting white matter fibres involved in memory. Mamillothalamic tract is a solid white matter structure running along parallel to the fornicial columns connecting the anterior nucleus of the thalamus and mammillary body of the hypothalamus. The components of memory are registration, storage, retention and retrieval. The deficit in new learning is known as anterograde amnesia. The inability to retrieve memories acquired before the onset of amnestic state is known as retrograde dementia. There is usually in amnestic states attention, visuo-spatial skills, language and motivations are preserved. (63, 64)

The disorders causing memory disturbances vary from infections of the temporal lobe like herpes simplex encephalitis, nutritional deficiencies of diencephalon as in wernicke's encephalopathy, vascular occlusion of anterior and posterior cerebellar artery, tumours of the thalamus, corpus callosum, sphenoid, and third ventricle. All these anatomical sites form within the framework of limbic network involved in memory. The lesions are usually bilateral and not homologous. Memory can be classified based on modality like visual and auditory. Based on material that is processed, it is classified into verbal and non-verbal memory. It can also be classified as declarative memory and procedural memory or autonomic. Declarative memory is verbal reporting to conscious. Procedural memory is learning of a motor skill. The registration component of memory is involved in short term or immediate memory and its dependence on the limbic network is the least. It is associated with vigilance and concentration. The storage and retrieval components of memory are anatomically closely related and involved in anterograde and retrograde amnesia. The temporo cortical components of the limbic network are responsible for storing the memory traces for a critical period. Beyond this

period, the stored information is distributed massively and consolidated. After consolidation, the limbic network is not necessary for retrieval. (4, 65, 66)

4.3 White Matter Tracts

4.3.1 Superior Longitudinal Fasciculus:

Superior Longitudinal Fasciculus (SLF) contains group of white matter tracts that connect frontal, temporal and parietal cortices. It consists of horizontal and vertical parts. The horizontal part consists of fronto-parietal white matter tracts extending from the inferior parietal lobe of the parietal cortex to posterior and inferior portion of frontal cortex. It is divided into three components from dorsal to ventral: SLF I, SLF II, SLF III. The SLF I extends from the dorsal superior parietal cortex to the premotor and prefrontal cortex (BA 6, 8 and 9). The SLF II extends from the angular gyrus to the dorsal part of prefrontal and premotor cortex. The SLF III extends from the angular gyrus to the ventral part of pre frontal and premotor cortex. The vertical part consists of temporo-parietal fibres. It extends from posterior part of superior temporal gyrus and middle temporal gyrus. It runs vertically upward and terminates in the inferior parietal cortex. Superior longitudinal fasciculus subserves language function. (67, 68)

4.3.2 Arcuate Fasciculus:

The Arcuate Fasciculus (AF) consists of white matter tracts that extend from the temporal cortex to the frontal cortex. The boundaries of the termination of the posterior part are ill defined and arise from posterior and medial part of the superior temporal gyrus, middle temporal gyrus and inferior temporal gyrus. It arches around the posterior extension of the sylvian fissure and runs forward. During its course in the parietal and frontal white matter, it is related laterally to the horizontal part of superior longitudinal fasciculus and medially to the corticospinal tract. The fibres terminate anteriorly in the

precentral gyrus, pars opercularis and pars triangularis in the inferior frontal gyrus located in the frontal lobe. In the Broca's area it terminates in the anterior portion. The arcuate fasciculus subserves language function.

The arcuate fasciculus is considered the direct pathway connecting the frontal and parietal lobes. On the other hand, the horizontal and the vertical part of the superior longitudinal fasciculus traverses parallel and lateral to the arcuate fasciculus. It is considered the indirect pathway connecting the frontal and temporal cortices with inferior parietal lobe as a relay station emphasising the important role in the language function (69, 70)

4.3.3 Inferior Longitudinal Fasciculus:

The Inferior Longitudinal Fasciculus (ILF) consists of white matter fibres extending from the temporal lobe to the occipital lobe. It consists of direct pathways and indirect pathways.

The indirect pathway consists of U shaped fibres that extend between the adjoining gyri located in the convexity of the occipital lobe and the inferior temporal lobe. The direct pathway of the inferior longitudinal fasciculus extends antero-posteriorly from the anterior portion of superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, fusiform gyrus, parahippocampal gyrus, amygdala and hippocampus. It runs backwards inferior and lateral to the temporal horn of the lateral ventricle and as it reaches the atrium of the lateral ventricle, it lies lateral to the Inferior Fronto-Occipital Fibres and optic radiations and medial to the arcuate fasciculus and horizontal portion of the superior longitudinal fasciculus. The posterior part terminates in the occipital convexity, cuneus, posterior lingual gyrus and posterior fusiform gyrus. (71, 72)

4.3.4 Inferior Fronto-Occipital Fasciculus:

The inferior fronto-occipital fasciculus (IFOF) consists of fibres from the frontal lobe that traverses through the temporal lobe and the majority of the fibres terminate in the occipital lobe and minority of the fibres terminates in the parietal lobe.

The anterior connections of the IFOF consists of medial and lateral orbitofrontal cortex, fronto-polar cortex, superior frontal gyrus, middle frontal gyrus and pars opercularis, pars orbitalis and pars triangularis of the inferior frontal gyrus. The fibres from the above mentioned areas converge towards the external and extreme capsule and subsequently traverse the temporal lobe and end in the occipital lobe and parietal lobe. The terminations in the occipital lobe and parietal lobe include fusiform gyrus, cuneus, lingual gyrus, superior occipital gyrus, middle occipital gyrus, inferior occipital gyrus, post central gyrus, superior parietal lobule and angular gyrus. The IFOF forms the important component of the ventral stream of the language pathway. (73)

4.3.5 Uncinate Fasciculus:

The uncinate fasciculus is a hook-like white matter tract that extends from the anterior temporal lobe to the orbito-frontal cortex. The temporal origin probably arises from amygdala, hippocampus, superior and middle temporal gyri and temporal pole. At the level of external capsule, it winds around the limen insulae and it reaches the frontal lobe. The areas of frontal termination of the uncinate fasciculus include frontal pole, gyrus rectus, orbital gyrus, inferior frontal gyrus and area subcallosa. (7, 74)

4.3.6 Fornix:

Fornix forms the efferent pathway of the hippocampus. The fimbriae continues posteriorly as the hippocampus. The fornix consists of crura, body and columns. The crura of the fornix runs posteriorly, superiorly and medially underneath the splenium of

corpus callosum. It continues as the body where fornix from either side comes to lie together in the midline along the superior and medial part of the thalamus. It continues forward where it joins together below the body of the corpus callosum. The columns of the fornix run anterior to the foramen of munro. Each of the column of fornix divides into pre-commissural part and a post commissural part. The pre-commissural part terminates in the septal regions. The post commissural portion terminates in the mamillary body. The mamillo-thalamic tract connects the mamillary body with the anterior nucleus of the thalamus. (75)

4.3.7 Cingulum:

The cingulate fasciculus runs superior and parallel to the corpus callosum connects the posterior cortex, hippocampus and the prefrontal cortex. It receives fibres from the prefrontal gyrus, paracentral lobule, anterior thalamic nucleus and precuneus. The precuneus forms a major proportion of the cingulum. Anteriorly, the cingulate fasciculus curves around the gene of corpus callosum and terminates in the sub callosal gyrus and paraterminal gyrus. Posteriorly it terminates in the entorhinal cortex and presubiculam. (76)

4.4 Gray matter Hubs:

4.4.1 Broca's area:

Broca's Area includes BA 44 as its core, rim area of BA 6 from the premotor cortex as well as the rim areas of BA 45, 47 and 12 which are part of prefrontal heteromodal cortex. Broca's area acts as a bottle neck converting the neural word representations into corresponding articulatory sequences. The function of the Broca's area is to arrange morphemes, phonemes and inflections of words sequentially in a way

that would form a word and sentences influencing the syntax and thereby ascribing meaning. (42, 43, 44, 45)

4.4.2 Wernicke'area:

Wernicke's area is essentially restricted to posterior one third of the superior temporal gyrus but the core also includes the adjacent parts of heteromodal area 37, 39 and 40 within the limits along with auditory association cortex of the posterior superior temporal cortex. Wernicke's area provides an entry point of breaking down the auditory sequences into word components. They trigger the lexicon for meaning and thought. The lexicon is probably a multidimensional matrix containing a lot of information. Wernicke's area acts as a nodal bottle neck for access to the multidimensional information grid . It is a final common pathway for converting thoughts into meaningful words. (40, 41)

4.4.3 Geschwind's territory:

The inferior parietal lobule which includes both angular gyrus and supramarginal gyrus is also called as Geschwind's territory. This is named so, in honour of Norman Geschwind. This is one of the language territories apart from those described by Paul Broca and Wernicke. The Geschwind's territory has dense connections with both Broca's and Wernicke's territory via white fibre tracts. This is a multimodal cortex; receiving inputs from visual, auditory and somatosensory areas and hence they play a major role in processing the various aspects of language. The Geschwind's area is evolutionarily a recent one and it is one of the brain areas that matures late i.e by around 5 years of age. (67)

4.4.4 The cingulate cortex:

The cingulate cortex lies in the medial surface of the cerebral hemispheres it abuts the corpus callosum like a girdle hence the name cigulate. It is functionally and anatomically divided into 4 regions, namely anterior cingulate cortex, middle cingulate cortex, posterior cingulate cortex and retrosplenial cingulated cortex. They are further divided into 7 subregions. The anterior portion mainly deals emotions, the middle portion deals with executive and motor tasks, and the posterior portion deals with memory and spatial orientation. (77)

4.4.5 The frontal eye field:

Frontal eye field corresponds to the broadman's area 6 and it is situated in the dorsolateral prefrontal cortex near the posterior end of the superior frontal sulcus. The frontal eye field has its role in controlling oculomotor functions and in attention especially, orienting one to the environment. (78)

4.4.6 Hippocampus:

The hippocampus is situated in the medial temporal lobe and it lies in the floor of the temporal horn of the lateral ventricle. It resembles a seahorse, hence the name hippocampus. The human hippocampus can be divided into head, body and tail. It consists of two lamina of grey matter namely dentate gyrus and cornua ammonis. The white matter tract fibres of the hippocampus aggregates in the superior aspect of the hippocampus to form the alveus and this white matter tract of hippocampus continues posteriorly as the fornix of hippocampus. The hippocampus plays a crucial role in episodic memory and spatial memory. (79)

4.4.7 Uncus :

The uncus of hippocampus is the anterior most portion of the parahippocampal gyrus and it is separated from the entorhinal cortex below, by the uncal sulcus. The various sub- divisions within the uncus are gyrus ambiens, uncinate gyrus, Band of Giacomini and intralimbic gyrus. The uncus plays an important role in visual scene imagination and recall. (79)

4.4.8 Dorsolateral Prefrontal Cortex:

The dorsolateral prefrontal cortex is located superficially in the lateral aspect of prefrontal cortex. It is a heteromodal cortex and it corresponds to the Brodmann's area 46. It is primarily involved in executive function and working memory. It has two parts the ventral dorsolateral prefrontal cortex and the dorsal dorsolateral prefrontal cortex. The dorsal DLPFC primarily deals with monitoring of the working memory and the ventral DLPFC primarily deals with encoding and retrieval of working memory. (78)

4.4.9 Posterior parietal cortex:

The posterior parietal cortex is situated between the somatosensory cortex anteriorly and the visual cortex posteriorly. The intraparietal sulcus divides it further, into superior parietal lobule and inferior parietal lobule. The angular gyrus and supramarginal gyrus are parts of the inferior parietal lobule. The posterior parietal cortex is the hub for integrating somatosensory and visual inputs and thereby helping to guide movements and also for spatial orientation. (80, 81)

4.4.10 Nucleus accumbens:

Nucleus accumbens is a part of the ventral striatum. It is major node involved in reward network and it is also called as pleasure centre. It contains an outer shell and an inner core. The various neurotransmitters associated with the functioning of nucleus

accumbens are dopamine, acetylcholine and GABA of which the dopamine plays a major role in addiction. Normally, the increase in dopamine release with a rewarding stimuli wanes off with repeated stimulation. But such phenomenon will not happen with abuse drugs. fMRI studies have shown decreased activity in nucleus accumbens in patients with depression. (82)

4.4.11 Occipital eye fields:

The occipital eye field is located in the secondary visual area of the human visual cortex. The occipital eye field of one hemisphere is connected to the opposite hemisphere and with the superior colliculus via white fibre pathways. The function of the occipital eye field is conjugate movement of eye to the opposite side and the movements produced by occipital eye fields are reflexive unlike frontal eye field. (83)

4.5 Neuropsychology Tests to evaluate the three domains

4.5.1 Montreal Cognitive Assessment (MoCA):

MoCA is a rapid screening test to differentiate mild cognitive dysfunction. The various sub-sections for cognitive testing include visuo-spatial, executive, orientation, naming, memory, attention, language, abstraction, delayed recall. The total score is 30, of which 26 or above is considered normal. A study by Freitas et al., used MoCA and MMSE as screening tools to assess patients with MCI and AD. They reported that MoCA had higher sensitivity as compared to MMSE in identifying cognitive decline in patients with MCI and AD (84). MoCA has high content validity ($r = 0.87$), high sensitivity (identifying both Alzheimer's Disease and MCI patients 100% and 90%, respectively), high specificity (87%). Positive and negative predictive values are also high for both AD patients (89% and 100%, respectively) and MCI patients (89% and 91%, respectively), high test-retest reliability (patients tested 35 days apart), intra class

correlation coefficient of 0.92 and high internal consistency (Cronbach alpha on standardized items = 0.83) (85, 86).

4.5.2 Addenbrooke's Cognitive Examination Revised Version (ACE–III):

Addenbrooke's cognitive examination is a brief neuropsychological assessment battery useful for detecting dementia and mild cognitive impairment. ACE-III has elaborated examinations for several cognitive domains including Attention, Memory, Fluency, Language, Visuo-spatial. A validation study by Hsieh et al., evaluated sixty one demented patients including FTD, AD and controls with ACE III revised version and reported that ACE III could significantly identify the cognitive decline in attention, language, verbal memory, visuospatial domains (87). Matias et al., used ACE III as neuropsychological test tool to assess controls, MCI and AD patients and found that ACE III test could significantly differentiate control and MCI group with AUC value of 0.96. Also, ACE III significantly differentiated control and AD group with AUC value of 0.978 (88). ACE III was validated by Mathurnath et al., in patients with fronto-temporal dementia and Alzheimer's. The study reported that ACE III can be used to differentiate FTD group from Alzheimer's. The cut-off of 88 in ACE III had the highest sensitivity of 93%. At a lower cut off of 83, ACE III had the sensitivity of 83% (89).

4.5.3 Wechsler's Memory Scale (WMS):

WMS is a memory examination test consisting of seven sub-tests. Test 1 has personal and current information questions. Test 2 contains questions to assess the orientation. Test 3 contains counting the numbers from backwards, alphabets. Test 4 and test 5 includes digit span and two memory passages. Sixth test is to assess the visual reproduction wherein the subject is asked to draw figures after exposing for some time. The next sub-test comprises of associate learning having ten paired words which the

subjects are asked to learn and repeat in three trials. The raw scores obtained from the respective tests are added with subject's equivalent score according to the age group. The M.Q value is obtained from the table and used as the final score for Wechsler's test. WMS contains high consistency and Inter-scorer coefficients were above 0.90 and the test-retest reliabilities varied from 0.70 for seven subscales to 0.90 for two subscales (90). Gonçalves a et al., evaluated the Wechsler's memory scale in Portuguese version to differentiate Alzheimer's and sub-cortical vascular dementia. The patient group was compared with age-matched controls. The study reported the diagnostic ability of WMS III in discriminating SVD and AD patients from controls and also between SVD and AD groups. The SVD patient group exhibited a better performance in the memory domain than AD group (91). Adishesa MS et al., assessed Alzheimer patients with Wechsler's scale. ROC analysis revealed the utility of the test tool in various cognitive sub-tests including reasoning, processing speed, verbal comprehension and working memory. The test showed moderate diagnostic accuracy in deducing cognitive impairment (92).

4.5.4 Trail making test A & B:

This test is used to assess the attention domain of the subject. In trial making test A, the subject is asked to connect the numbers in ascending order within a stipulated time. The average time taken for this test is 29 seconds. Subjects completing the test at more than 78 seconds are considered deficient. Trial making B involves connecting the numbers and alphabets in the ascending order. The average time taken to complete this task is around three minutes. The time taken by the subject is noted and patients taking prolonged time than the average are classified as deficient. TMT B score differentiates Alzheimer's from healthy subjects with a higher specificity and sensitivity. At a threshold value of 356 seconds for both TMT A & B, the test exhibited a sensitivity of 82% and a specificity of 90% (93). A study by Campanholo KR in Brazilian population

analyzed the effects of age, gender, education effects on TMT A & B and reported a significant differences between the genders on the TMT A and TMT B tests (94).

4.5.5 Auditory Verbal Learning Test (AVLT):

Auditory Verbal Learning Test (AVLT) is performed by reading a list of fifteen words to the subjects. A trial list of another fifteen words is given. The subject is asked to recollect the initial list of fifteen words that was read out at first. A study by Powell JB assessed the diagnostic utility of AVLT in patients with cognitive impairments and controls. The study reported that AVLT test could significantly differentiate between the two groups (95).

4.6 Diffusion Tensor Imaging:

The diffusion Magnetic Resonance sequences measure the diffusion of water molecules. The measure of degree of freedom of water molecules is denoted as isotropy or anisotropy. A water molecule that is free to move in all directions is isotropic. On the other, water molecules that are able to diffuse in only one direction is anisotropic. These are exemplified by the anisotropic nature of the water molecules in the white matter tracts due to the axon and the myelin covering it restricting its movement to one axis of motion and the isotropic nature of the water molecules in the cerebrospinal fluid limited only by the ependyma lining the ventricles. The sequences used in the measurement of diffusion Magnetic resonance imaging include Diffusion Weighted MRI and Apparent Diffusion Coefficient. In the diffusion sequences, the diffusion of the water molecules is measured along a specified direction. When the direction of measurement of the diffusion is chosen perpendicular to the diffusion of the water molecule, the measured values are low. When the direction of measurement of the diffusion is chosen parallel to the diffusion of the water molecule, measured values are high. The use of the ADC in the

imaging of the white matter tracts is limited by the unidirectional nature of measurement. However, the hurdle of the directional limitation in the imaging of white matter tracts can be overcome by Diffusion Tensor Imaging. (96)

4.7 Diffusion Tensor Imaging Metrics

Diffusion tensor imaging uses a mathematical model, diffusion tensor, to measure the diffusion of water molecules. Using diffusion tensor, diffusion of water molecules can be measured in six directions. The diffusion tensor considers diffusion of water molecule in ellipsoid. The diffusion coefficient is measured by three eigenvalues and the directionality is measured as eigenvectors. The axial diffusivity (E1) measures the diffusion of water molecules along the long axis, which is the principle direction of the diffusion tensor and hence the orientation of the fibre bundle. If axial diffusivity is measured along the 'x' axis, then radial diffusivity is the average of the diffusion measured along the 'y' (E2)and 'z' (E3) axis along the plane perpendicular to the axial diffusivity. Mean diffusivity is measured as an average of the diffusion along the three axes. It reflects the average mean of diffusion of water molecules along the three axes x, y and z. (96)

$$\boldsymbol{AD = E1,}$$

$$\boldsymbol{RD = \frac{E2+E3}{2},}$$

$$\boldsymbol{MD = \frac{E1+E2+E3}{3},}$$

E1 = Axial diffusivity,

E2, E3 = Diffusion in the plane perpendicular to the axial diffusivity along the y axis and z axis,

FA = Fractional Anisotropy.

The degree of anisotropy is measured as fractional anisotropy with values between 0 and 1. A value close to 0 denotes isotropy and close to 1 denotes anisotropy. A value close to 1 refers to high anisotropic nature of the measured bundle. A decrease in the measured value refers to decreased anisotropy and increase in isotropy of the water molecular diffusion. (96)

$$\boldsymbol{FA} = \frac{\sqrt{\boldsymbol{3((E1-E)^2(E2-E)^2(E3-E)^2)}}}{\sqrt{\boldsymbol{2(E1^2+E2^2+E3^2)}}}$$

E1 = Axial diffusivity

E2, E3 = Diffusion in the plane perpendicular to the axial diffusivity

E = Mean diffusivity

FA = Fractional Anisotropy

Virtual Reconstruction of the White Matter Pathways:

Further, the use of above metrics including fractional anisotropy, axial diffusivity, radial diffusivity and mean diffusivity, it is possible to reconstruct the fibre tracts non invasively. This is possible with the use of diffusion tractography that uses mathematical algorithms to decipher the probable tract orientation with the use of metrics and maps it on a voxel by voxel basis. This is possible with the routinely used MRI systems for clinical purpose with an acquisition time of 5 to 20 minutes. This provides the possibility to create white matter fibre tracts and its connectivity patterns. The diffusion metrics are useful in assessing the composition, microstructure organisation and integrity of the fibre tracts. (97, 98)

4.7.1 Elucidation of Pathology using Diffusion Tensor Metrics:

The changes in diffusion tensor imaging in axonal integrity, cytotoxic edema and vasogenic edema are summarised below. Radial diffusivity is a sensitive parameter that increases with decrease in myelination and increased loss of axonal integrity. Mean diffusivity increases with the decrease in myelination and increased loss of axonal integrity. Axial diffusivity increases with the decrease in myelination and increased axonal integrity. Fractional Anisotropy decreases with the loss of fibre integrity. Cytotoxic edema results from loss of maintenance of ion balance across cell membrane as a result of which there is intracellular accumulation of water and decreased extracellular content of water. This results in reduction in diffusion of water molecules. Hence measuring a voxel that contains cytotoxic edema reveals decreased Mean diffusivity. Vasogenic edema is characterised by blood brain barrier dysfunction and hence there is increased extracellular fluid accumulation Measurement of voxel that contains vasogenic edema causes increased Mean diffusivity and reduced Fractional anisotropy. (96, 98)

4.7.2 Diffusion tensor imaging in Primary dementia:

Diffusion tensor imaging in dementia patients assesses microstructure integrity which is evidenced by decreased anisotropy and increased diffusivity in the white matter tracts. However, it has been thought to be secondary to cortical atrophy. However, recent studies have suggested that white matter changes occur primarily and not secondary to cortical changes. This is evident from studies in Alzheimer's disease. Diffusion tensor imaging in Alzheimer's disease shows decreased anisotropy and increased diffusion in white matter tracts. These include direct and indirect connections to the medial temporal cortex including anterior cingulum, posterior cingulum, superior longitudinal fasciculus, uncinate, fornix, parahippocampal white matter and also the corpus callosum. The

involvement of the anterior cingulum, posterior cingulum and fornix in Alzheimer's disease showed correlation with the presence of neuropsychiatric symptoms in these patients. The analysis of parahippocampal white matter has revealed the presence of microstructure changes with loss of axonal integrity in those with normal hippocampal volume that cannot be explained by the ageing process alone. Further in patients with mild cognitive impairment, who present with cortical atrophy limited to the medial temporal cortex, the involvement of white matter tracts is widespread. These findings suggest the possibility if involvement of white matter tracts prior to the cortical atrophy. This further correlated with the Beta amyloid load that could explain the white matter dysfunction caused by its accumulation. (99, 100, 101, 102, 103, 104, 105)

In behavioural variant Fronto-temporal dementia, changes in fractional anisotropy was noted in right paracallosal cingulum and left uncinate fasciculus (106). Primary progressive aphasia includes Progressive non fluent aphasia, Semantic variant and logopenic variant. In the Progressive non fluent variant of primary progressive aphasia, microstructure changes were noted in the components of the superior longitudinal fasciculus in the left side connecting frontal cortex with parietal and temporal cortex. However, sparing of the inferior longitudinal fasciculus and the uncinate fasciculus was noted. In semantic variant of the primary progressive aphasia, the microstructural changes were noted in the uncinate fasciculus that connects the temporal cortex with the orbitofrontal cortex and the inferior longitudinal fasciculus that connects the temporal cortex and the occipital cortex bilaterally. The involvement of the uncinate fasciculus was more prominent than the inferior longitudinal fasciculus. The microstructural changes involved the subcomponents of the superior longitudinal fasciculus in the semantic variant. These included the fibres of the superior longitudinal fasciculus that connects the temporal and the parietal cortex and in the arcuate fasciculus.

In logopenic variant of the primary progressive aphasia, microstructural abnormalities were noted in the component of superior longitudinal fasciculus connecting temporo-parietal region and arcuate fasciculus. The microstructural changes were more prominently noted in the progressive non-fluent aphasia than the semantic and the logopenic variant. (107)

4.8 Diffusion Tensor Imaging of Attention, Memory and Language Network:

The interhemispheric analysis of the structural integrity of the white matter tracts did not show any side predominance. This is contrary to the usual concept of hemispheric predominance for the cognitive domains. However, this finding can be explained by the fact that dominance is at the functional level and is lacking at the structural level.

4.8.1 DTI of the language networks:

Diffusion tensor imaging images the components of language network which includes dorsal and ventral streams. In the dorsal stream the diffusion tensor imaging assess the arcuate fasciculus and the superior longitudinal fasciculus. In the ventral stream the diffusion tensor imaging assesses the extreme capsule, middle longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus. The superior longitudinal fasciculus connects the parietal lobe with the frontal lobe. The arcuate fasciculus connects the superior and middle temporal lobe with frontal lobe (60, 108). In the diffusion tensor imaging study of language network by kantarci et.al, they have observed a good correlation between the FA values of inferior longitudinal fasciculus, and posterior cingulate bundle with the neuropsychological tests for language assessment. (109)

4.8.2 DTI of the attentional network:

Diffusion tensor imaging is useful in imaging the various white matter tracts that constitute the components of attention network.

Alerting network: The various nodes involved in attention are locus coeruleus, frontal and parietal areas especially of the right hemispheric and the fibre pathway involved is posterior limb of internal capsule and the neurotransmitter involved is norepinephrine

Orienting network: The various nodes involved in orientation are superior temporal lobe, superior parietal lobe, frontal eye field, temporo-parietal junction, pulvinar, superior colliculus and splenium of corpus callosum are involved in integrating these nodes. The neurotransmitter involved is acetylcholine.

Executive attention network: The various hubs involved in executive function of attention are the anterior cingulate cortex and the dorsolateral prefrontal cortex and the white matter pathway involved is anterior corona radiata. The neurotransmitter involved is dopamine. (110, 111)

In the diffusion tensor imaging study of human attentional networks by Sumitniogi et.al a statistically significant relationship between the various functional components in the attentional network test and the average fractional anisotropy of the relevant regions of interests have been demonstrated. According to their study, the executive task in the ANT test has a good correlation with the FA values of anterior corona radiata; the alerting task in the ANT test has a good correlation with the FA values of the posterior limb of internal capsule and the orienting task has a good correlation with the FA values of the splenium of corpus callosum when the average FA

values of all the these three ROI are compared against the scores for the various functional components of attention tested using attentional network tests. (112)

4.8.3 DTI of the Memory network:

The diffusion tensor imaging is also used to assess the integrity of various white matter tracts involved in memory including fornix, cingulum bundle, uncinate fasciculus and inferior fronto- occipital fasciculus. Mc Donald et.al, observed correlation between diffusion tensor imaging parameters in left uncinate fasciculus, left parahippocampal cingulum, left inferior fronto-occipital fasciculus with poor verbal memory performance in neuropsychological tests. In the study of Vanessa douet et.al it has been shown that, the episodic memory impairment correlates well with the abnormal DTI metrics of fornix. (113, 114)

4.8.4 Limitations of Diffusion Tensor Imaging:

Diffusion tensor imaging is based on voxel by voxel analyses of diffusion of water molecules. The resolution of voxel is not sufficient enough to trace small fibre tracts. The low signal noise ratio of the diffusion sequences in MRI and the artefact interferes with the reconstruction of the tracts by the tractography. The MR tractography assumes the fibres in a voxel to be single orientation and is not considerate for crossing over, convergence and divergence of fibres within voxel and hence does not account for it. The recent developments with the use of High Angular Resolution Diffusion Imaging (HARDI) method helps overcome the issue of crossing, convergence and divergence of white matter tracts. (96)

4.9 FDG PET - Concepts, Acquisition and Analysis

4.9.1 Introduction to FDG PET imaging:

The use of 18 F- Fluoro-2-deoxy-D-glucoseas a radio-labelled tracer in Positron Emission Tomography has evolved in the recent years in aiding the diagnosis of dementia. After the administration of radio labelled tracer, the fluorodeoxyglucose is taken up into the neuron and is metabolised by hexokinase and converted to a phosphate metabolite of the tracer and is confined to the cell. Hence, imaging the brain after administration of the radiolabelled tracer reflects the normal functioning cortical areas. In patients with dementia, the cortical areas reveal decreased metabolism due to hypo functioning of the neurons and synaptic dysfunction. The pattern of this hypometabolism aids in the clinical diagnosis of the dementia. The signature pattern of the hypometabolism may help identify the various primary dementias such as Alzheimer's disease, Fronto-temporal dementia, Dementia with lewy bodies, Vascular dementia and other primary dementia. (115)

4.9.2 Image Acquisition, processing and pitfalls:

Patient preparation prior to the procedure requires a maintenance of euglycemic state <140 mg/dl. Benzodiazepines and barbiturates may interfere and hence should be avoided. When sedation is required for the patient, benzodiazepine may be administered 30 minutes after the administration of the tracer prior to the imaging acquisition. The use of caffeine, tea, alcohol and nicotine should be avoided prior to the procedure. Patient should be awake with eyes open to avoid false positive hypo metabolism of the visual cortex. Thirty minutes following administration of the radio labelled tracer, image acquisition is performed. Using 3D Stereotactic Surface Projection, the images are projected and analysed. The image acquired is projected on to standard Thalaiarch atlas. The corresponding Z scores of the cortical areas are obtained based on the comparison

with reference data acquired following global normalisation. The images are colour coded based on the Z scores. A positive Z score indicates hypo metabolism and negative Z score indicates hyper metabolism. A corresponding CT of the brain is performed to compare with the FDG PET data. (116, 117, 118)

The acquisition may be affected by motion artefact that may interfere with quality of the FDG PET. The presence of hyperglycaemia interferes with the uptake of glucose into the neuron and hence may produce patterns of hypo metabolism. The hypo metabolism may be noted in posterior cingulate, precuneus, parietal association cortex, temporal association cortex and frontal association cortex mimicking Alzheimer's disease. The presence of structural lesions such as arachnoid cyst may present with hypo metabolism in FDG PET. Hence it is essential to perform concurrent CT imaging to rule out confounding factors.(117, 119, 120)

4.10 Pattern of hypometabolism in Primary Dementia

4.10.1 Pattern Recognition:

The pattern of hypo metabolism is useful in the diagnosis of various primary dementia. The FDG PET in a normal individual reveal increased metabolism in the caudate, putamen, thalamus and the cortex with decreased uptake in the white matter and the globus pallidum. The areas such as the cingulum and the precuneus are affected early in the disease process. The pattern of hypo metabolism in various cortical areas are summarised below. Closure of eyes during image acquisition may mimic hypo metabolism in the occipital cortex.

4.10.2 Alzheimer's Disease:

In Alzheimer's disease (AD), the hypo metabolism is noted in the posterior cingulate gyrus early in the course of the disease. Decreased metabolism in also noted in

precuneus, posterior parietal cortex, posterior temporal cortex (middle temporal gyrus and inferior temporal gyrus). As the disease progresses, prefrontal association cortex also reveals hypo metabolism. The pattern of involvement may be unilateral or bilateral and asymmetric. When both hemispheres are asymmetrically involved, the involvement is homogenous with one hemisphere more severely involved than the other hemisphere. The anterior cingulate, primary sensorimotor cortex and primary visual cortex are spared in Alzheimer's disease. (121, 122)

4.10.3 Fronto-temporal Dementia:

In Fronto-temporal dementia (FTD), the hypo metabolism depends on the subtype of the FTD. The pattern of involvement is usually prominent in the frontal cortices, temporal cortices and anterior cingulate gyrus with an anterior to posterior gradient. In classical FTD, the hypometabolism is noted in the frontal cortex with anterior to posterior gradient, anterior part of temporal lobe and anterior cingulate gyrus. In frontal variant of FTD, the frontal cortex is predominantly involved with sparing of temporal cortex. In semantic variant FTD, the anterior temporal cortex is more involved with involvement of the left hemisphere more than the right side. (123, 124)

4.10.4 Dementia with Lewy Bodies:

In dementia with Lewy Bodies (DLB), the clinical triad is characterised by Parkinsonism, visual hallucination and fluctuations in cognitive levels of the patients. The signature pattern of cortical involvement in these patients include hypo metabolism of the primary visual cortex, posterior parietal cortex, posterior temporal cortex, precuneus. The involvement of the visual cortex helps differentiate DLB from AD. However, the absence of cortical involvement does not help differentiate between AD

and DLB. In posterior cortical atrophy variant of AD demonstrates hypo metabolism in the visual cortex. (125)

4.10.5 Vascular Dementia:

The evidence of FDG PET in vascular dementia is limited. This is due to the evidence of the infarct and ischemic changes being clearly visible in CT / MRI of the brain. The incidence of vascular dementia is decreasing. However, if FDG PET is performed in these patients, hypo metabolism is noted with abrupt margins restricted to vascular territories. The hypo metabolism corresponds to areas of gliosis in CT / MRI of the brain. In patient with involvement of the frontal lobe, contralateral cerebellum also reveals hypo metabolism due to crossed cerebro-cerebellar diaschisis. (126)

4.10.6 Corticobasal degeneration:

Conrticobasal generation is characterised by clinical features that include extra pyramidal features and neurological deficits suggestive of cortical involvement such as agnosia, apraxia and alien limb phenomenon. In corticobasal degeneration, hypometabolism is evident in the primary sensory and motor cortex, basal ganglia, thalamus, cingulate gyrus, frontal and parietal cortex with asymmetric involvement of the areas. (127)

It is important to consider these patterns as they may help in assisting the diagnosis. However, the use of it as a standalone is flawed and should be considered in the background of clinical information.

4.11 Voxel Based Morphometry: Concepts and Acquisition

4.11.1 Voxel based morphometry:

Voxel based morphometry is an automated technique in which a damaged focal area or atrophy or expansion of the tissue in the brain can be viewed in three dimensional image by using T1 weighted magnetic resonance images with statistical analysis (128). In brain the gray matter areas are better viewed and studied in voxel based morphometry. There are four steps involved in the generation of the image. They are A) Tissue classification , in which brain is segmented into CSF, gray matter and white matter. B) Spatial normalization , in which the structured images are organized into same space and these images are segmented into gray and white matter C)Spatial smoothing ,by smoothing process the sensitivity and accuracy of these images can be increased D) Statistical analysis. (129)

4.11.2 Tissue classification:

The brain is segmented into Cerebrospinal fluid, white matter and gray matter based upon their intensity values. The obtained image is corrected by means of Bias correction. In the border zones there will be overlapping of the tissues will be seen even after the correction . Hence after this process a partial volume image is obtained. Hence these processed partial volume images are used accurately to calculate local volume and for tissue classification. (130)

4.11.3 Spatial normalization:

Spatial normalization is the process in which T1 weighted magnetic resonance image from each one is matched spatially and registered so that its corresponds one location in one subject to other in same location. This can be achieved by registering all images from a study on a same template image in same space. These template images are

divided in linear and nonlinear normalization. The linear normalisation process includes translation, rotation, shearing and scaling. The shape and size of the brain is not altered in translation and rotation but changes the position in space to form a 6 parameter transformation called as rigid- body transformation. This rigid -body transformation helps in detecting the changes in the same brain over the period of time. The size and shape is altered by scaling and shearing and again 6 parameter transformation image is formed. Totally 12 parameter transformation image so called affine transformation image is used to register the voxel image in a template space. The position change, size change and shape change can be allowed by application of nonlinear transformation. A deformed field is obtained as a result of these spatial transformations. The voxel images are exactly obtained from deformation field as Jacobian determinant. The volume changes (gray matter changes) occurred due to spatial normalization and is determined from Jacobian determinant. (130)

4.11.4 Spatial smoothing:

Smoothing makes the images more closely to Gaussian field model and increases the sensitivity of the images, increases the parametric test validity and reduces the inter-subject variability. At each point, averaged voxels numbers is determined by the smoothing kernel size. Excess smoothing results in error introduction, reduction in sensitivity and reduction in variability in the statistical analysis. (131)

4.11.5 Statistical analysis:

The final step in VBM is statistical analysis. These smoothed segmented images are statistically analysed by general linear model and gaussian random field theory. (132)

4.12 Gray matter hubs in voxel based morphomerty :

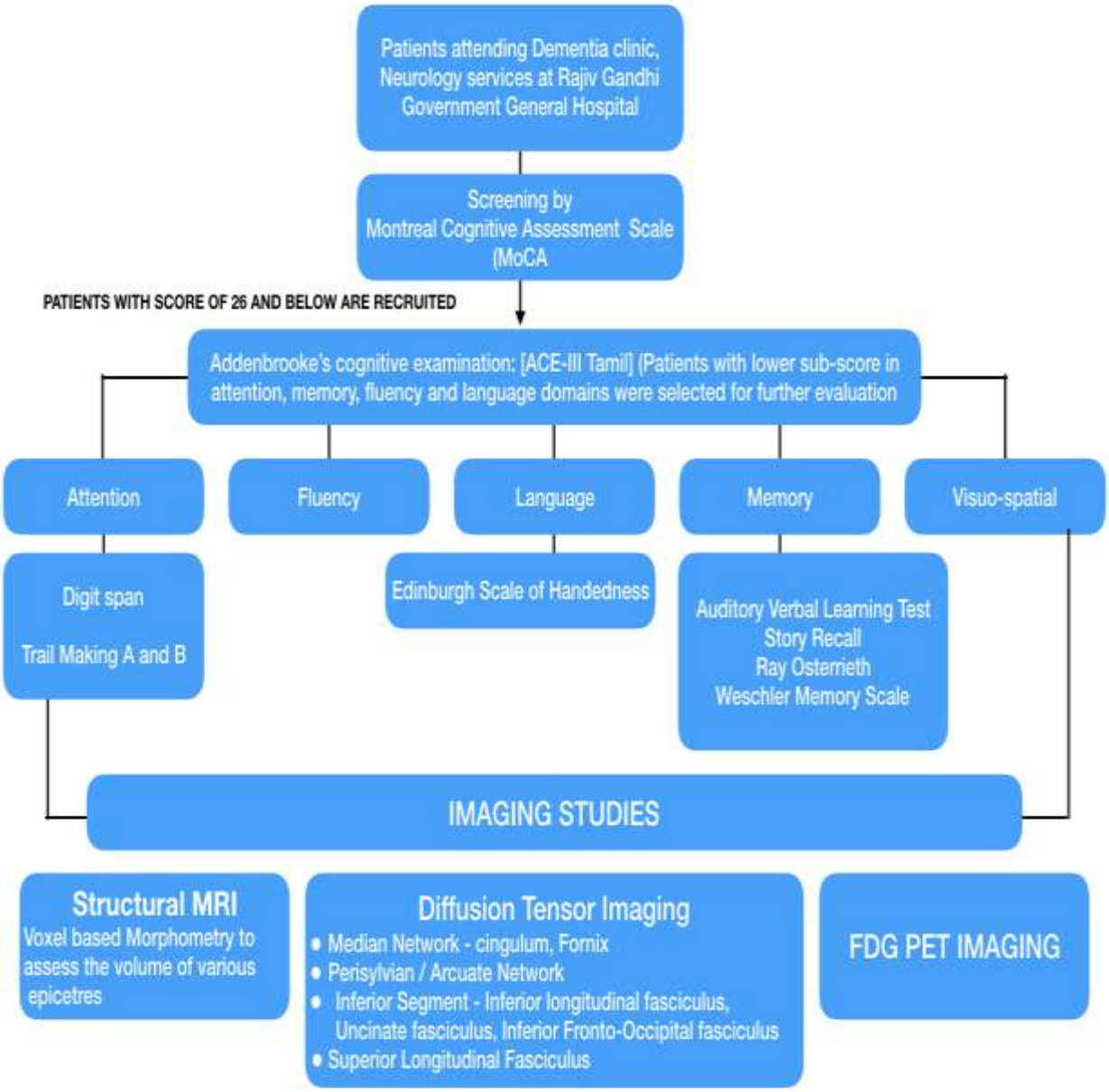
Kantarci et al (2011) and colleagues observed that hippocampus, Para hippocampal gyrus and amygdala in both hemispheres showed significant cortical diffusivity in memory domain. In language domain, there is significant cortical diffusivity in left temporal pole, amygdala , fusiform gyrus, posterior inferior temporal gyrus. There is no cortical diffusivity specific area associated with attention domain. (109).

Hartley and Harlow et al (2012) observed that volume of hippocampus, anterior temporal neocortex and insula are associated with performance of topographical memory in healthy individuals. (133)

Dirk T.Leube et al (2008) and colleagues used automated morphometric technique (VBM) to detect atrophic changes in brain in patients with cognitive deficit in mild cognitive impairment and Alzheimer's disease. They found that impaired episodic memory function associated with atrophic changes in anterior hippocampus, entorhinal and perirhinal cortex, Para hippocampal and middle temporal cortex and cingulate cortex especially anterior region. (134)

5. SCOPE AND PLAN OF WORK

5. SCOPE AN1D PLAN OF WORK



6. MATERIALS AND METHODS

6. MATERIALS AND METHODS

6.1 Patients & Methods:

6.1.1 Patients:

Subjects attending dementia and cognitive neurosciences clinic at Rajiv Gandhi Government General Hospital, Chennai (RGGGH) were enrolled in the study. A total of 60 patients and 30 controls were recruited for the study. All the subjects were well informed about the study and the consent forms were obtained prior to the assessments. All the patients in the study underwent clinical examination for establishing the diagnosis of dementia. After the clinical assessment the subjects under investigation underwent four different types of assessments. The assessments include neuro-psychological assessments, Voxel based Morphometry, Diffusion Tensor Imaging (for both controls and cases), and FDG-PET (for cases alone).

6.1.2 Neuropsychological tests:

6.1.2 (a) Montreal Cognitive Assessment (MoCA):

MoCA is a brief screening test that has various sub-sections for Visuospatial / executive (5), orientation (6), naming (3), memory, attention (6), language (3), abstraction (2), delayed recall (5). The total score for MoCA is 30 which are divided for definite subsections. The visuo-spatial section comprises of trail making test with numbers and alphabets. The subject is asked to connect them in the ascending order. Next, the subject is asked to copy a cube followed by clock drawing test. Trial making test, copying of the cube has one mark each. The clock drawing test has three marks. The second section is naming which has the pictures of three animals. Scoring is based on the identification of the animals by the subject. Third section is for memory wherein five words are read out loud to the subject and the subject is asked to repeat them. This is

repeated twice. Next section is attention that includes digit span forward and backward, Letter reading and subtraction. Scores are based on the subject's performance in each test. The language sub section consists of sentence repetition and recollecting words that start with a specific alphabet. Abstraction part involves finding the similarities between two words. In delayed recall, the subject is asked to recall the five words which were red out loud to them initially. The final section is orientation where in the subject is asked about the date, day, place information. One point is added to subjects who have had education of 12 or less.A cut off score of 27 and above were considered normal. (85)

6.1.2 (b) Addenbrooke's Cognitive Examination Revised Version (ACE–III):

Addenbrooke's cognitive examination comprises detailed examinations for various cognitive domains including Attention (18), Memory (26), Fluency (14), Language (26), Visuo-spatial (16).

Attention:

The attention part in ACE-III consists of questions related to orientation such as date, day, place etc. The next task for the subject is to repeat three words and the scores are noted. Third task in the attention section is subtraction of numbers. The total score for this sub-section is 18.

Memory:

The first task in memory section is repetition of address by the subject. Three trials are given and the scoring is based on number of the details recollected in the address.

The subject is then asked names of four famous personalities after giving definite clues. The final part of the memory test is to recall the address particulars. The total score for this section is 26.

Fluency:

An alphabet is given to the subject and the subject is asked to recollect as many words as possible. This is followed by recollecting the names of animals and birds.

Language:

The language section consists of writing task where in the subject is asked to write sentences about himself or about a festival. Then, the subject is asked to repeat the word/sentences that are read out. Third part is naming of the objects printed on the questionnaire. This is followed by asking the subject to read five words.

Visuo-spatial:

The visuo-spatial section consists of clock drawing, copying of pictures, counting the dots and identifying the alphabets. The scores for this section is 16.

The total score for Addenbrooke's cognitive examination is 100. A score of 88 and above is considered normal in our study. (89)

6.1.2 (c) Wechsler's Memory Scale:

Wechsler's memory test constitutes seven sections. First two sections are of orientation and questions based on current affairs. Third section is recalling the numbers backward, followed by recalling alphabets and multiplications of 3. The fourth part has digit span test (both digit forward and digit backward). Fifth task is story recall. A story is read aloud to the subject and the subject is asked to repeat the story. Scoring is based on the number of details recollected by the subject.

Next task is to copy diagrams. The subject is asked to copy diagrams. The scoring is based on the efficiency of the subject to copy the diagrams. The seventh section in Wechsler's is associate learning. The subject is asked to recall the paired words. Three trials are given for this test. All the scores are added along with age-corrected score. The MQ equivalent score was taken as the final score. A score of 100 and above is considered normal in our study. (90, 135)

6.1.2 (d) Trail making test A & B:

In trial making test A, the subject is asked to connect the numbers in ascending order within a specified time. The average time taken for this test is 29 seconds. Subjects completing the TMT A test at more than 78 seconds are considered deficient. Trial making B involves connecting the numbers and alphabets in the ascending order. The average time taken to complete this task is around three minutes. The time taken by the subject is noted. Subjects taking prolonged time than the average time mentioned are classified as deficient. (93)

6.1.2 (e) AVLT:

A list of fifteen words was read to the subjects in native language. The subjects were asked to recall as many words as possible after every trial. Five trials were given to the subjects. A list of another fifteen words was read to the subjects. The subjects were asked to recall the initial list of fifteen words that was read out at first. The scores were noted according to the number of words recollected after the trials.

6.1.3 Inclusion Criteria:

6.1.3 (a) Cases:

- All-cause dementia presenting to Dementia Clinic, Department of Neurology, Madras Medical College, Chennai with DSM 5 diagnosis of dementia (Major Neurocognitive Disorder).
- Age between 30 - 85 years.
- Total number of patients included in the study: 60

6.1.3 (b) Controls :

- Age, Sex matched subjects
- Total number of controls : 30

6.1.4 Exclusion Criteria:

- Any neurological disorder with cognitive impairment,
- Any self reported genetic disorder,
- Any serious psychiatric illness like Schizophrenia, Bipolar Affective Disorder and substance dependence other than tobacco,
- Previous significant Head Injury,
- Current use of Medications that interfere with cognition,
- Structural lesions in the brain, and
- Pregnancy

A brief description of other clinical assessments, MRI Voxel based Morphometry (Grey Matter Track), MR Diffusion Tensor Imaging(White Matter Tract), and FDG-PET is outlined in the following section:

6.1.5 MRI Voxel Based Morphometry:

T1-weighted images were processed using the computational anatomy toolbox (CAT; http://www.neuro.uni-jena.de/cat/) for the statistical parametric mapping software (SPM; http://www.fil.ion.ucl.ac.uk/spm) was implemented within Matlab (The MathWorks Inc., Sherborn, MA, USA). Standard routines and default parameters of the CAT toolbox were applied. Apriori region of interest based analyses were done for the following regions using masks created with the Wake Forest University school of medicine (WFU) Pickatlas: Attention Network: 1) Dorsolateral Prefrontal Cortex, 2) Frontal Eye Field, 3) Occipital Eye Field, 4) Cingulate Cortex, 5) Superior Parietal Lobule; Language Network: 1) Broca's Area, 2) Wernicke's Area, 3) Geschwind's Area (Inferior Parietal Lobule); Memory Network: 1) Uncus, 2) Hippocampus, 3) Nucleus Accumbens. The group comparisons were performed controlling for the potential confounding effects of age, sex, intracranial volume, years of education. The significance threshold was set at $p < 0.001$ (uncorrected) with multiple comparison correction using small volume correction using a sphere of 10 mm radius.

6.1.6 MR Diffusion Tensor Imaging:

Diffusion Tensor Imaging was performed on 3T Siemens magnetom SPECTRA TIM 4G + DOT MRI system. Spin echo diffusion weighted echo planar imaging (DW-EPI) sequence was performed with 70 axial slices with a resolution of 2.0x2.0x2.0mm3 . The diffusion parameters used were TR = 10,600ms; TE = 103ms; b-value of 1000s/mm 2 acquired with 64 gradient directions. The Field of view (FoV) was set at 256mm and bandwidth of 1302Hz/Px. For DTI analysis, images were post-processed in Siemens workstation using Neuro 3D software for extracting DTI data and FA values. Fractional Anisotropy, Apparent diffusion Coefficient, Axial diffusivity, Mean diffusivity and Radial diffusivity were measured. E1 is the axial diffusivity, Mean diffusivity is

(E1+E2+E3) / 3 and radial diffusivity is (E2+E3) / 2, where E1, E2, E3 are eigen vectors in three directions. General information on anatomy of principal white matter tracts is given by the FA maps of the right hemisphere. The left hemisphere colour maps provide information on local orientation of the tracts. The red colour indicates latero-lateral direction (i.e. right to left; left to right). Anterior and posterior direction and vice versa is indicated by green colour and the blue colour indicates dorso-ventral direction and vice versa. ROI's are characterized on the axial FA pictures and these were used as initial seed points for tracking representing essential "obligatory passages" along the tracts whereas other methods use cortical masks as starting regions. These passages corresponds to the regions in the brain that all the fibres in each of the tracts be required to traverse to attain their respective sub-cortical or cortical ends. Therefore, using these passages as a starting point for tracking enables us to see all fibres of a single tract. In this study, single ROI approach is used wherein all the fibres passing through the ROI region are regarded as belonging to a specific tract. One-ROI approach has been followed for Superior longitudinal fasciculus, Inferior longitudinal fasciculus, Cingulate fasciculus, Arcuate fasciculus, Inferior fronto-occipital fasciculus and Uncinate fasciculus. The ROI regions were marked by a single individual for all the images to reduce the inter-subject variability.

The DTI metrics of the white matter tracts that were analysed for the domains studied include: Superior longitudinal fasciculus, Inferior longitudinal fasciculus, Cingulate fasciculus for Attention domain.

Superior longitudinal fasciculus, Inferior longitudinal fasciculus, Arcuate fasciculus, Inferior Fronto-occipital fasciculus for language domain.

Uncinate fasciculus, fornix and cingulate fasciculus for memory domain.

6.1.7 FDG-PET:

Subjects were maintained in a fasting state. Intravenous fluids were administered for hydration and to enable the renal elimination of radioactive substance. Fluids containing dextrose were avoided and of glucose were maintained at levels less than 140mg/dl. 30 minutes after infusing radioactive tracer, sedation was induced. Drugs that might interfere with imaging such as Benzodiazepines, barbiturates and glucocorticoids were avoided. Efforts were taken to make sure that patients stay wide awake with their eyes open and head held motionless during the imaging procedure.

FDG PET Imaging was carried out for 30 minutes after injecting the radioactive tracer. After acquiring, the images were mapped and compared to the Thalaiarchatlas. The atlas consists of standardized images on the axial plane. The grey scale images are colour coded in the post- processing. The voxel activity is normalized by taking the reference point that is considered to be unaffected by the disease. In the current study global reference was taken as reference point. To analyse the reconstructed images, 3D stereotactic surface projection is used and results were yielded in Z scores. A positive Z score indicates Hypometabolism and negative Z score indicated hypermetabolism.

The cortical areas that were studied include:

- Frontal association, parietal association, anterior cingulate, posterior cingulate and caudate for attention domain.
- Frontal association, Parietal association, Temporal association for language domain.
- Anterior cingulate for memory domain.

The various grey matter nodes that were analysed using voxel based morphometry, white matter tracts using diffusion tensor imaging, cortical function using FDG PET imaging are summarised in Table 1

6.2 METHODOLOGY

A random sample of 60 patients and 30 age-gender matched controls were selected from dementia and cognitive neurosciences clinic at Rajiv Gandhi Government General Hospital(RGGGH), Chennai during Dec. 2014 – Feb. 2018. The study was approved by Institutional Ethical Committee of Rajiv Gandhi Government General Hospital, Chennai. Neuropsychological tests were performed after obtaining consents from the subjects or caretakers. Patients were selected on the basis of MoCA scores where a case with a MoCA score of below 27 and satisfying the inclusion/exclusion criteria has been treated as a patient and included in the present study. The following clinical assessments were made on each patient: Addenbrooke's Cognitive Examination III (ACE III), Wechsler's Memory Scale (WMS), Trail Making Test A &B (TMT),Auditory Verbal Learning Test (AVLT) and scores were assessed accordingly. Neuropsychological aspects of both patients and controls were assessed by a single trained clinical psychologist.

Imaging studies such as MRI, DTI and FDG-PET were performed by Radiologists within one month of performing Neuropsychological assessment. Neuro-imaging was performed within one month of neuropsychological assessment. Confidentiality and privacy of the subject data has been maintained throughout the study. All applicable codes of ethics have been followed in the present study (Figure 2).

6.2.1 Statistical tools applied:

Rigorous statistical analyses were carried out based on the observation and the assessments made from the patients as well as the controls. Statistical tools such as formation of frequency tables, summarized statistics such as Mean, Median, SD and standard error of mean were computed for the two groups. Some of the tests used in the present study include tests such as Chi-square, Mann whitney test, Proportions test, Independent sample t test, Paired sample t test, One way Analysis of Variance, Correlation analysis, Regression analysis, and discriminant analysis. The data collected from the patients and controls were coded, entered into a personal computer and analysed using the well-known statistical package, IBM Statistical Package for Social Sciences (Version 21.0).

7. RESULTS AND ANALYSIS

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7.1 Reliability:

Before carrying out the major study, a pilot study was conducted taking a random sample of 10 patients and 10 controls. Reliability and validity of the protocols used for carrying out the major study were computed using appropriate statistical tools such as Cronbach's alpha for reliability and expert opinion on the validity of the protocols. Reliability analysis was carried out using split half method and the Cronbach alpha for part 1 of the protocol was obtained as 0.913 and for part 2 it was 0.993. The overall reliability of the protocol was 0.937 indicating high reliability of the test schedule used in the present study. Table 2

Some of the findings of neuro-psychological aspects in the present study are given below:

Nearly, 85% of the patients are above 46 years of age and about 83% of controls were in the same age group. Mann Whitney U test was used to test the null hypothesis that the proportion of patients in the two groups, viz., patients and controls, remains the same against the alternate hypothesis that two groups have different proportion of subjects. If the P-value (significance value) is less than or equal to 0.05, the null hypothesis is rejected and inferred that the proportion of respondents in sub-categories are not the same. If the P value is more than 0.05, it is concluded that there is no reason to reject the null hypothesis. Since the P values of age categories and gender categories are more than 0.05, it is concluded that the proportions of patients in the age groups and gender categories remain the same in the two groups, patients and controls. In the present study, 70% of the patients are males and about 63% of males are in the control group. The proportion of males and females found in the two groups remains the same since the

significance values of Mann Whitney is more than 0.05. As far as education levels of respondents are concerned, nearly 83% of patients have studied up to the high school level. More than 90% of the controls have studied beyond the high school level.

7.2 Neuro Psychological Aspect:

Neuro psychological assessments were made on both patients and controls on the following:

Montreal Cognitive Assessment (MoCA) with a maximum score of 30, Addenbrooke's Cognitive Examination-III (ACE-III) with a maximum score of 100 which includes sub tests such as attention with a maximum score of 18, memory with a maximum score of 26, fluency with a score of 14, language with a score of 26 and visuospatial with a score of 16. Since fluency is an integral part of language, for analysis purpose we have combined the fluency scores with language scores amounting to an overall score of 40. Wechsler's Memory Scale (WMS) includes an age corrected score, Auditory Verbal Learning Test (AVLT) with a maximum score of 15, Digit span with a maximum score of 15, story recall with a maximum of 24 and complex figure with a maximum of 14. The mean values of each one of neuro-psychological aspects were compared between patients and controls. The null hypothesis formulated in each case is that the mean values of the two groups compared remains the same between patients and controls in the aspect under consideration against the alternative hypothesis that the mean values of the two groups are not the same. The test that was used to validate the hypothesis is independent sample t-test. The null hypothesis is rejected if p-value (significance value) is less than 0.05. If the significance value is greater than 0.05, it is concluded that there is no reason to reject the null hypothesis.

From the table 3 it is evident that the mean values of each one the neuropsychological aspect are found to be significantly different between patients and controls since the p values of independent sample t test are all less than 0.001. A close scrutiny of the mean values indicates that the controls have higher levels of mean values compared to the patients in MoCA, ACE III (Attention, Memory, Language, Fluency), WMS, AVLT, Digit Span, Story recall and complex figure.

Correlation analysis indicates that all the parameters are found to have significantly high positive correlations. Table 4

Correlation analysis of both patients and controls indicate that the correlation coefficient between Addenbrook's cognitive score and attention is only 0.439 in controls whereas it is 0.943 in patients. Addenbrooke's Cognitive score is highly significantly correlated with other neuropsychological aspects such as memory, fluency etc. among the patients. Values of correlation coefficient are slightly lower in the control group. Table 5.

Step wise discriminant analysis has been used to formulate a mathematical equation that would segregate patients & controls using the 12 neuro-psychological aspects covered in the present study. The analysis indicated only 5 parameters namely attention, memory, AVLT, digit span and complex figure test are needed to differentiate the patients from the controls. Using the discriminant function, discriminant scores were obtained for both patients and controls in the present study and classified as belonging to the patients group or controls group. Out of the 60 patients, 59 were correctly classified into the patients group by the discriminant function and all the 30 in the control group were correctly credited in the control group. The overall success rate of the discriminant function correctly classifying into the two groups is about 99%.

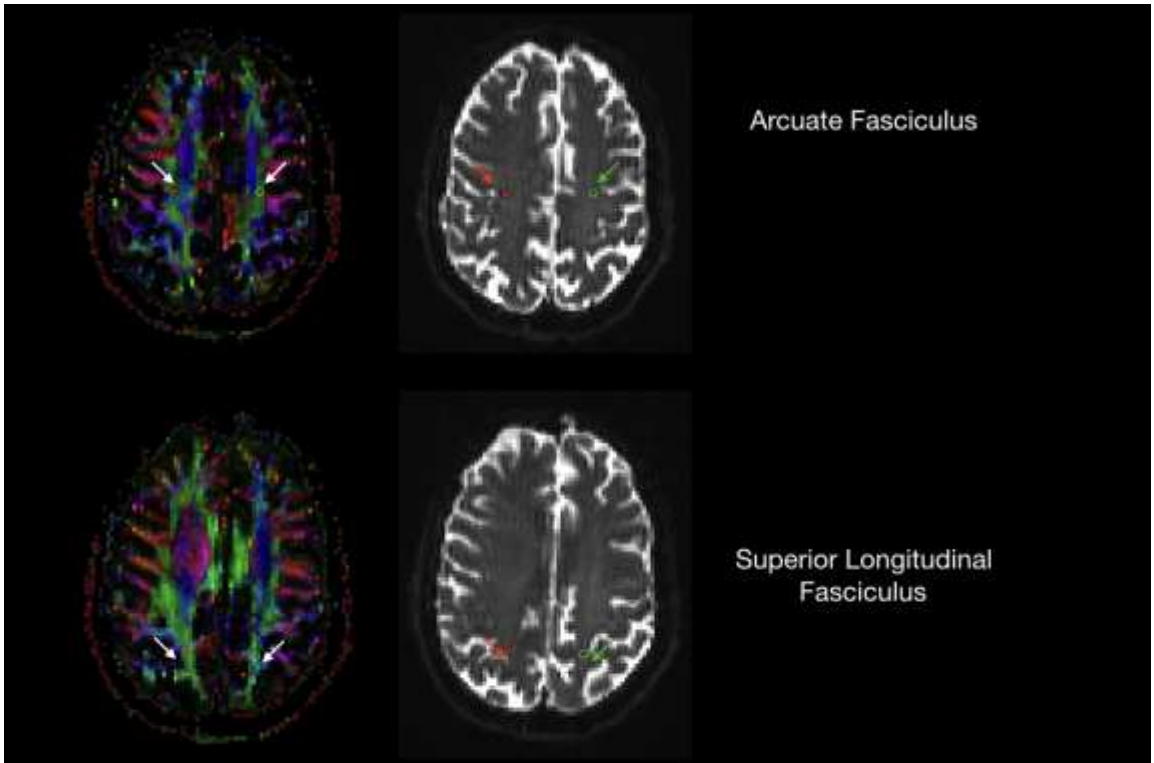

Figure 3 (A). Diffusion Tensor Imaging of Arcuate Fasciculus and Superior Longitudinal Fasciculus in a patient.

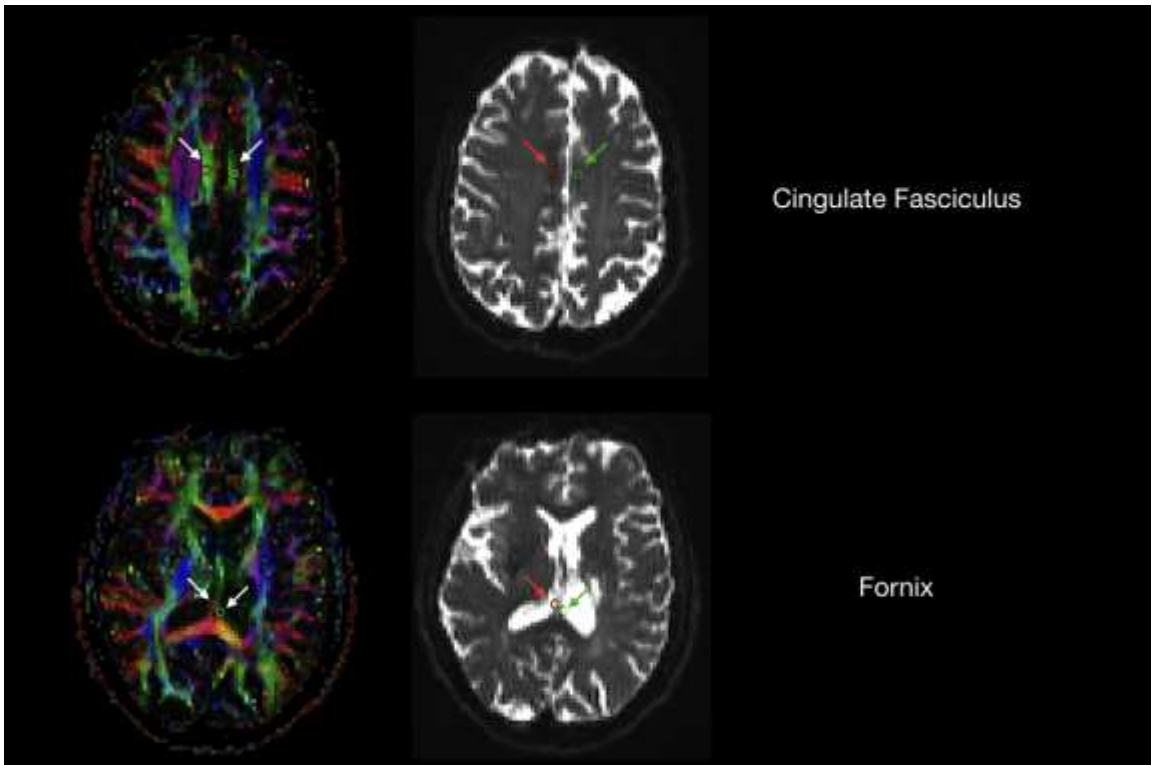

Figure 3 (B). Diffusion Tensor Imaging of Cingulate Fasciculus and Fornix in a patient.

7.3 Diffusion Tensor Imaging (DTI):

The DTI Metrics such as Fractional Anisotropy (FA), Apparent Diffusion Coefficient (ADC), Axial Diffusivity (AD), Mean Diffusivity (MD), Radial Diffusivity (RD) values were obtained the images analysed through the software Neuro 3D for the white matter tracts. The Association pathways such as cingulate fasciculus, Superior Longitudinal Fasciculus, Inferior Longitudinal Fasciculus, Inferior Fronto-Occipital fasciculus (IFO), Arcuate fasciculus, Uncinate fasciculus and Projection pathways such as fornix of both sides covering the networks of the domains attention, language and memory were studied. These assessments were compared for the two sides of the brain separately between patients and controls and also between the two sides namely left and right among patients and controls separately. The Diffusion tensor imaging of various fasciculi are shown in Figure 3 (A-H).

7.3.1 Left hemispherical Analysis:

In the left hemisphere, patients were found to have significantly increased RD in the SLF, decreased FA, increased RD in ILF, increased ADC in IFO and increased ADC, AD, MD in arcuate fasciculus compared to the controls. Patients have significantly increased ADC, AD, MD, RD in the fornix and significantly increased ADC, MD & RD of the Uncinate fasciculus. Table 6

7.3.2 Right Hemispherical Analysis :

Patients have increased ADC, MD & RD in cingulum fasciculus, increased MD, RD in ILF, decreased FA and increased ADC, MD, RD in IFO, increased ADC, AD, MD, RD in arcuate fasciculus in comparison to controls. Patients were also found to have increased MD in uncinate fasciculus, increased ADC, MD, RD in fornix and

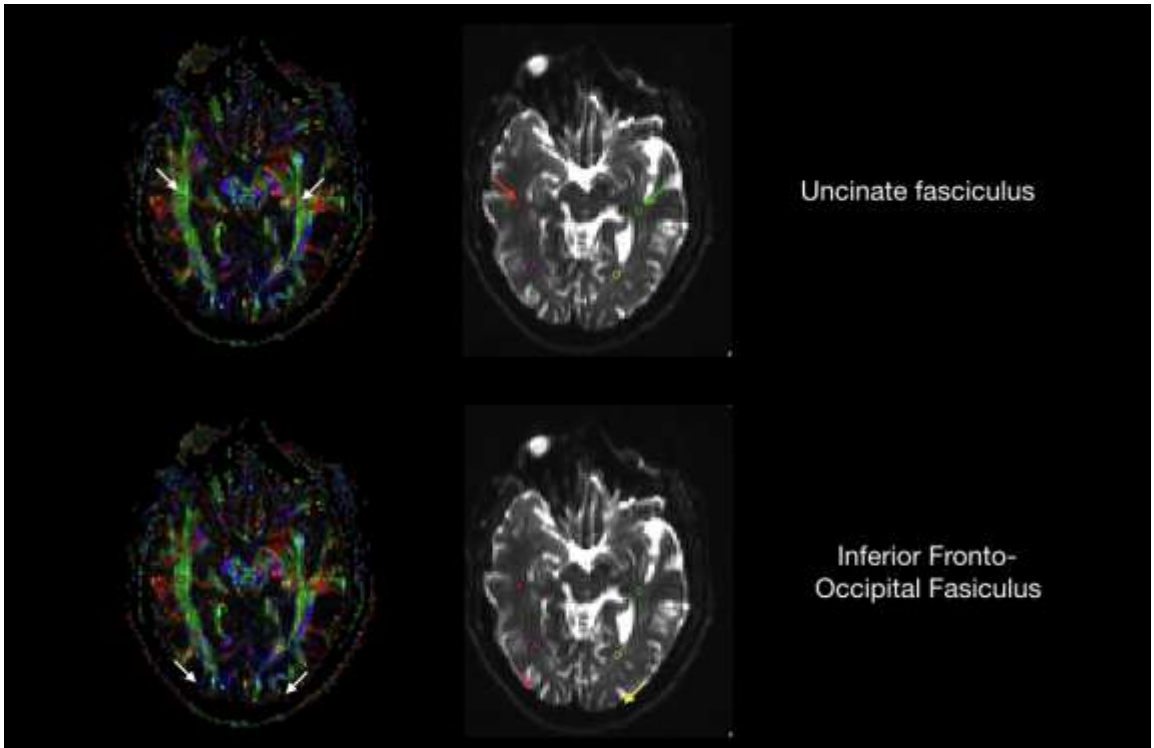

Figure 3 (C). Diffusion Tensor Imaging of Uncinate Fasciculus and Inferior Fronto-Occipital Fasciculus in a patient.

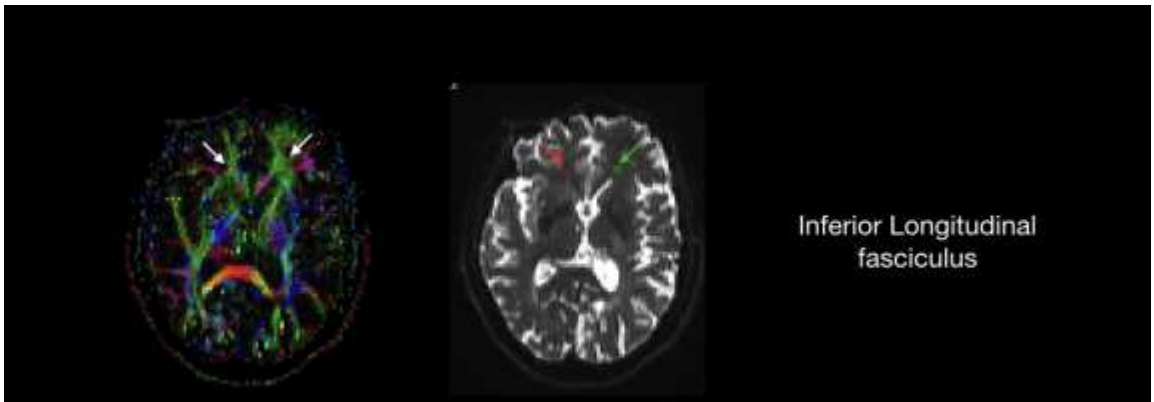

Figure 3 (D). Diffusion Tensor Imaging of Inferior Longitudinal Fasciculus in a patient.

cingulate fasciculus in comparison to controls. There is no significant difference between the mean values of patient s and controls in all the five DTI parameters in SLF. Table 6.

7.3.3 Interhemispheric Analysis:

The two sides were compared separately for patients and controls in DTI parameters of the white matter tracts in the three domains. It was interesting to find that no significant differences were found between the two sides of the five parameters namely FA, ADC, AD, MD & RD in all white matter tracts. Similar scenario is seen with the controls except FA in ILF where controls were found to have significantly higher mean values in the left side compared to the right side. It can be concluded that DTI parameters have same mean values among the patients and the controls in the two sides of the brain.

Since the two sides of the brain have the same DTI metric values, the average of the both sides were computed for the each one of DTI parameters and compared for all the white matter tracts between patients and controls. The mean values of patients in ADC and MD in the cingulate fasciculus are found to be significantly higher compared to that of controls. There is no significant difference between patients and controls in all the five parameter of DTI in the white matter tract SLF. Patients have decreased FA and increased MD & RD in ILF in comparison to controls. Patients have decreased FA and increased ADC, MD and RD in IFO and increased ADC, AD, MD, RD in arcuate fasciculus in comparison to controls. The patients have significantly increased ADC, MD and RD of the uncinate fasciculus compared to controls. FA was decreased and AD, RD, MD, ADC were increased in fornix in patients compared to controls. Table 7.

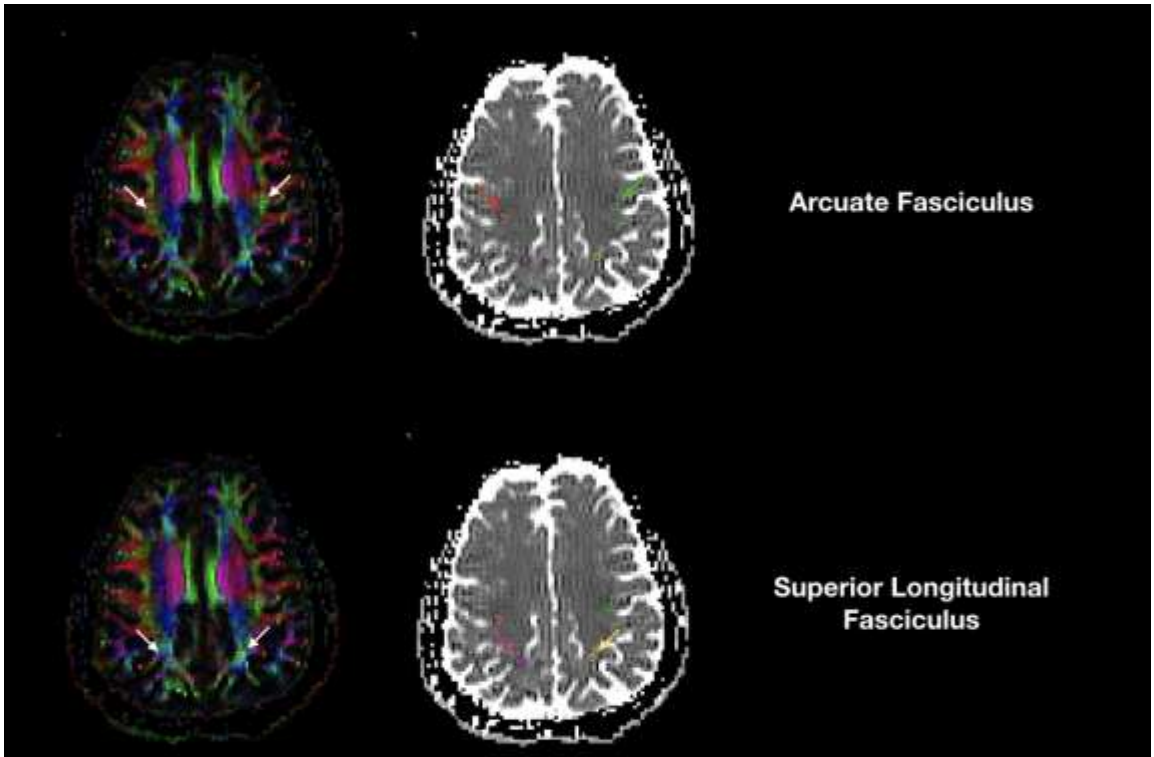

Figure 3 (E). Diffusion Tensor Imaging of Arcuate Fasciculus and Superior Longitudinal Fasciculus in a healthy control.

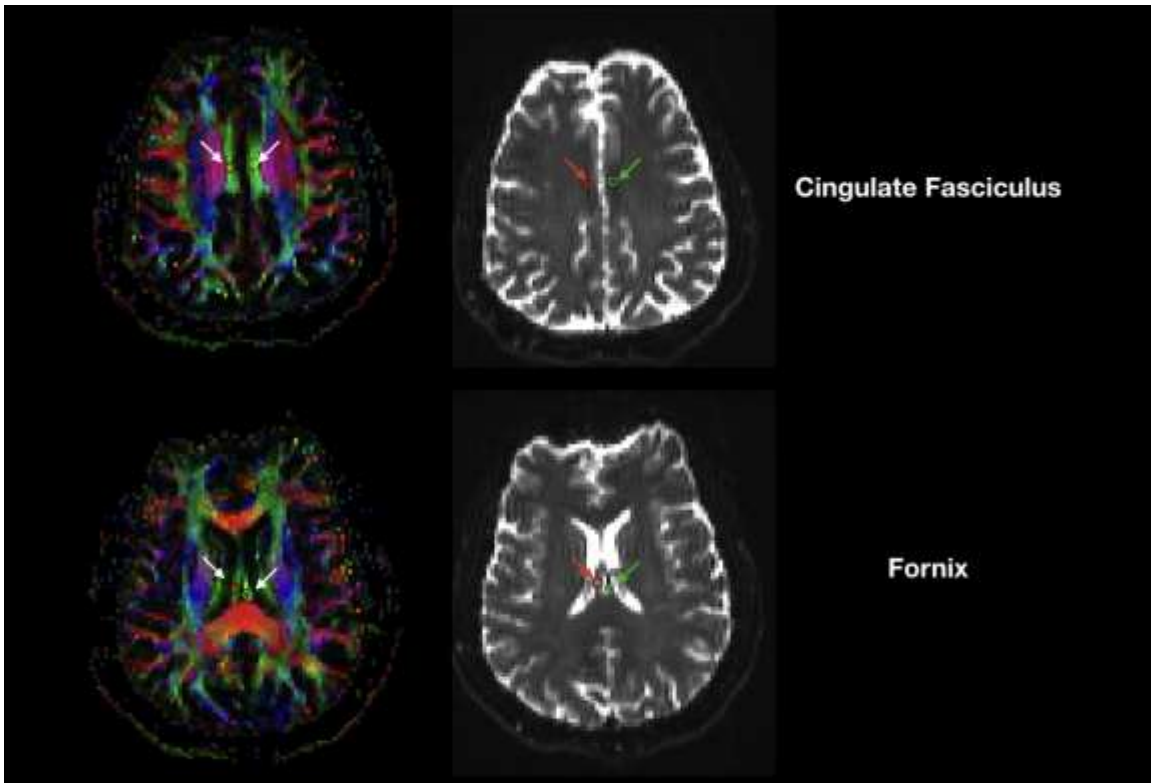

Figure 3 (F). Diffusion Tensor Imaging of Cingulate Fasciculus and Fornix in a healthy control.

7.3.4 Attention Domain

The attention, memory and language domains were compared with FA, ADC, MD, RD, AD of white matter tracts in diffusion tensor imaging. In attention, language and memory domain, the patients were divided based on the median (median is 12, 34, 12 for the attention, language and memory sub scale of ACE III respectively) into two groups as high score, low score. Statistical analysis for significance was assessed using one way ANOVA between any of the groups: high score patients, low score patients and control subjects. Post hoc analysis was performed to identify the groups that were significant.

In the attention domain, the white matter tracts superior longitudinal fasciculus, inferior longitudinal fasciculus and cingulate fasciculus were analysed in both right and left hemisphere. In the right cingulate fasciculus, there was significant increase in RD, MD, ADC in low attention score patient group in comparison with control group. In the left cingulate fasciculus, the FA was decreased and RD was increased significantly in low attention score patient group compared to high attention score patient group. In the right inferior longitudinal fasciculus, RD and MD was significantly increased in low attention score patient group compared to control group. In the left inferior longitudinal fasciculus, FA was significantly reduced and RD, MD were significantly increased in low attention score patient group in comparison to control group. In superior longitudinal fasciculus, no significant difference between the three groups were noted on either side.

7.3.5 Language Domain

Superior Longitudinal Fasciculus

The white matter tract, right superior longitudinal fasciculus of the language and fluency domain, none of the DTI parameters showed any significant difference among

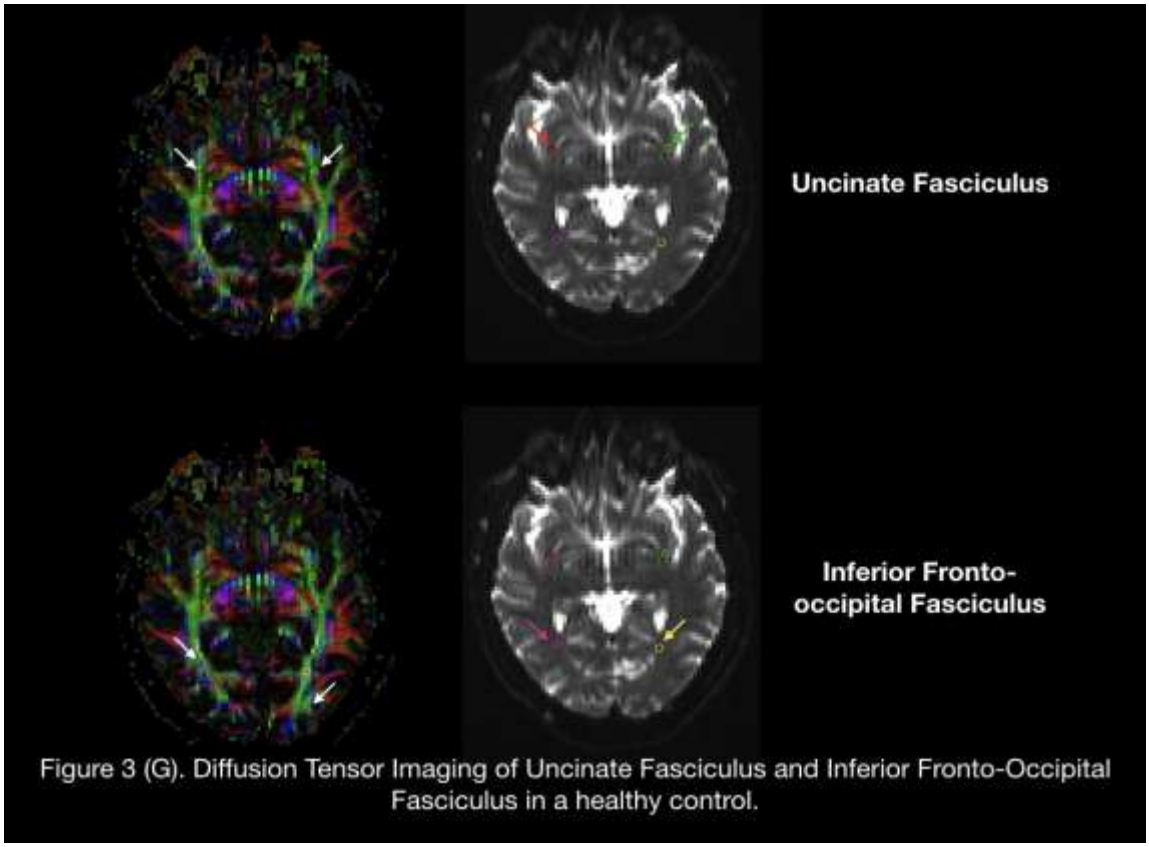

Figure 3 (G). Diffusion Tensor Imaging of Uncinate Fasciculus and Inferior Fronto-Occipital Fasciculus in a healthy control.

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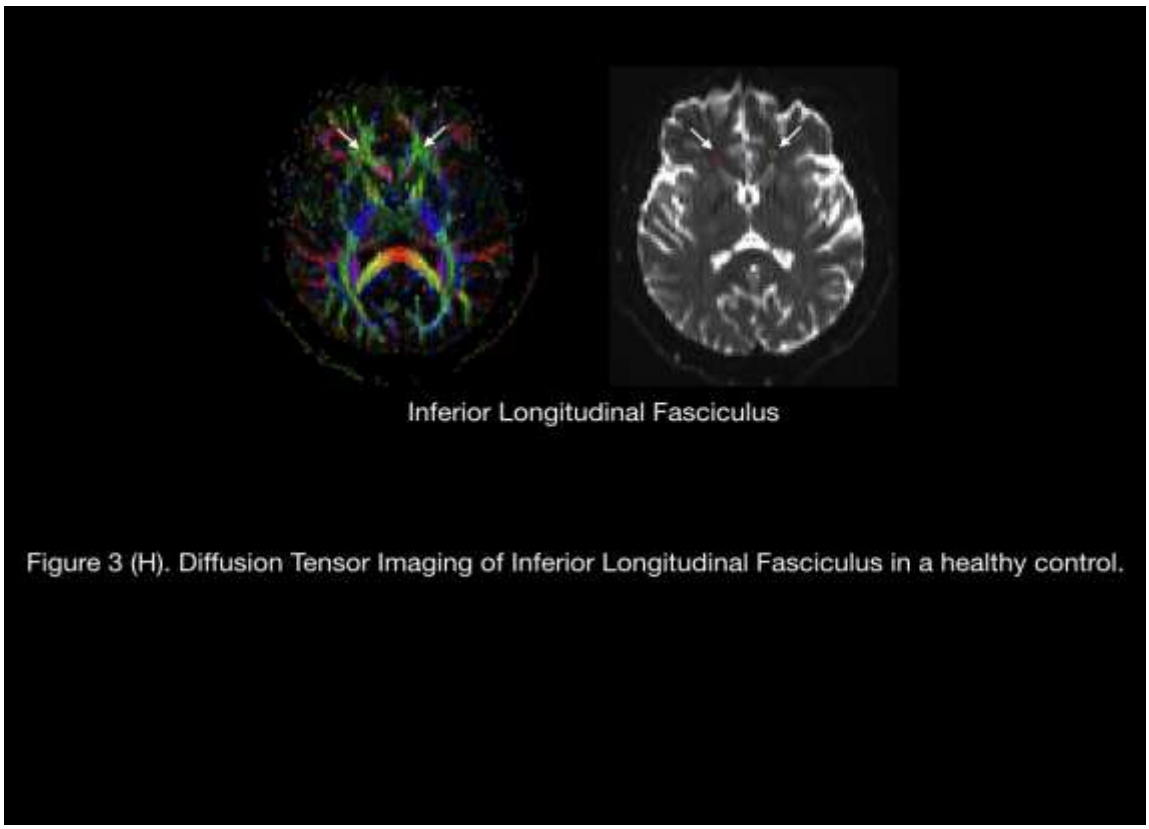


Figure 3 (H). Diffusion Tensor Imaging of Inferior Longitudinal Fasciculus in a healthy control.

the three groups compared, viz., patients with low or high language and fluency scores and the controls. Similar scenario is seen on the left side of the brain also in the white matter tract Superior Longitudinal Fasciculus, except the DTI parameter, FA. In FA, Patients who got low or high language scores remain as a separate group, and controls have higher mean values in the language and fluency scores.

Inferior Longitudinal Fasciculus

As far as the white matter tract, right Inferior Longitudinal Fasciculus and DTI metric, FA is concerned, patients with high score in language and fluency remain as a different group compared to patients with low score. The control group does not have any different entity as it stands as part of both patients with low and high scores – In the same white matter tract and in the same DTI parameter, patients with low score remain as a separate group, and controls have higher level of language and fluency and patients with high score remain in PL and Controls. In DTI parameter ADC, controls and PL remain as a single group and PH remain as a different group on the right side brain. In contrast, on the left side of the brain, controls have low language and fluency scores, the group PH has got the highest level, whereas the group PL stands in both control and PH. In both AD and MD, there is no significant difference between the mean values of the three groups, viz., PL, PH and controls in the two sides of the brain. Controls have a low mean value and the group PL have higher level of language and fluency on the two sides of the brain in the DTI parameter RD.

Inferior Fronto-Occipital Fasciculus:

In all the five DTI parameters, the PL and controls remain as separate groups while PH remains part of both PL and Control groups. PL has the highest level whereas

the Control group has least levels in ADC, AD, MD and RD whereas in FA, control group has got higher value compared to PL group in the two sides of brain.

Arcuate Fasiculus

In the right hemisphere, both PL and PH remain as a single group having higher levels of ADC, AD and MD while PL group has got higher value in RD and the control group has the least value. In contrast, on the left side of brain, in the DTI metrics, ADC, AD, MD and RD, control group has the least values, the group PL has higher levels.

7.3.6 Memory Domain

In the evaluation of memory domain, the white matter tracts that were studied include uncinate fasciculus, fornix and cingulum. In the right uncinate fasciculus, RD was increased in the low memory score patient group compared to control group. In left uncinate fasciculus, FA was decreased and RD, MD and ADC were increased in low memory score patient group in comparison to control group. In right fornix, FA was decreased and RD, MD and ADC were increased in low memory score patient group in comparison to control group. In left fornix, FA was decreased and AD, RD, MD and ADC were increased in low memory score patient group in comparison to control group suggesting the crucial role of fornix in the memory domain. In right cingulum, RD, MD, ADC were increased in low memory score patient group compared to control group. In left cingulum, FA was decreased and RD, MD, ADC were increased in low memory score patient group compared to control group. The summary of findings has been tabulated below.

The results of the findings in the diffusion tensor imaging in the corresponding networks are noted in table 8. The significant findings are summarized in table 9.

7.4 Analysis of FDG PET Imaging:

The FDG PET imaging yielded results as Z scores with positive score indicating Hypometabolism and a negative score indicating hyper metabolism in comparison to predetermined control data set. The various regions studied in FDG PET Imaging for attention include frontal association, parietal association, anterior cingulate, posterior cingulate and caudate nucleus. Regions for language include frontal association, parietal association and temporal association cortices. Regions for memory include anterior cingulate cortex.

A descriptive analysis of the FDG PET data in the patients revealed Hypometabolism in 79.63%, 88.89%, 88.89%, 85.19%, 70.37%, 75.93%, 81.48%, 90.74%, 90.74%, 92.59%, 77.78%, 79.63% of patients in right and left frontal association areas, right and left anterior cingulate cortex, right and left posterior cingulate cortex, right and left parietal association cortex, right and left caudate, right and left temporal association cortex respectively. Table 10.

The attention, memory and language domains were compared with Z scores indicating metabolism in FDG PET. The regions studies for attention domain include frontal association, parietal association, anterior cingulate, posterior cingulate and caudate regions. The areas studied for language include frontal association cortex, parietal association cortex and temporal association cortex. The areas studied for memory include anterior cingulate cortex. In attention, language and memory domain, the patients were divided based on the median (median is 12, 34, 12 for the attention, language and memory sub scale of ACE III respectively) into two groups as high score, low score. A descriptive analysis was performed comparing the percentage of patients in low score group and high score group who had Hypometabolism in the region studied.

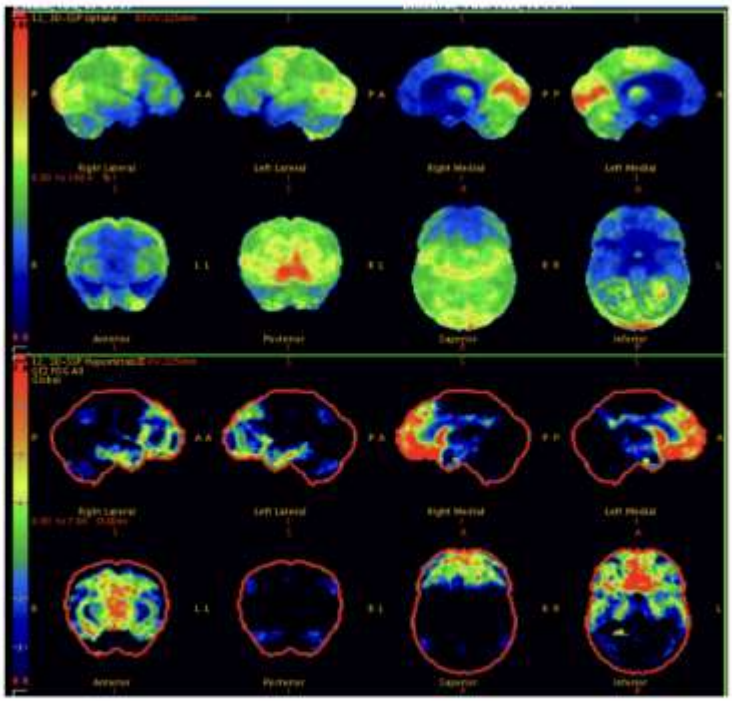


Figure 4 A. FDG PET imaging showing Moderate to sever reduction in FDG uptake is seen in bilateral frontal lobes and bilateral temporal lobes. in a patient with Fronto-temporal dementia

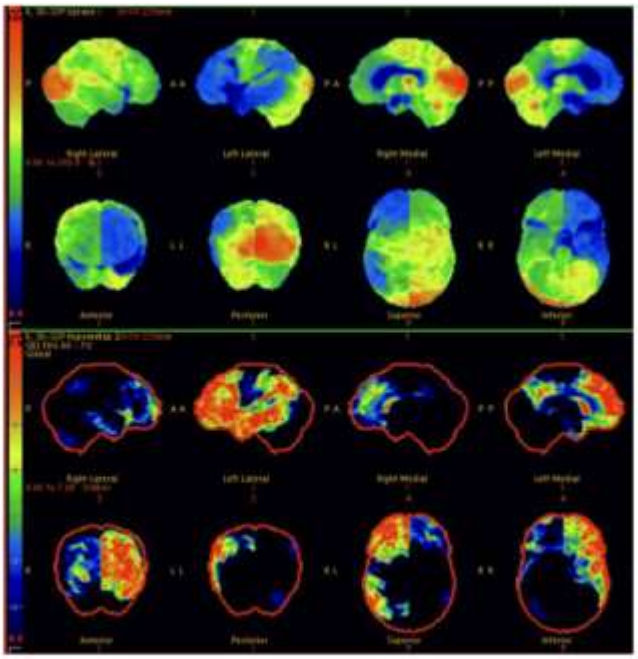


Figure 4 B. FDG PET imaging showing severe hypo metabolism in left frontal, parietal and temporal lobes, moderate hypometabolism in right frontal, parietal and temporal lobes and moderate hypometabolism in left thalamus and basal ganglia in a patient with Corticobasal ganglionic degeneration.

In the analysis of attention domain the above mentioned regions were studied. In right frontal association cortex 87.88% of low attention score patient group and 66.67% of the high attention score patient group showed Hypometabolism. In left frontal association cortex 93.94% of low attention score patient group and 80.95% of the high attention score patient group showed Hypometabolism. In right anterior cingulate cortex 90.91% of low attention score patient group and 85.71% of the high attention score patient group showed Hypometabolism. In left anterior cingulate cortex 87.88% of low attention score patient group and 80.95% of the high attention score patient group showed Hypometabolism. In right posterior cingulate cortex 72.73% of low attention score patient group and 66.67% of the high attention score patient group showed Hypometabolism. In left posterior cingulate cortex 81.82% of low attention score patient group and 63.63% of the high attention score patient group showed Hypometabolism. In right association cortex 84.85% of low attention score patient group and 76.19% of the high attention parietal score patient group showed Hypometabolism. In left parietal association cortex 96.97% of low attention score patient group and 80.95% of the high attention score patient group showed Hypometabolism. In right caudate, 87.88% of low attention score patient group and 95.24% of the high attention score patient group showed Hypometabolism. In left caudate, 93.94% of low attention score patient group and 90.48% of the high attention score patient group showed Hypometabolism. Table 11(a).

In the language and fluency domain, nearly 84 per cent of patients who scored low, have hypometabolism in the right frontal association, whereas about 60 per cent of patients who have high language and fluency scores have high metabolism in this cortical area. Among low language and fluency score group, Hypometabolism is seen in

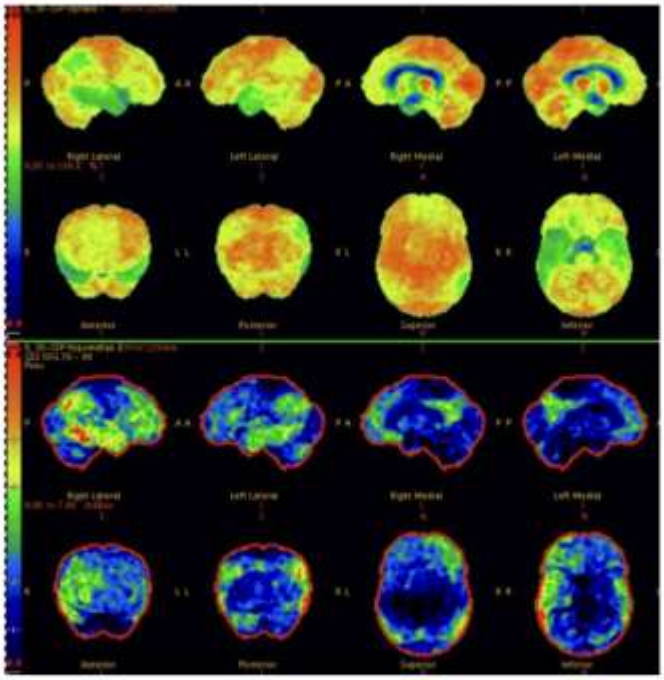


Figure 4 C. FDG PET imaging showing moderate asymmetric hypometabolism in bilateral parietal and temporal lobes and with mild asymmetric hypometabolism in bilateral frontal lobes in a patient with Alzheimer's disease

right frontal association in about 93 per cent of patients, observed in right temporal association in about 75 per cent of patients, found in left temporal association in about 77 per cent of patients, seen in right parietal association in about 80 per cent of patients, and about 93 per cent in left parietal association.

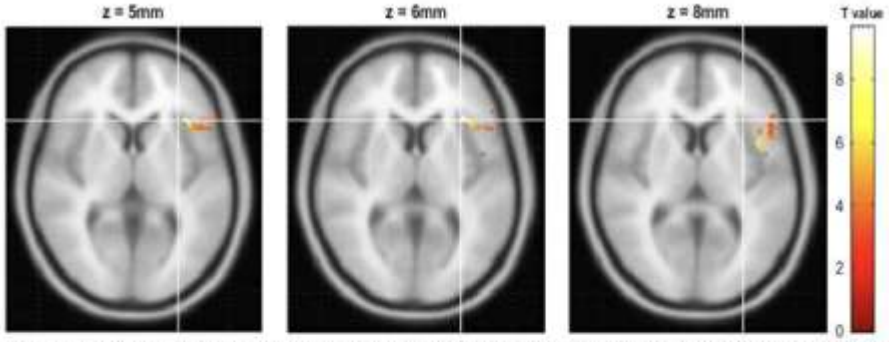
As far as low language and fluency score group is concerned, hypometabolism is seen among left frontal association (70%), right temporal association (90%), left temporal association (90%), right parietal association (90%) and left parietal association (80% of patients).Table 11 (b).

In the analysis of the memory domain the above mentioned areas were studied. In right anterior cingulate cortex, 90.32% of low memory score patient group and 86.96% of the high memory score patient group showed Hypometabolism. In left anterior cingulate cortex, 87.10% of low memory score patient group and 82.61% of the high memory score patient group showed Hypometabolism. Table 11 (c).

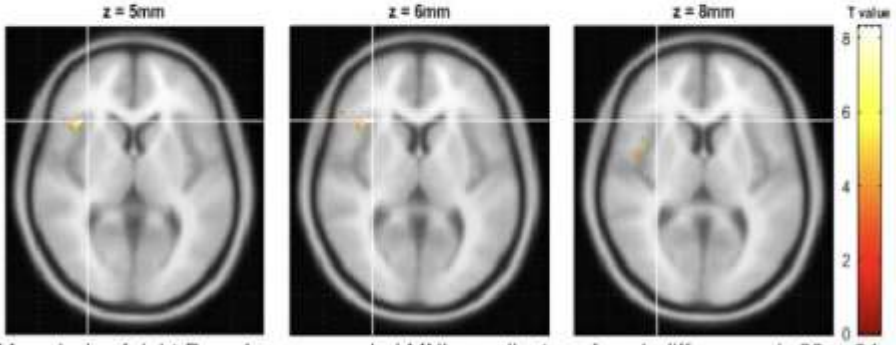
Correlation analysis was performed between the Z scores in the FDG PET indicative of metabolism as opposed the scores obtained in attention, memory and language. A significant positive correlation was noted between attention domain and the cortical areas including Left parietal association, Left Frontal Association, Right Parietal Association, Left Posterior Cingulate cortex. The FDG PET images are shown in Figure 4 (A-C)

7.5 Voxel Based Morphometry:

T1-weighted images were processed using the computational anatomy toolbox (CAT; http://www.neuro.uni-jena.de/cat/) for the statistical parametric mapping software (SPM; http://www.fil.ion.ucl.ac.uk/spm) was implemented within Matlab (The

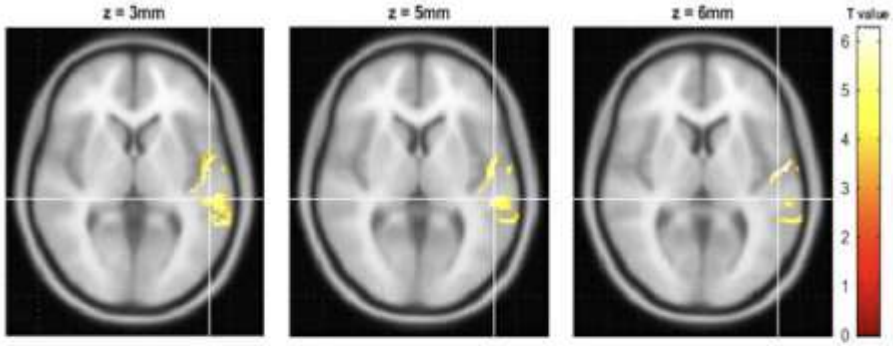


VBM analysis of left Broca's area revealed MNI coordinates of peak differences (x -32, y 24, z 6)

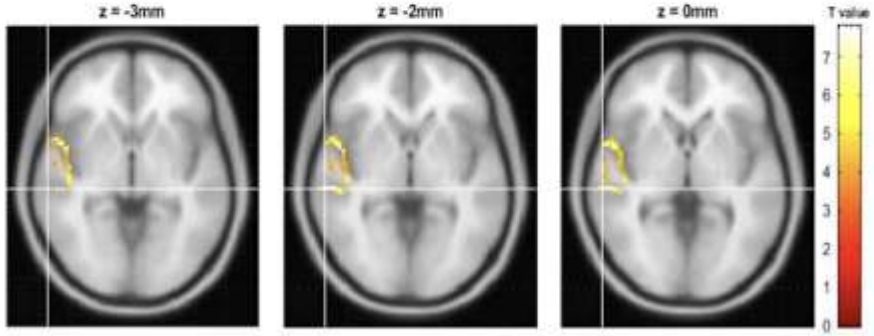


VBM analysis of right Broca's area revealed MNI coordinates of peak differences (x 33, y 24, z 6)

Figure 5A. Voxel Based Morphometric analysis of Broca's area



VBM analysis of left Wernicke's area revealed MNI coordinates of peak differences (x -53, y -30, z 5)



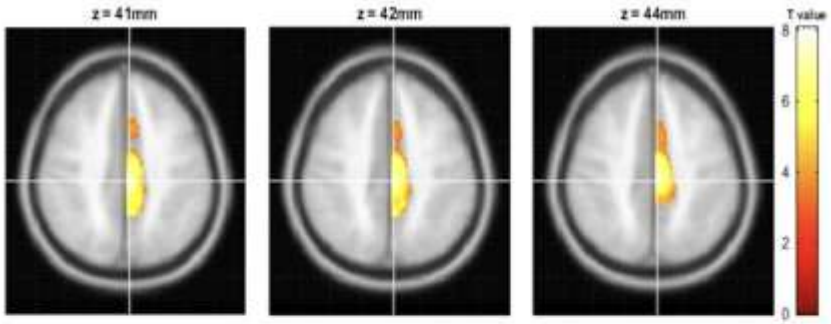
VBM analysis of right Wernicke's area revealed MNI coordinates of peak differences (x 62, y -27, z -2)

Figure 5B. Voxel Based Morphometric analysis of Wernicke's area

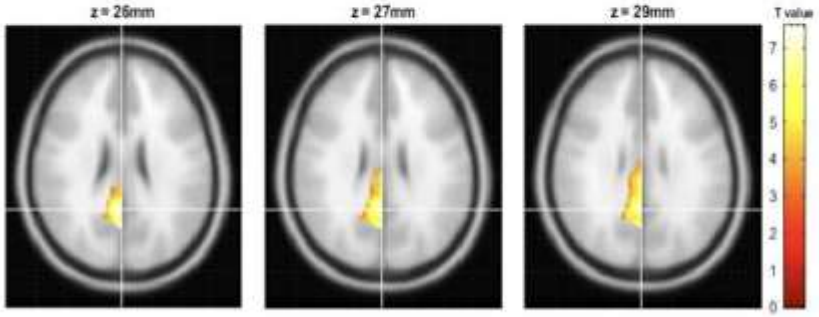
MathWorks Inc., Sherborn, MA, USA). Standard routines and default parameters of the CAT12 toolbox were applied.

Images that have optimal quality (Patients N=53; Controls N=28) were processed further.

After setting the image origin to the anterior commissure, images were bias corrected, pre-registered to standardized International consortium for brain mapping (ICBM- East Asian brains) space using affine transformation with regularization and segmented using the "unified segmentation" approach. Image pre-processing of CAT12 was started with a denoising and initial inhomogeneity correction to stabilize the SPM12 pre-processing that creates the initial segmentation and registration. The segmentation was refined and used for intensity normalization of the anatomical image. A template independent AMAP approach was used to generate the final segmentation that used spatial registration to the IXI555 template. The spatial adaptive non-local-means (SANLM) denoising filter was further modified by a local correction field to avoid to strong filtering. Low resolution images were interpolated for more accurate and robust results. The AMAP approach includes a noise-controlled MRF-filter. Finally, a cleanup routine removes remaining blood vessels and meninges in predefined regions. Grey matter segments were modulated by the Jacobian determinants of the deformations to account for local expansion and compression introduced by non-linear transformation. Finally, the gray matter images were smoothed with an 8-mm full-width at half-maximum (FWHM) isotropic gaussian kernel. This was done to reduce errors related to inter-subject variability in local anatomy and to render the imaging data more normally distributed.

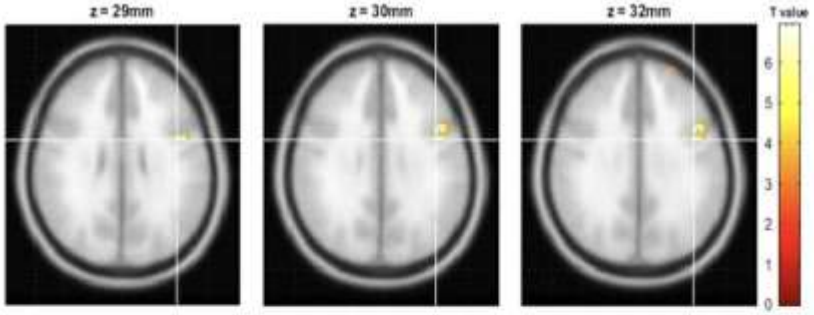


VBM analysis of left cingulate gyrus revealed MNI coordinates of peak differences (x -3, y -26, z 42)

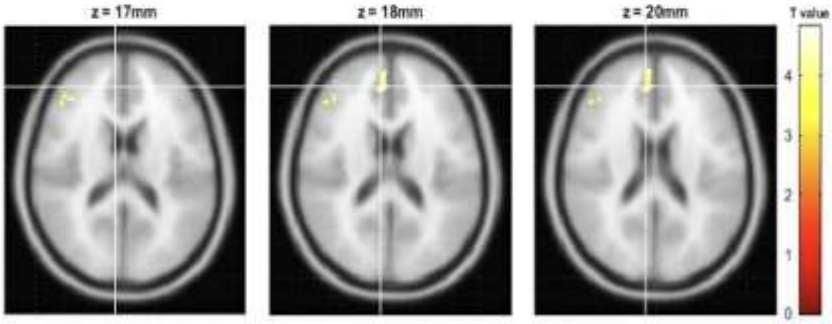


VBM analysis of right cingulate gyrus revealed MNI coordinates of peak differences (x 2, y -51, z 27)

Figure 5C. Voxel Based Morphometric analysis of Cingulate gyrus



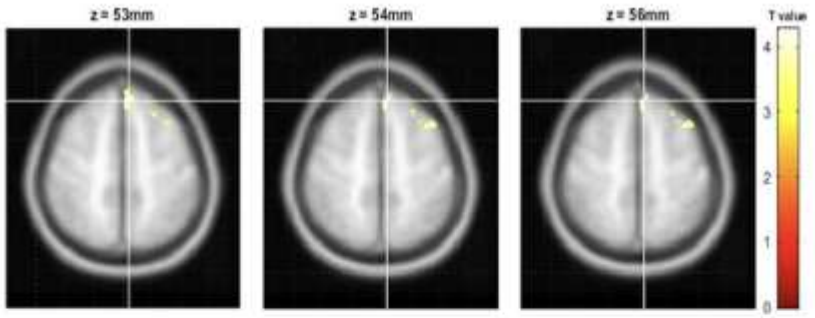
VBM analysis of left DLPFC (BA 9, BA 46) revealed MNI coordinates of peak differences (x -42, y 2, z 30)



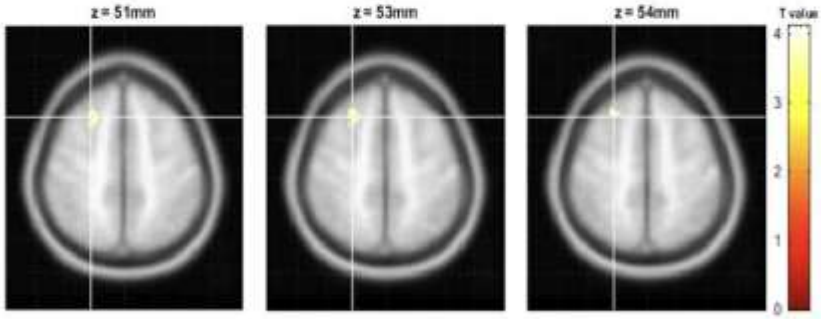
VBM analysis of right DLPFC (BA 9, BA 46) revealed MNI coordinates of peak differences (x 8, y 45, z 18)

Figure 5D. Voxel Based Morphometric analysis of Dorsolateral Prefrontal Cortex

Apriori region of interest based analyses were done for the following regions using masks created with the Wake Forest University school of medicine (WFU) Pickatlas: Attention Network: 1) Dorsolateral Prefrontal Cortex, 2) Frontal Eye Field, 3) Occipital Eye Field, 4) Cingulate Cortex, 5) Superior Parietal Lobule; Language Network: 1) Broca's Area, 2) Wernicke's Area, 3) Geschwind's Area (Inferior Parietal Lobule); Memory Network: 1) Uncus, 2) Hippocampus, 3) Nucleus Accumbens. The group comparisons were performed controlling for the potential confounding effects of age, sex, intracranial volume, years of education and Socio-economic status. The significance threshold was set at $p < 0.001$ (uncorrected) with multiple comparison correction using small volume correction using a sphere of 10 mm radius. The MNI co-ordinates of peak differences were reported and are tabulated in table 12. The Voxel Based Morphometry analysis and the various MNI coordinates are shown in Figure 5 (A-K).

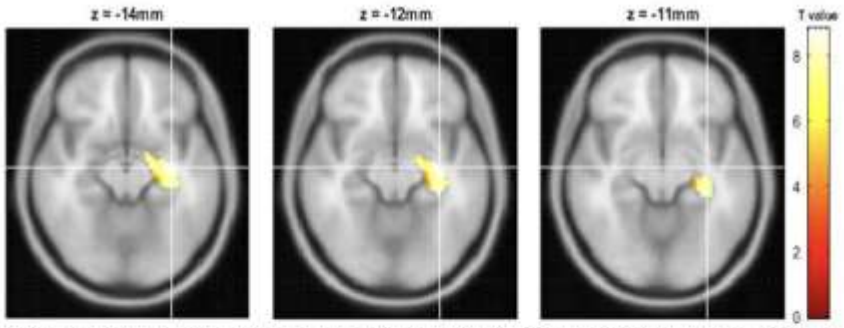


VBM analysis of left Frontal Eye Field revealed MNI coordinates of peak differences (x -42, y 2, z 30)

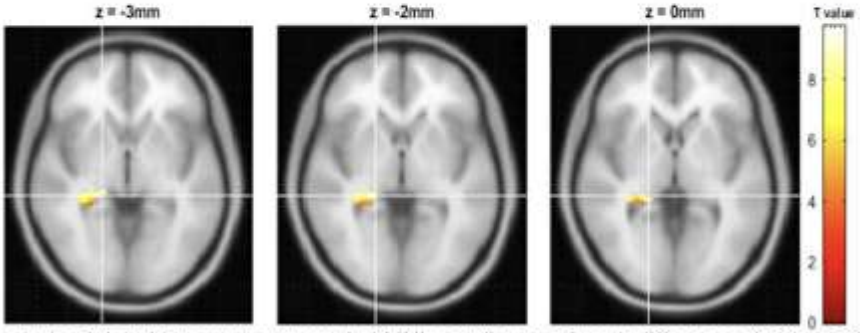


VBM analysis of right Frontal Eye Field revealed MNI coordinates of peak differences (x 8, y 45, z 18)

Figure 5E. Voxel Based Morphometric analysis of Frontal Eye Field

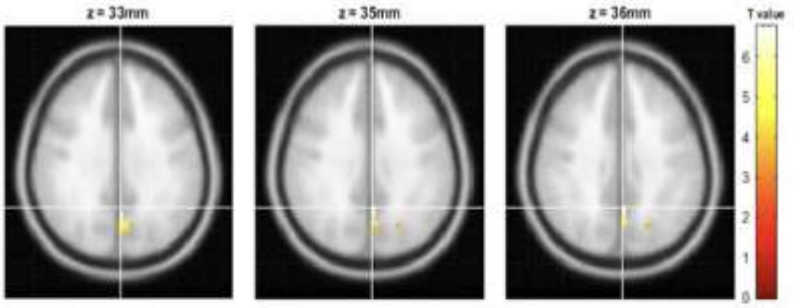


VBM analysis of left hippocampus revealed MNI coordinates of peak differences (x -33, y -14, z -12)

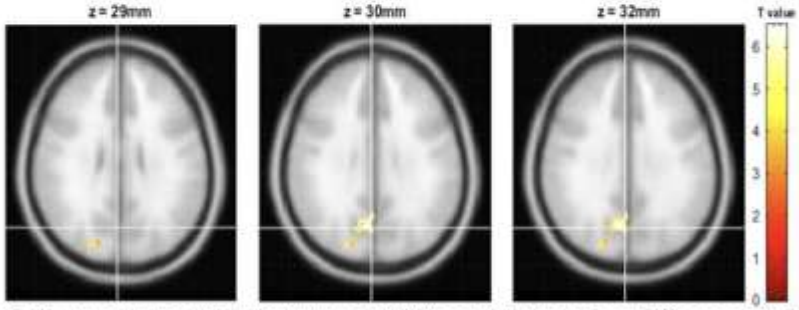


VBM analysis of right hippocampus revealed MNI coordinates of peak differences (x 20, y -33, z -2)

Figure 5F. Voxel Based Morphometric analysis of hippocampus

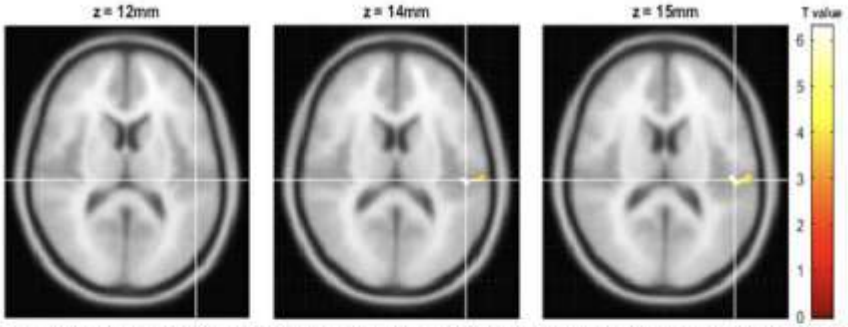


VBM analysis of left superior parietal lobule revealed MNI coordinates of peak differences (x -2, y -54, z 35)

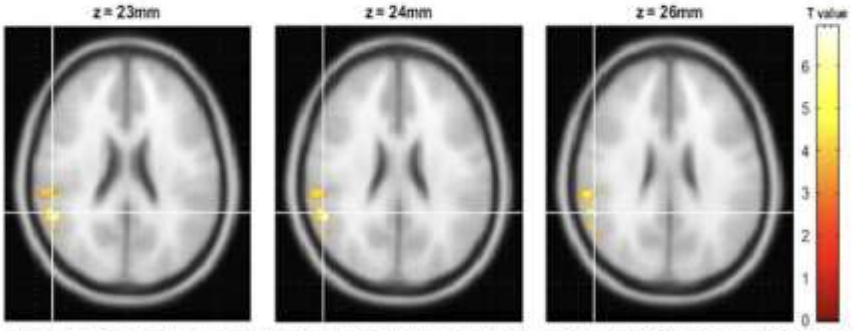


VBM analysis of right superior parietal lobule revealed MNI coordinates of peak differences (x 3, y -69, z 30)

Figure 5G. Voxel Based Morphometric analysis of Superior Parietal lobule

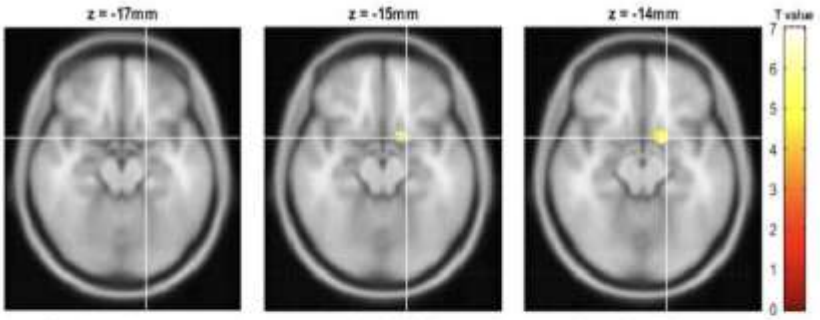


VBM analysis of left inferior parietal lobe revealed MNI coordinates of peak differences (x -51, y -24, z 14)

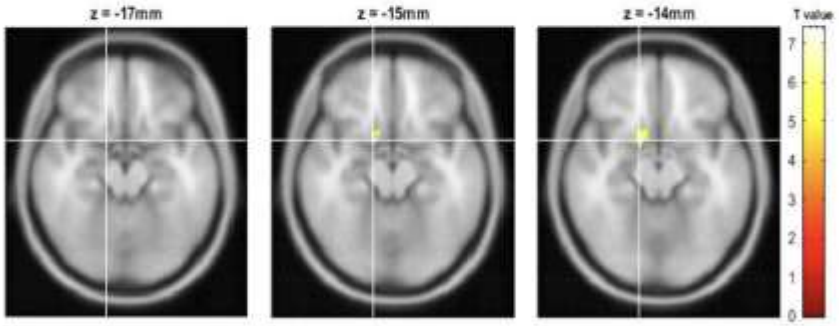


VBM analysis of right inferior parietal lobe revealed MNI coordinates of peak differences (x 56, y -47, z 24)

Figure 5H. Voxel Based Morphometric analysis of Inferior Parietal lobule

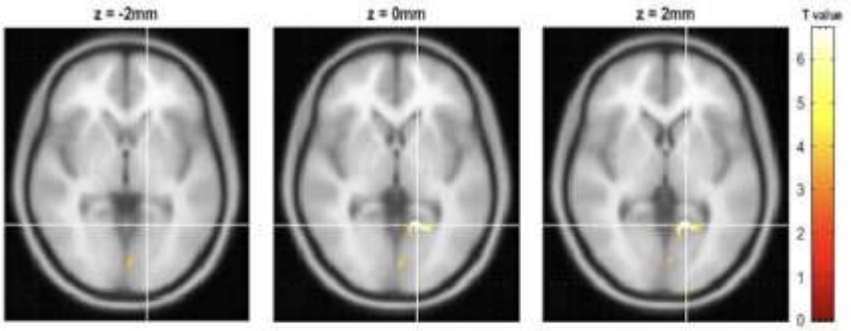


VBM analysis of left nucleus accumbens revealed MNI coordinates of peak differences (x -18, y 6, z -15)

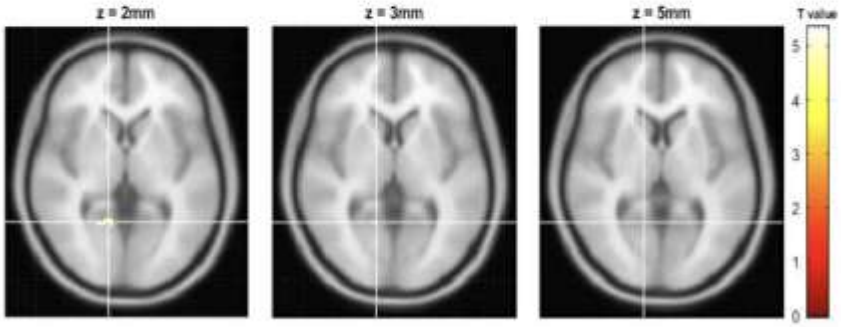


VBM analysis of right nucleus accumbens revealed MNI coordinates of peak differences (x 15, y 6, z -15)

Figure 5I. Voxel Based Morphometric analysis of Nucleus accumbens

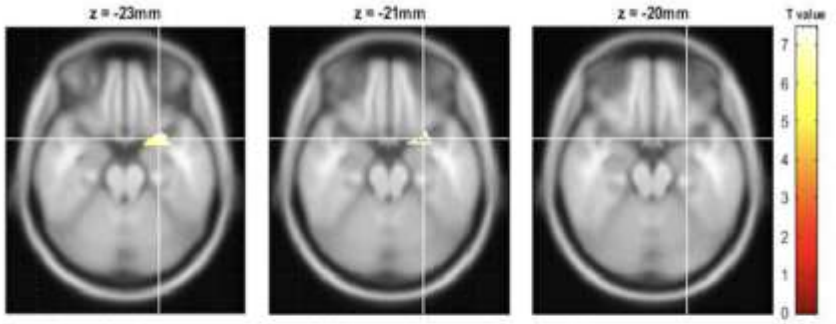


VBM analysis of left occipital eye field revealed MNI coordinates of peak differences (x -15, y -56, z 0)

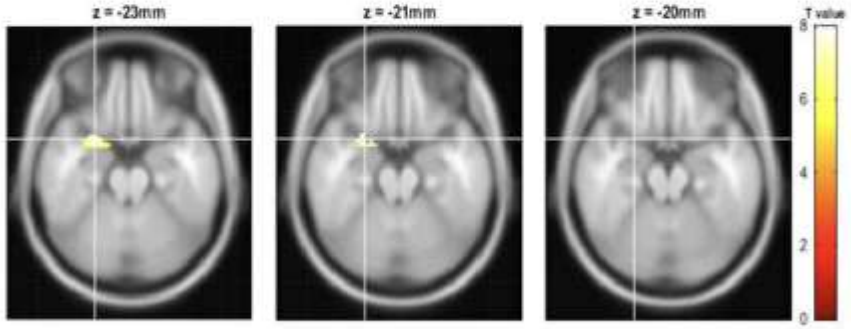


VBM analysis of right occipital eye field revealed MNI coordinates of peak differences (x 14, y -56, z 3)

Figure 5J. Voxel Based Morphometric analysis of Occipital Eye Field



VBM analysis of left uncus revealed MNI coordinates of peak differences (x −26, y 6, z -21)



VBM analysis of right uncus revealed MNI coordinates of peak differences (x 26, y 8, z -21)

Figure 5K. Voxel Based Morphometric analysis of Uncus

8. DISCUSSION

8. DISCUSSION

8.1 Prevalence

The age group of the patients in the present study is comparable to the other dementia studies. 85% of the patients were above 46 years of age and the dementia was increasing with advancing age of the patients. The prevalence of dementia increases with increasing age (136). A study in the rural region of south Africa reported that risk of dementia was increased with older age. (137)

8.2 Gender

There was a male preponderance in our study with 70% of subjects being males. Many studies have reported various values for prevalence of dementia in with respect to the gender. Framingham study reported that the decline in the frequency of dementia in Germany was prominent in women than men (138, 139). On the contrary, the Matthews FE et al., has reported that a decline in the occurrence of dementia is limited to men in the UK whereas it was found greater in the male population of Spain (140. 141). The prevalence trend of dementia with respect to gender may vary across countries. This is because dementia is attributed by multiple variables such as age, education, economic background etc.

8.3 Educational status

Incidence of dementia is higher in population with lower education status in the present study. This is in accordance with other studies (136, 142).In our study, around 83% of patients have had education till high school whereas more than 90% of controls have had education beyond high school. Education serves as a protecting factor for dementia. A meta-analysis by Wei Xu et al (2015)., included fifteen cohort studies to

assess the relationship between education and dementia. The study reported that the chances of dementia were decreased by 7% for per year surge in education. (143)

8.4 All cause dementia

Alzheimer's disease was the most common cause of dementia in our study. The distribution of patient diagnosis in our study is comparable to other studies in dementia performed in South India. This is also in accordance with the prevalence of dementia reported in other studies in India and in Global scenario. The other causes of dementia in our study include fronto-temporal dementia, vascular dementia, Parkinson's dementia, mixed dementia and CBGD.

8.5 Neuropsychological test

8.5.1 MoCA:

The average scores of all patients were significantly lower in the dementia population compared to healthy controls in our study. S Hoops et al in his study on MoCA for the diagnosis of dementia described a sensitivity of 100% and specificity of 53% when a cut off score of 26 / 27 was used as cut off for diagnosis of dementia in Parkinson disease (144). Jordi A. Matias-Guiu demonstrated statistically significant lower MoCA scores in dementia patients in comparison to healthy controls (145).

8.5.2 ACE:

The average scores of all patients were significantly lower in the dementia population compared to healthy controls in our study. The subsets of ACE III including attention, memory, fluency, language, visuo-spatial had lower scores in patients compared to control groups in our study. Jordi A. Matias-Guiu demonstrated statistically significant lower ACE III scores in dementia patients in comparison to healthy controls.

In his study, he demonstrated a sensitivity of 95.57% and specificity of 67.65% with a cut off of less than or equal to 73. (145)

8.5.3 WMS

The average scores of all patients were significantly lower in the dementia population compared to healthy controls in our study. Mary Tierney C et al described Wechsler's memory scale along with 3 other tests: animal fluency tests, RAVLT short delayed verbal recall test and WAIS-R digit symbol test that were good predictors of 5 year incidence of dementia (146).

8.5.4 Trail Making test

The average scores of all patients were significantly lower in the dementia population compared to healthy controls in our study. Lee Ashendorf et al in his study described the use of parameters time to completion and number of errors in combination for the classification into normal and dementia subjects with greater accuracy than using either alone. (147)

8.5.5 AVLT

The average scores of all patients were significantly lower in the dementia population compared to healthy controls in our study. Zhao Q et al reported in his study better detection of conversion from MCI to dementia with a balanced sensitivity and specificity. (148)

8.5.6 Discriminant Function Analysis

The administration of the whole panel of neuropsychological tests to the subjects with dementia is a laborious process. It is further difficult in those patients with impaired attention. Hence linear discriminant function analysis was performed to identify those

parameters, isolated or in combination, amongst the neuropsychological tests administered that has the maximum ability in differentiating between the patients and controls. Among the 12 neuropsychological parameters considered, it was evident that only 5 parameters were required to classify the subjects as either patients or controls. These include attention and memory subset of Addenbrooke cognitive examination III (ACE III), AVLT, digit span and complex figure test. On applying the discriminant function analysis to our study population, 59 out of the 60 patients and 30 out of the 30 controls were correctly classified into the corresponding groups with an overall success rate of 99%. The success rate in classifying the patient group was 98.3% and 100% for the control group. This is in concordance with the study Bonnie M et al in which the classification of the controls had a better success rate compared to the patient group. The use of linear discriminant function analysis helps reduce the time for administration of neuropsychological tests and helps reduce economic burden in resource poor setting. However, linear discriminant function analysis is subject to shrinkage. Shrinkage is the decrease in the efficacy of classification into patient and control groups by the discriminant function formula during the process of cross validation. Shrinkage is dependent on sample size involved in the study and the number of parameters used in the classification process. The efficacy of classification process is greatly decreased when the classification groups are not mutually exclusive and is overlapping. (149, 150)

8.6 DTI imaging

The comparison of the diffusion tensor imaging metrics in healthy controls did not show any differences between the two sides. This is due to the fact that the differences between the hemispheres are at the functional level as described by Corballis et al (151). The hemispheric symmetry at the structural level as evidenced by diffusion tensor imaging was similar to the description by Hardyck et al who described that several

brain regions involved in cognitive functions do not differ between the two hemispheres. (152)

8.6.1 Diffusion Tensor Imaging in Attention domain:

The diffusion tensor imaging of the attention domain involved study of superior longitudinal fasciculus, inferior longitudinal fasciculus and cingulum. The superior longitudinal fasciculus did not show any statistically significant involvement on either side in our domain in our study. This was consistent with the findings from Kantarci et al, who also did not find any significant involvement of the SLF. The inferior longitudinal fasciculus revealed increased diffusivity in the right side and decreased fractional anisotropy and increased diffusivity in the left side in our study. The cingulum revealed increased diffusivity in the right side and decreased fractional anisotropy and increased diffusivity in the left side in our study. The left sided fasciculus revealed decreased fractional anisotropy but it was not noted in the right sided fasciculus in our study. Kantarci et al found similarly, involvement of inferior longitudinal fasciculus and cingulum. Similar involvement of cingulum evident in diffusion tensor imaging with reduction in fractional anisotropy was also noted by Grieve et al. The radial diffusivity was consistently involved in both inferior longitudinal fasciculus and cingulum in our study similar to a few other studies. (96, 109)

8.6.2 Diffusion Tensor Imaging in Language:

Dorsal stream

The dorsal stream concerned with language included superior longitudinal fasciculus and arcuate fasciculus. The fractional anisotropy and diffusivity of the SLF did not show any statistical significance on either sides. Their role was negligible in language in our study. This was consistent with Kantarci et al, who also had similar

finding in superior longitudinal fasciculus (109). The arcuate fasciculus showed significantly increased diffusivity in both right and left side. The radial diffusivity was more commonly and consistently involved in arcuate fasciculus.

Ventral Stream.

Ventral stream concerned with language included inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, extreme capsule and middle longitudinal fasciculus. Diffusion tensor imaging of the inferior longitudinal fasciculus revealed decreased fractional anisotropy and increased diffusivity in both right and left side in our study. There was no side predisposition. This was in concordance with Kantarci et al, who had similar findings in inferior longitudinal fasciculus. In his study, similar to our study, no side predisposition was noted (109). Inferior fronto-occipital fasciculus also revealed decreased anisotropy and increased diffusivity in inferior fronto-occipital fasiculus on either side in our study. The radial diffusivity was more commonly and consistently involved in ILF.

The diffusion tensor imaging of the middle longitudinal fasciculus and extreme capsule was not performed due to technically demanding nature of these fasciculi. The uncinate fasciculus was not performed because it is concerned with the emotive component of auditory input and did not major role in the language domain. However, its role was noted in the memory domain is as mentioned below.

8.6.3 Diffusion tensor imaging in memory

Diffusion tensor imaging in memory domain involved study of uncinate fasciculus, fornix and cingulum. The left uncinate fasciculus revealed decreased fractional anisotropy and increased diffusivity in patients with impaired attention. In the right uncinate fasciculus, only the radial diffusivity was increased in our study. This

probably suggests the increased sensitivity and early identification of the microstructural disintegration by the radial diffusivity (96). The fornix revealed increased diffusivity and decreased anisotropy in patients with impaired attention on either side. Cingulum on the right side showed increased diffusivity and on the left side showed decreased fractional anisotropy and increased diffusivity. These tracts which are connected to the medial temporal lobe such as uncinate fasciculus, fornix and cingulum showed significant changes detectable in diffusion tensor imaging in our study. Kantarci et al revealed similar changes in the cingulum and ILF when the memory domain was impaired. According to his study changes in fornix were not significant. (109)

The finding of involvement of fornix with reduction in FA and increased diffusivity was robust among the fasciculus studied for memory in our study. The studies on the role of fornix is largely underrepresented in the diffusion tensor imaging studies. However, the fact that its role is significant is plausible considering the fact that fornix is the main efferent from the hippocampus to the mamillary bodies, anterior thalamus and frontal cortices and plays a major role in the memory network especially episodic memory. Findings in the fornix was supported by findings from Aggleton et al, who described that forniceal injuries presented with memory deficit especially episodic memory. The corollary was studied by Zahr et al 2009, who found that increased FA and decreased diffusivity was associated with improved memory. Further, the role of fornix as an imaging biomarker was demonstrated by the Fletcher et al 2013, who demonstrated the involvement of fornix with low fornix volume and increased axial diffusivity was associated with increased conversion to mild cognitive impairment / dementia. Our study also suggests that fornix may evolve as an imaging biomarker for the memory connectome (154, 155, 156)

8.7 FDG-PET

8.7.1 FDG-PET in Attention Domain

The FDG PET imaging in attention domain was analysed for parietal association, frontal association, anterior cingulate, posterior cingulate and caudate. In subjects with low attention scores, hypometabolism was noted in the parietal association cortex, frontal association cortex, caudate, anterior cingulate and posterior cingulate in the descending order of prevalence of hypometabolism in our study. The left side was more commonly involved in the attention hubs involving the parietal association, frontal association, caudate and posterior cingulate cortex. The right sided preponderance was noted for anterior cingulate. Similar finding of hypometabolism in posterior cingulate cortex was demonstrated by Salmon E et al in his study. In his study, he also found the posterior cingulate hypometabolism also correlated with severity of dementia. (157)

8.7.2 FDG-PET in Language and Fluency Domain

The FDG PET imaging in language and fluency domain was analysed for parietal association, frontal association and temporal association cortex. In subjects with low language and fluency scores, hypometabolism was noted in the frontal association cortex, parietal association cortex and temporal association cortex in the descending order of prevalence of hypometabolism in our study. The left side was more commonly involved in the language and fluency hubs involving the frontal association, parietal association, and temporal association cortex. Similar to our study, Rabinovici et al demonstrated hypometabolism in left temporal and temporal association cortex in those patients with fronto-temporal dementia. (158)

8.7.3 FDG-PET in Memory Domain

The FDG PET imaging in memory domain was analysed for anterior cingulate cortex. In subjects with low memory scores, hypometabolism was noted in the anterior cingulate cortex in our study. The right side was more commonly involved in the memory hubs involving the anterior cingulate cortex. However, Schroeter ML et al demonstrated hypometabolism in the hippocampus, retrosplenial cortex and precuneus in those patients diagnosed with AD and having long term memory deficits. Salmon E et al demonstrated hypometabolism in the posterior cingulate cortex in patients with impaired memory. Frisch et al has demonstrated that memory deficit in AD correlated with hypometabolism in medial parietal cortex. He also demonstrated that memory deficit in FTD correlated with hypo metabolism in frontal cortical region. (157, 159, 160)

8.8 Voxel Based Morphometry

8.8.1 Voxel based Morphometry in Attention:

The cortical grey matter areas studied for attention include Dorsolateral prefrontal cortex, frontal eye field, occipital eye field, cingulate cortex and superior parietal lobule. The ROI of the dorsolateral prefrontal cortex, frontal eye field, occipital eye field, cingulum and superior parietal lobule in both hemispheres, concerned with the attention domain revealed significant atrophy in the patient group compared to healthy controls in our study. In contrary to our study, Kantarci et al did not identify any volumetric changes in the cortical areas that correlated with attention impairment. However, he noted involvement of white matter tracts, anterior cingulum, posterior cingulum and inferior longitudinal fasciculus in these patients, the findings of which were concordant with our study. (109)

8.8.2 Voxel based Morphometry in Language :

The cortical grey matter areas studied for language include Broca's area, Wernicke's area and Geschwind area (Inferior parietal lobe). The ROI of the cortical areas Broca's area, Wernicke's area and Geschwind area (inferior parietal lobe) in both hemispheres, concerned with the language domain revealed significant atrophy in the patient group compared to the control group in our study. Kantarci et al in his study demonstrated cortical involvement in left temporal pole, posterior inferior temporal gyrus, amygdala and fusiform gyrus in patients with language impairment. (109)

8.8.3 Voxel based Morphometry in Memory:

The cortical grey matter areas studied for memory include uncus, hippocampus and nucleus accumbens. The ROI of the cortical areas hippocampus, uncinate and nucleus accumbens in both hemispheres, concerned with the memory domain revealed significant atrophy in the patient group compared to the control group in our study. Similar finding was also demonstrated by Kantarci et al, where atrophy as detected in volumetric analysis in the medial temporal lobe in the temporal lobes correlated with significant memory deficits. He also noticed that white matter tracts anterior cingulum, posterior cingulum and inferior longitudinal fasciculus was involved in addition to the cortical involvement similar to our study where we found involvement of both gray matter and white matter. Patric Meyer et al in his study described the correlation between mnemonic tests for memory correlated with the integrity of medial temporal lobar cortex.(99, 109). This finding was not in concordance with our study.

9. SUMMARY

9. SUMMARY

9.1 Demographic aspects

The proportions of patients in the age groups and gender categories remain the same in the two groups, patients and controls.

It is clearly evident that the age and gender matched controls are used in the present study. The control-cases are in the proportion 1:2. Sixty cases and thirty controls were assessed by the researcher in the present study.

Significant differences between patients and controls are seen in educational levels, and place from where the subjects come from.

Literacy level is found to be low among patients compared to controls and Most of the subjects come from urban and rural areas of Tamilnadu. Only three people out of 90 come from other states in the country.

9.2 Neuro-Psychological aspects

In all the 12 neuro psychological aspects such as MoCA, Adenbrook's Cognitive Score (comprising attention, language, fluency, memory and visuo-spatial, WMS, AVLT, Digit Span, Story recall and complex figure, patients have significantly lower levels compare to controls.

Correlation analysis of the Neuro-psychological aspects of all subjects (both patients and controls together) indicates that all the 12 neuro-psychologial aspects are highly significantly correlated with one another.

Correlation analysis of patients and controls separately indicates that all the 12 neuro-psychological tests are highly significantly correlated among patients.

9.2.1. Discriminant analysis

An attempt has been made to formulate a mathematical model that would segregate the patients and controls using the scores obtained in the 12 neuro-psychological aspects. Step wise discriminant analysis has been used for this purpose.

The step wise analysis clearly indicated that only five neuro-psychological tests, viz., attention, memory, AVLT, digit span and complex figure test are needed to differentiate the two groups, namely patients and controls. Using the constructed mathematical model, all the 90 subjects were tested for the group each one belongs to.

Out of 60 subjects in the patients group, 59 are correctly predicted to belong to patients and all the 30 controls are correctly predicted to belong to the control group by the stepwise discriminant model.

The success rate of correct prediction by the model is nearly 99 per cent.

Given the scores in the five neuro-psychological aspects, attention and memory subscores of ACE III, AVLT, digit span and complex figure test of an individual, he/she may be correctly identified as a dementia patient or a normal person by the discriminant model with a success rate of prediction of 99 per cent.

9.3 Diffusion Tensor Imaging

In the white matter tract, Superior Longitudinal Fasciculus in the right hemisphere of brain, no significant differences were found between patients and controls

whereas, patients have higher levels compared to controls in RD of the white matter tract, SLF, on the left hemisphere of brain.

Patients are found to have higher levels compared to controls in the right side of brain, in the DTI metrics MD, RD of white matter tracts, ILF, IFO, Arcuate, Fornix and Cingulate fasciculus.

Similarly patients have higher levels in ADC of IFO, Arcuate, Fornix and Cingulate Fasciculus in the right hemisphere of brain.

Patients have lower level in the DTI metric FA in the white matter tracts, IFO and Fornix on both right and left hemispheres of brain.

Patients have higher level in the metric MD of Uncinate white matter tract on the right side.

Fornix of the memory domain has shown significant difference between patients and controls in all the five metrics of DTI on left side and four DTI metrics on the right side of brain.

Comparisons made between the two sides of hemispheres, separately for patients and controls, using the DTI metrics of all the white matter tracts indicated that none of the metrics showed any significant difference between left and right hemispheres for both patients and controls.

Hence average value of each one of the DTI metrics as computed and compared between patients and controls in all the white matter tracts.

Patients are found to have higher levels compared to controls in the DTI metric ADC and MD of white matter tract, Cingulate fasciculus; metrics MD and RD in ILF; ADC, MD, and RD in IFO and Uncinate; DTI metrics ADC, AD, MD, RD in the white matter tracts, Arcuate and Fornix.

Patients have lower level in the DTI metric FA in the white matter tracts, ILF, IFO and Fornix.

There is no significant difference between patients and controls in all the five DTI metrics of the White matter tract, Cingulate fasciculus.

9.3.1 Attention, Language and Memory Domains

Attention Domain:

The DTI metric, FA is found to be low among patients on left cingulate fasciculus and left ILF in the Attention domain implying reduction in the directionality in these fasciculi whereas the metric RD is found to be high among patients in both left and right hemispheres in the white matter tracts, cingulate fasciculus and ILF implying increased diffusivity suggesting their involvement .This suggests that cingulate fasciculus and ILF are the WM tracts involved in the Attention domain in our study.

Similarly MD and ADC are found to be high among patients in white matter tract right cingulate fasciculus of this domain suggesting its role in the attention domain.

However, The white matter tract, SLF does not show any significant difference between patients (with low score or high scores) and control in the attention domain on the two sides of brain implying insignificant role of SLF in the attention domain.

Language Domain:

Dorsal Stream:

Patients are found to have higher levels in the metrics, AD, RD, MD and ADC in the white matter tracts Arcuate fasciculus on both sides of brain of the Language and Fluency domain.

The white matter tract, SLF does not play any significant role among patients and controls in any of the DTI parameters studied.

Ventral Stream:

Patients are found to have higher levels in the metrics, RD, MD and ADC in the white matter tracts IFO on both sides of brain of the Language and Fluency domain.

Both RD and MD have higher levels on the two sides of brain among patients in the white matter tract, ILF in the language and fluency domain.

The DTI metric, FA is found to be low among patients on both sides of brain in the tracts, IFO and ILF in the language and fluency domain.

All the DTI metrics suggests the role of Arcuate fasciculus of the dorsal stream and ILF and IFO of the ventral stream in the language and fluency domain and the insignificant role of SLF.

Memory Domain:

In the memory domain, the DTI metric, RD is found to be higher among patients on the two sides of brain in the white matter tracts, Uncinate, Fornix, and cingulate fasciculus.

Both MD and ADC are seen to be higher among patients on left Uncinate, both sides of Fornix and cingulate fasciculus of the memory domain.

The metric, AD is higher in patients on the left Fornix and FA is found to be low in this group on left Uncinate and cingulate fasciculus, and both sides of Fornix.

In the memory domain, fornix plays a significant role along with uncinate and cingulate fasciculus.

9.4 Analysis of FDG PET Imaging

The FDG PET imaging yielded results as Z scores with positive score indicating Hypometabolism and a negative score indicating hyper metabolism in comparison to predetermined control data set.

As of the attention domain, nearly 93 per cent of patients have hypometabolism in left caudate, followed by about 91 per cent having hypometabolism in left parietal association, and about the same percentage of patients having hypometabolismin right caudate.

Nearly 89 per cent of patients have hypometabolism in left frontal association and in right anterior Cingulate. About 85 per cent have hypo problem in left anterior cingulate and about 82 per cent have on the right parietal association.

Between 70 and 80 per cent of patients have hypometabolism in right frontal association, left or right posterior cingulate in the attention domain.

In the language domain, nearly 91 per cent of patients have hypometabolim in left parietal association, about 89 per cent have in left frontal association, nearly 80 per

cent have hypometabolism in right frontal association or left temporal association regions.

About 78 per cent of patients have hypometabolism in right temporal association regions.

In the memory domain, about 89 per cent of patients have hypometabolism in right anterior cingulate and about 85 per cent have in the left anterior cingulate regions.

More than 85 per cent of patients who scored high or low in attention, have hypometabolism in the following cortical regions: right or left frontal association, right or left anterior cingulate, right or left caudate, or left parietal association regions.

In the language and fluency domain, nearly 84 per cent to 93 per cent of patients with low scores are found to have hypometabolism in right or left frontal association, or left parietal association. Nearly 90 per cent of patients who scored high in language and fluency have hypometabolism in cortical areas, right or left temporal association, or right parietal association regions.

In the memory domain, nearly 87 to 90 per cent of patients who scored low have hypometabolism in left or right anterior cingulate regions. About 83 to 87 per cent of patients, who scored high in memory domain, have hypometabolism in right or left anterior cingulate regions.

A significant positive correlation was noted between attention domain and the cortical regions including Left parietal association, Left Frontal Association, Right Parietal Association, Left Posterior Cingulate regions.

9.5 Voxel Based Morphometry

T1-weighted images were processed using the computational anatomy tool box, CAT and the statistical parametric mapping software, SPM implemented within Matlab. The eleven grey matter areas were analysed as specified below for each network.

Attention Network:

1) Dorsolateral Prefrontal Cortex, 2) Frontal Eye Field, 3) Occipital Eye Field, 4) Cingulate Cortex, 5) Superior Parietal Lobule;

Language Network: 1) Broca's Area, 2) Wernicke's Area, 3) Geschwind's Area (InferiorParietal Lobule);

Memory Network:

1) Uncus, 2) Hippocampus, 3) Nucleus Accumbens.

The group comparisons were performed controlling for the potential confounding effects of age, sex, intracranial volume, years of education and Socio-economic status. The significance threshold was set at $p < 0.001$

Only quality images for processing were used for Voxal based Morphometry analysis. Images of 53 patients and 23 controls found to be good enough to process were used for the analysis.

On two sides, left and right hemispheres of brain, patients and controls were found to be significantly different in all eleven areas of ROI covering the three network domains, Attention, Language, and Memory.

This confirms the involvement of the five cortical grey matter areas 1)Dorsolateral Prefrontal Cortex, 2) Frontal Eye Field, 3) Occipital Eye Field, 4) Cingulate Cortex, 5) Superior Parietal Lobule in attention network.

This confirms the involvement of the three cortical grey matter areas 1) Broca's Area, 2) Wernicke's Area, 3) Geschwind’s Area (Inferior Parietal Lobule) in language network.

This confirms the involvement of the three cortical grey matter areas : 1) Uncus, 2) Hippocampus, 3) Nucleus Accumbens in memory network.

10. CONCLUSIONS

10. CONCLUSIONS

Patients and controls were well differentiated in all the neuro-psychological parameters, MoCA, Addenbrook's Cognitive Score, WMS, AVLT, Digit Span, Story Recall, and Complex figure. Patients are found to have low scores in all these aspects compared to controls. Stepwise regression analysis indicates scores in only five parameters, namely attention, memory, AVLT, Digit span, and complex figure are enough to classify a person as having dementia or a normal person with a prediction accuracy of nearly 99 per cent. All these neuro psychological parameters are inter-related to one another. Inter correlations of neuro psychological parameters are very high among patients compared to controls in the present study.

Analysis of Diffusion Tensor Imaging indicates that the white matter tract, Superior Longitudinal Fasciculus does not play any major role in attention and language domain. In contrast, Fornix has a major role to play in the memory domain. All the metrics of DTI show significant difference between patients and controls in the white matter tract Fornix on either side of the brain. As far as the DTI metrics are concerned, all the metrics have the same levels on both sides of brain of patients and controls. In most of the white matter tracts, the metrics, RD, MD, and AD are found to be high among patients compared to controls. FA is found to be low among patients in white matter tracts like IFO and Fornix. The analysis of diffusion metrics suggests the varying involvement of the white matter fasciculi of the respective domains.

Analysis of FDG PET data indicates that about 70 per cent to 93 per cent of patients have hypometabolism in all the five cortical areas of attention domain- frontal association, posterior cingulate, parietal association, anterior cingulate, and caudate regions on either side of brain. Similarly 77 to 91 per cent of patients have

hypometabolism in cortical areas of language domain, frontal association, temporal association and parietal association regions on either side of brain. About 85 to 89 per cent of patients have hypometabolism on either side of anterior cingulate regions.

Voxel based Morphometry analysis clearly indicated that the patients and controls are significantly different in the following gray matter hubs of Attention Network :Dorsolateral Prefrontal Cortex, Frontal Eye Field, Occipital Eye Field, Cingulate Cortex and Superior Parietal Lobule. Similar scenario is seen in gray matter hubs of language Network: Broca's Area, Wernicke's Area, and Geschwind's Area (Inferior Parietal Lobule).

In gray matter hubs of Memory Network: Uncus, Hippocampus, and Nucleus Accumbens areas, patients are found to be significantly different from the controls.

11. IMPACT OF THE STUDY & FUTURE DIRECTIONS

11. IMPACT OF THE STUDY & FUTURE DIRECTIONS

A. Newer imaging biomarkers for individual cognitive domains will emerge in future.

B. The subset analysis of various sub functions of each domain is likely to refine the connectome models. For example, correlation of the microstructural integrity of the white matter tracts and the volumetric analysis of gray matter hubs involved in language domain with the various sub components of the language would result in precise localisation.

C. The various networks will get remodelled as newer information, newer fasciculi are getting identified by more and more sophisticated fibre tracking technologies.

D. The neurosurgical approach, the trajectories and the extent will also likely to change based on the newer domain connectome models.

E. Intralobar hemispherical connections are also likely to get evolved and play a major role in the connectomics.

F. The functional connectomics will evolve into an important arena in dementia, epilepsy, neurodevelopmental and neurorehabilitation.

12. LIMITATIONS

12. LIMITATIONS

Extended sessions for neuropsychological tests, the presence of claustrophobia and longer duration for neuroimaging due to non-cooperation, limited availability of these high end in vivo virtual dissection techniques like FDG PET, VBM, DTI and limited availability of technical expertise to image, to interpret and post process the results and cost are the limitations of our study.

13. APPENDICES

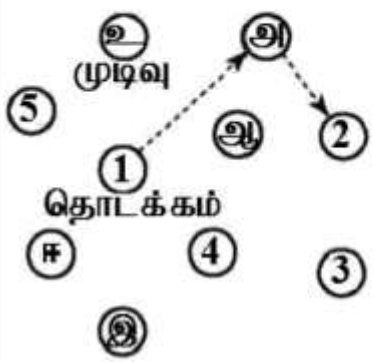
APPENDIX – I MoCA

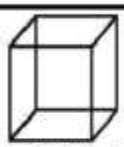
மொன்றியல் அறிவாற்றல் மதிப்பீடு (MOCA)
Tamil Version

பெயர்:
கல்வி:
பால்:

பிறந்த திகதி:
திகதி:

காட்சி அமைப்பு / நிறைவேற்று செயலாண்மை — புள்ளிகள்





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[ ] உருவரை [ ] இலக்கம் [ ] கைகள் — /5

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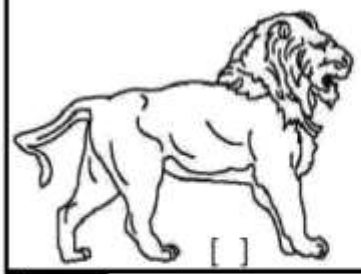
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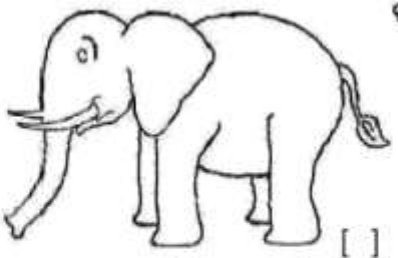
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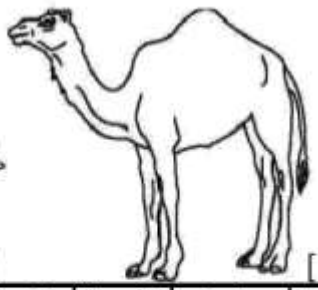

[ ]

/3

நினைவு

நூப்பட்டுள்ள சொற்களை வாசித்தல். தேர்வுநாடி இவற்றை ஒப்புவிக்க வேண்டும். முதலாவது முடிவையில் சரியாக கூறியிருப்பினும், இரு முடிவைகள் தேர்வு செய்யவும். 5 நிமிடங்களின் பின் சொற்களை நினைவுபடுத்தி மீண்டும் சொல்லச் சொல்லவும்

	முகம்	பட்டு	கோயில்	மல்லிகை	சிவப்பு
1வது தேர்வு					
2வது தேர்வு					

புள்ளிகள் இல்லை

கவனம்

நூப்பட்டுள்ள எண்களை வாசித்தல்(1எண்/தொடி) — தேர்வுநாடி இந்த எண்களை முன்னோக்கிய ஒழுங்கில் சொல்ல வேண்டும் [ ] 21854
தேர்வுநாடி இந்த எண்களை பின்னோக்கிய ஒழுங்கில் சொல்ல வேண்டும் [ ] 742 — /2

நூப்பட்டுள்ள எழுத்துக்களை வாசித்தல். இதனை செய்பவர் ஒவ்வொரு "ஏ" க்கும் கை தட்ட வேண்டும். ≥ 2 பிழைகள் இருப்பின் ஒரு புள்ளியும் இல்லை. [ ] **க டி ஏ உ ந டி ஏ ஏ த ம ட டி ஏ க ஏ ம ன வ ஏ ஏ ஏ த ஏ ந ப க ஏ ஏ டி** — /1

தொடர் 7 கழித்தல். 100 இருந்து ஆரம்பிக்கவும். [ ]93 [ ]86 [ ]79 [ ]72 [ ]65
4 அல்லது 5 சரியான கழித்தல்:3 புள்ளிகள், 2 அல்லது 3 சரியான கழித்தல்: 2 புள்ளிகள், 1 சரியான கழித்தல்:1 புள்ளி, 0 சரி:0 புள்ளி — /3

மொழி

ஒப்புவித்தல்: யோல் ஒருவரே இன்று எனக்கு உதவி செய்யக் கூடியவர். [ ]
அதிக இனிப்புக் கொடுக்கப்பட்ட குழந்தைகள் வயிற்றுவலியால் இன்னல் பட்டனர். [ ] — /2

வாய்ச்சொல்லோட்டம் / ஒரு நிமிடத்தில் இயலுமான அளவில் "அ" என்ற எழுத்தில் ஆரம்பிக்கும் சொற்களை கூறவும். [ ] ___ (N>11 சொற்கள்) — /1

கருத்துப்பொருள்

பொதுவான தன்மை. உதாரணம் வாழைப்பழம் - தோடம்பழம் = பழம்
[ ] தொடர்வண்டி - மிதிவண்டி [ ] கைக்கடிகாரம் - அடிமட்டம் — /2

காலந்தாழ்த்திய நினைவு கூர்தல்

	முகம்	பட்டு	கோயில்	மல்லிகை	சிவப்பு
எவ்வித நினைவுச் சொற்களுமின்றி சொற்களை நினைவு கூரல் வேண்டும்	[ ]	[ ]	[ ]	[ ]	[ ]

தானாக நினைவு கூர்ந்தசொற்களுக்கு மட்டுமே புள்ளிகள் — /5

கட்டாயமற்றது

பலவகை நினைவுச் சொல்	
பல்தேர்வு நினைவுச் சொல்	

ஆற்றப்படுத்தல் [ ] திகதி [ ] மாதம் [ ] ஆண்டு [ ] கிழமை [ ] இடம் [ ] நகரம் — /6

இயல்பான நிலை ≥ 26/30

மொத்தம் — /30
12ம் வகுப்புத்திற்கும் அதற்கும் குறைந்த கல்வியாயின் 1 புள்ளியினை சேர்க்குக.

APPENDIX – II ADDENBROOKE'S COGNITVE EXAMINATION (ACE-III)

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-III
Tamil Literate Version

பெயர்:
பிறந்த தேதி:
மருத்துவ மனை என் அல்லது முகவரி:
அறிந்த மொழிகள்:
தாய்மொழி:

பரிசோதனை தேதி: ___/___/___
பரிசோதிப்பவர் பெயர்: _____
முழு நேர கல்வியை விட்ட வயது: _____
தொழில்: _____
எந்த வகை உபயோகித்தீர்கள்: _____

ATTENTION

கேளுங்கள் இது என்ன	நாள்	தேதி	மாதம்	வருடம்	பருவம்	**Attention** [Score 0-5]
கேளுங்கள் எந்த	மாடி	மருத்துவ மனை	நகரம்	நாடு	தேசம்	**Attention** [Score 0-5]

ATTENTION

சொல்லுங்கள்: நான் உங்களுக்கு மூன்று வார்த்தைகள் சொல்லப்போகிறேன். அதை நீங்கள் திரும்பி சொல்லுங்கள்: எலுமிச்சம், எலி, பந்து. அவர்கள் சொன்ன பிறகு (சொல்லட்டும்), நீங்கள் சொல்லுங்கள் இந்த மூன்று வார்த்தைகளை ஞாபகம் வைத்துக்கொள்ளவும், ஏன் என்றால் நான் அப்புறமாக அதைக் கேட்கப்போகிறேன்.
முதலில் பரிசோதித்ததை மட்டும் பதிவு செய்யுங்கள். தேவையானால் மூன்று தடவை சொல்லுங்கள்.
எத்தனை முறை பரிசோதனை செய்தீர் என பதிவு செய்யவும்:_____

Attention [Score 0-3]

ATTENTION

தொடர்வியைக் கேட்கவும்: 100-லேந்து 7 கழிக்க முடியுமா? மறுபடியும் அதிலிருந்து 7 கழித்து கொண்டு வாருங்கள் நான் நிறுத்தும் வரைக்கும்.
தொடரி தப்பா சொன்னால் அவர்களை நிறுத்துங்கள். அவர்கள் சொல்லிட்டே இருக்கட்டும் ஆனால் அவரோட பதில்களைக் கவனிக்கவும்
(உதாரணமாக,. 93, 84, 77, 70, 63- பதிவு 4)
5 தடவை கழித்ததுக்கு அப்புறம் நிறுத்துங்கள் (93, 86, 79, 72, 65): _____ _____ _____ _____ _____

Attention [Score 0-5]

MEMORY

கேளுங்கள்: நான் உங்களை எந்த மூன்று வார்த்தைகள் ஞாபகம் வைக்க சொல்லிருந்தேன்? _____ _____ _____

Memory [Score 0-3]

FLUENCY

அக்ஷரங்கள்
சொல்லுங்கள்: நான் உங்களுக்கு ஒரு அக்ஷரம் சொல்லப்போகிறேன். அந்த அக்ஷரத்தோடே ஆரம்பிக்கிற சில வார்த்தைகள் நீங்கள் சொல்லவேண்டும். ஆனால் பலரிகள் அல்ல இடங்கள் பெயர் இருக்க கூடாது. உதாரணமாக, நான் உங்களுக்கு எ என்ற அக்ஷரத்தை கொடுத்தால், நீங்கள் கண்ணாடி, ஏடு, கோபி என்ற வார்த்தைகளை கூறலாம் ஆனால் கல்பாணி, கன்யாகுமரி என்ற வார்த்தைகள் சொல்லக் கூடாது. புரிகிறதா? நீங்கள் தயாரா? உங்களுக்கு ஒரு நிமிடம் நேரம் இருக்கு. நான் உங்களுக்கு ப என்ற அக்ஷரத்தை கொடுக்கிறேன்.

Fluency [Score 0 - 7]

>14	7
11-14	6
8-10	5
6-7	4
3-5	3
2	2
1	1
0	0
Total	Correct

நுற்றுகள்
சொல்லுங்கள்: உங்களுக்கு தெரிந்த எல்லா நுற்றுகள் பெயர்களைச் சொல்லுங்கள். அது எந்த அக்ஷரத்தாலும் ஆரம்பிக்கலாம்.

Fluency [Score 0 - 7]

>16	7
14-16	6
11-13	5
8-10	4
6-7	3
3-5	2
1-2	1
0	0
Total	Correct

MEMORY

நான் உங்களுக்கு ஒரு பெயர் மற்றும் முகவரி சொல்லப்போகிறேன். அதை நீங்கள் மறுபடியும் சொல்லவேண்டும். நீங்கள் நன்றாக கற்றுக்கொள்வதற்காக நாம் மூன்று முறை சொல்வோம். நான் உங்களை அந்த பெயர் மற்றும் முகவரி கொஞ்ச நேரத்திற்கு அப்புறம் மறுபடியும் கேட்பேன்.

மூன்றாவது சோதனை மாத்திரம் பதிவு செய்யவும்.

Memory [Score 0 - 7]

	1-ம் சோதனை	*2-ம் சோதனை*	*3-ம் சோதனை*
சிவக்குமார் ஐயர் 52, ஸ்டேஷன் சாலை மீனம்பாக்கம் கோடைக்கானல்	______ ______ ____ ______ ______ ____________ ____________	______ ______ ____ ______ ______ ____________ ____________	______ ______ ____ ______ ______ ____________ ____________

MEMORY

Memory [Score 0 - 4]

இப்போ இருக்கிற முதல்வர் பெயர் என்ன?..

இந்தியப் பிரதம மந்திரி பெயர் என்ன?..

புகழ் பெற்ற ஆண் நடிகர் மற்றும் முதலமைச்சராக இருந்தவர் யார்?..

நமது தேச தந்தை யார்? ....

LANGUAGE

Language [Score 0-3]

நோயாளி எதிரில் ஒரு பேப்பர் மற்றும் பென்சில் வையுங்கள். ஒரு நடைமுறை சோதனைக்கு ([illegible]) நோயாளிக்கு சொல்லுங்கள் பென்சில் எடுத்தப்புறம் பேப்பரை எடுங்கள். நோயாளி சரியாக செய்துவிட்டால், (பண்ணிவிட்டால்) 0 பதிவு கொடுங்கள் மற்றும் நிறுத்தவும்.

நோயாளி நடைமுறை சோதனையைச் சரியாக் பண்ணவில்லை , கீழே இருக்கும் 3 கட்டளை கொடுங்கள்:

- **நோயாளிக்கு சொல்லுங்கள் பேப்பரை பென்சில் மேலே வையுங்கள்**
- **நோயாளிக்கு சொல்லுங்கள் பென்சில் எடுங்கள் ஆனால் பேப்பர் வேண்டாம்**
- **நோயாளிக்கு சொல்லுங்கள் பென்சிலை எனக்கு கொடுங்கள் பேப்பரைத் தொட்டுவிட்டு**

கவனம்: பென்சிலும் பேப்பரையும் ஒரு ஒரு கட்டளைக்கு அப்புறம் நோயாளி முன்னாடி வையுங்கள்.

LANGUAGE

Language [Score 0-2]

நோயாளியை அவருடன் கடைசி விடுமுறை / வார இறுதி / பண்டிகை பற்றி 2 (இல்லாத அதிக) முழு வாக்கியங்களில் எழுத சொல்லுங்கள். சுருக்கு வாக்கியங்களில் எழுத கூடாது. 2 இல்லாத அதிக முழு வாக்கியங்கள் எழுதினால் 1 என் பதிவு கொடுங்கள் ; மற்றும் இலக்கணம் மற்றும் சொற்பிழை சரியாக இருந்தால் இன்னும் 1 என் பதிவு கொடுங்கள்.

LANGUAGE

Language [Score 0-2]

நோயாளி திரும்பி சொல்லும்படி சொல்லுங்கள்: வர்ஷாந்தரம், சர்வார்த்தி.
வாழைப்பழம்.காண்டாமிருகம்

எல்லாமே சரியாக சொன்னால் 2 என் பதிவு கொடுங்கள் ; 3 சரியாக இருந்தால் 1 என் பதிவு கொடுங்கள் ; 2 அல்லது குறைவாக சரியாக இருந்தால் 0 என் பதிவு கொடுங்கள்.

LANGUAGE

நோயாளியை திரும்பி சொல்லும்படி சொல்லுங்கள்: மின்னுவதெல்லாம் பொன்னல்ல

Language
[Score 0-1]

நோயாளியை திரும்பி சொல்லும்படி சொல்லுங்கள்: காற்றுள்ளபோதே தூற்றிக் கொள்

Language
[Score 0-1]

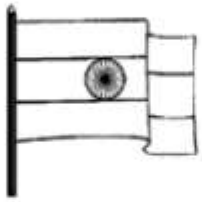
LANGUAGE

நோயாளி கீழே இருக்கும் படங்களின் பெயர் சொல்லும்படி சொல்லுங்கள்:

Language
[Score 0-12]












LANGUAGE

மேலே இருக்கிற படங்களைப் பார்த்து நோயாளியை:

- மழைக்கு எது உபயோகப்படும் என்று காட்டச் சொல்லவும்
- வெளிச்சம் கொடுப்பது எது காட்டச் சொல்லவும்
- விவசாயத்துக்கு எது உபயோகப்படும் காட்டச் சொல்லவும்
- பாலைவனங்களில் எது காணப்படும் காட்டச் சொல்லவும்

Language
[Score 0-4]

LANGUAGE

நோயாளியை கீழே எழுதிய வார்த்தைகளை உரக்க படிக்க சொல்லவும். (எல்லாமே சரியாயிருந்தால் 1 என் பதிவு கொடுக்கள்)

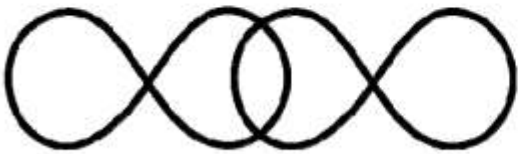
Language [Score 0-1]

ஞாபகம்
பிரம்மாண்டம்
மகரிஷி
நிஷப்தம்
லக்ஷணம்

VISUOSPATIAL ABILITIES

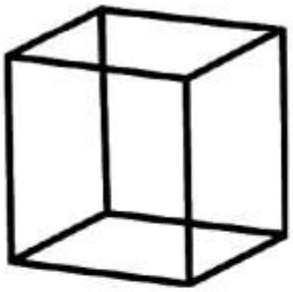
Infinity Diagram: நோயாளியை இந்தப் படத்தை காப்பி செய்ய சொல்லவும்

Visuospatial [Score 0-1]



Wire Cube: நோயாளியை இந்த படத்தை காப்பி செய்யச் சொல்லவும். (பதிவு கொடுப்பதற்கு instruction guide பாருங்கள்)

Visuospatial [Score 0-2]



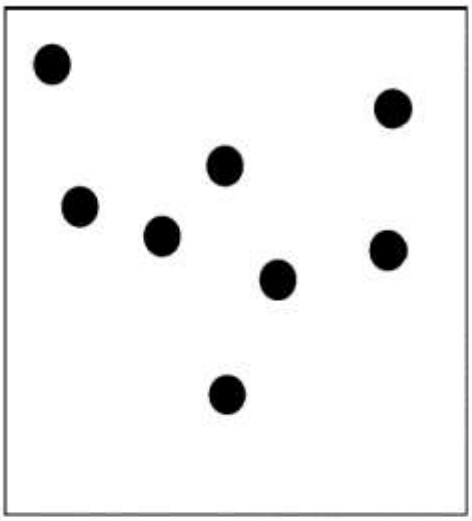
கடிகாரம்: நோயாளியை ஒரு கடிகாரம் மற்றும் அதில் என் வரைந்து அதில் முன் மணி நூற்று பத்து (5:10) காட்டும்படி வரைய சொல்லுங்கள்.
(பதிவு கொடுப்பதற்கு Instruction guide பாருங்கள்: எல்லாமே சரியாக இருந்தால் வட்டம் = 1, எண்கள் 2, முள்கள் = 2 கொடுக்கள்)

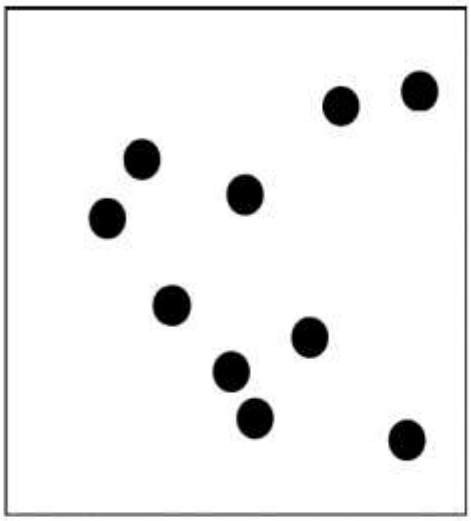
Visuospatial [Score 0-5]

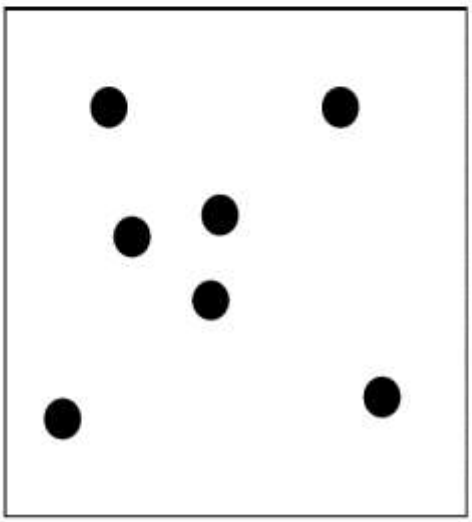
VISUOSPATIAL ABILITIES

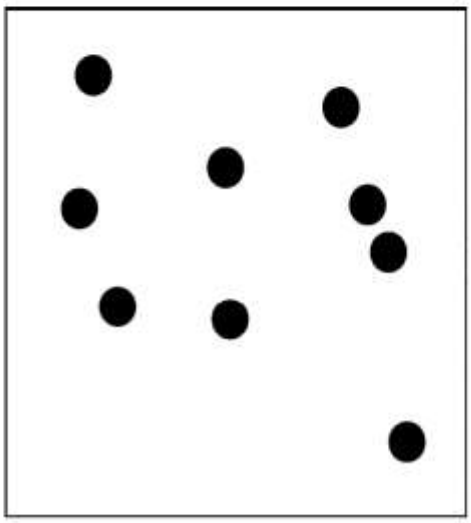
நோயாளியை குறிப்பிட்டு காட்டமம், புள்ளிகளை என்னச் சொல்லுங்கள்

Visuospatial
[Score 0-4]





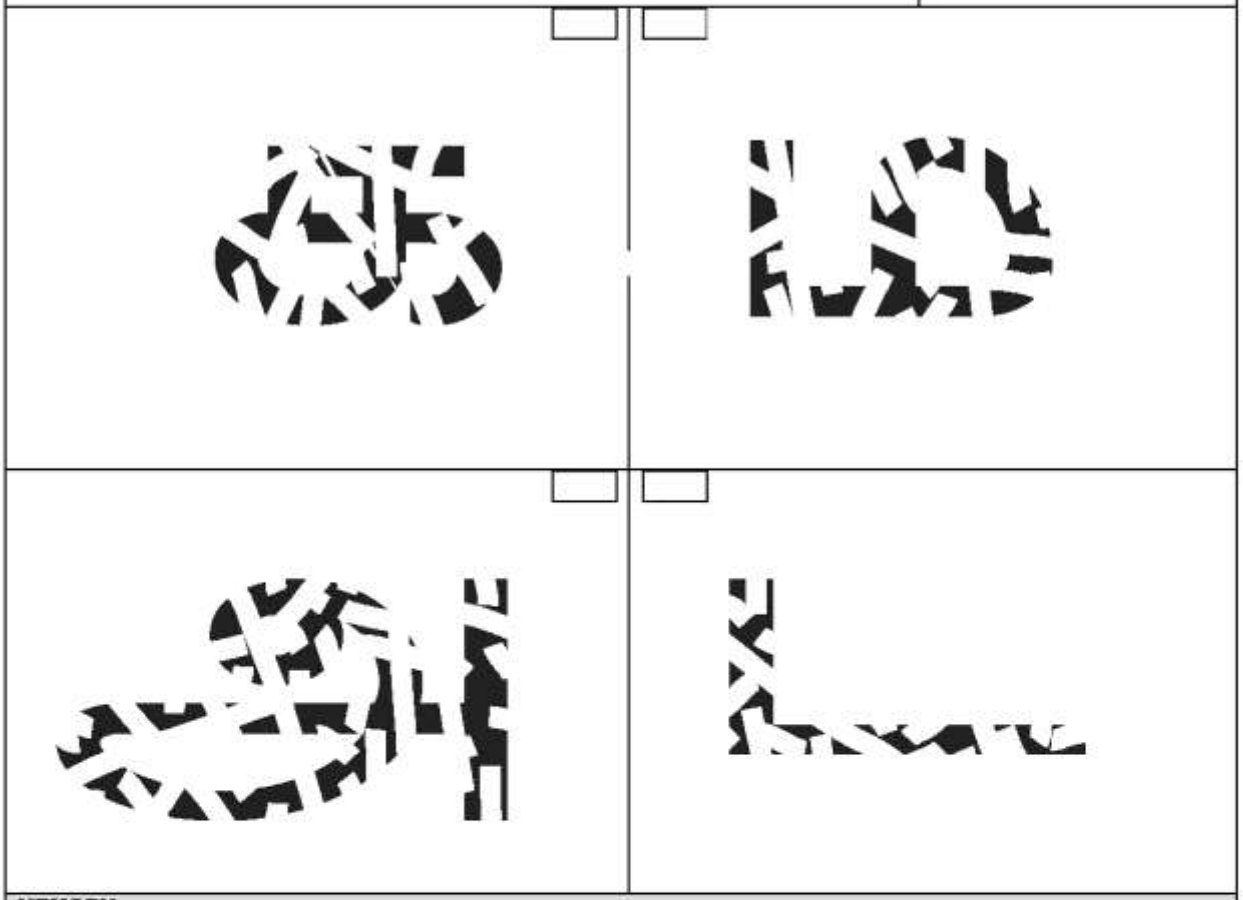




VISUOSPATIAL ABILITIES

நோயாளியை அக்கருவுகளின் அடையாளம் கண்டுபிடிக்க சொல்லுங்கள்

Visuospatial [Score 0-4]



MEMORY

வேலுங்கள்: இப்போ, நாம் முதலில் திருப்பி திருப்பி சொன்ன பெயர் மற்றும் முகவரியை சொல்லுங்கள்.

சிவக்குமார் துபர் 52, ஸ்டேஷன் சாலை மீனம்பாக்கம் சோடைக்காளம்	. . .	**Memory [Score 0-7]**

MEMORY

நோயாளி மேலே கொடுத்த ஒரு இல்லாத அதிக வார்த்தைகள் (items) மறந்து விட்டால் இந்த சோதனை செய்ய வேண்டும். எல்லா வார்த்தைகளும் (learning) சரியாக சொன்னால் இந்த சோதனை செய்ய வேண்டாம். மற்றும் 5 என் பதிவு கொடுங்கள். சில வார்த்தைகள் சரியாகச் சொன்னால் வரது பக்கத்தில் இருக்கிற கவர் (shadow) செய்யப்பட்ட கட்டத்தில் அந்த வார்த்தைகளை டிக் செய்யவும். அதற்கு அப்புறம் மறந்து விட்ட வார்த்தைகளை சோதனை செய்வதற்கு நோயாளிக்கு சொல்லுங்கள். நான் உங்களுக்கு சில குறிப்புகள் கொடுக்கிறேன்: பெரு x, y இல்லாத z ஊர்? இதில் சரியாக சொன்னால் ஒரு ஒரு வார்த்தைக்கும் (item/sum) 1 என் பதிவு கொடுங்கள். இதை ஞாபகம் வைத்துக்கொண்டு சொன்ன வார்த்தைகளுக்கு (items/sum) கொடுத்த பதிவு உடன் சேர்க்கவும்

Memory [Score 0-5]

செந்தில் குமார் துபர்		சிவக்குமார் துபர்		சீதா பதி சவாரி		நினைவுப்படுத்து	
25		52,		36		நினைவுப்படுத்து	
ஸ்டேஷன் சாலை		போக் சாலை		மார்கெட் சாலை		நினைவுப்படுத்து	
நுங்கம்பாக்கம்		மீனம்பாக்கம்		தாம்பரம்		நினைவுப்படுத்து	
சோடைக்காளம்		கள்பாகுமரி		பழ்சேரி		நினைவுப்படுத்து	

SCORES

TOTAL ACE-III SCORE	/100
Attention	/18
Memory	/26
Fluency	/14
Language	/26
Visuospatial	/16

APPENDIX – III WECSHLER'S MEMORY SCALE (WMS)

வெக்ச்லர் நினைவு அளவை -1

பெயர்: வயது: ஆ/பெ:

தேதி:

I.தன்னைப்பற்றிய மற்றும் தற்போதைய விவரங்கள்:

1. உன் வயது என்ன ? ____
2. நீ பிறந்த தேதி என்ன? ____
3. இந்தியாவின் பிரதம அமைச்சர் யார்? ____
4. இதற்கு முன் இருந்த பிரதம அமைச்சர் யார்? ____
5. தமிழ்நாடு முதலமைச்சர் யார் ? ____
6. இம்மாநிலத்தின் கவர்னர் யார்? ____

மொத்தம் ____

மொத்தம் பெற்ற எண் :
வயதுக்காக பெறும் எண் :
இறுதியாகப் பெறும் எண் :
நினைவு ஈவு :

II.சூழ்நிலையோடு ஒன்றிய விவரங்கள் :

1. இது எந்த வருடம் ? ____
2. இது எந்த மாதம் ? ____
3. இன்று தேதி என்ன ? ____
4. இந்த இடத்தின் பெயர் என்ன ? ____
5. இது எந்த நகரத்தில் இருக்கிறது ? ____

மொத்தம் ____

III மனக்கட்டுப்பாட்டுத் திறன் பற்றியது : காலம் - தவறுகள் - பெற்ற எண்

1. 20-லிருந்து பின்னால் 1-வரை எண்ணவும் (30") ____ ____ ____

2. அ -முதல் ∴ -வரை சொல்லவும் (15") ——— ——— ———

3. ஒன்றுடன் மூன்று மூன்றாகக் கூட்டி ——— ——— ———

40 வரை சொல்லவும் (45")

மொத்தம் ———

IV உடன் நினைவு கூர்தல் :

1. எண்கள் முன்னோக்கி :

(4) 6439
7286

(5) 42731
75836

(6) 619473
392487

(7) 5917423
4179386

(8) 58192647
38295174

பெற்ற எண் .....

2. எண்கள் பின்னோக்கி :

(3) 283
415

(4) 3279
4968

(5) 15286
61843

(6) 539418
724853

(7) 8129365
4739126

பெற்ற எண் .....

V தொடர்வுடன் கற்றல் :

(அ) தென் சென்னையை சேர்ந்த / தேன் மொழி / ஓர் அலுவலகத்தில் / வேலை செய்து வந்தாள்./அவள் ஒரு நாள் / நகர காவல் / நிலையத்திற்கு சென்று / தான் கடை வீதியில்/ சென்ற இரவு/ தாக்கப்பட்டதோடு/ பதினைந்து ரூபாயையும்/ பறி கொடுத்ததாகப்/ புகார் செய்தாள்./ அவளுக்கு/ நான்கு/ குழந்தைகள்./ வீட்டு வாடகை பாக்கியோடு/ அவர்கள் இரண்டு நாட்களாக உண்ணவும் இல்லை/ அதிகாரிகள்/ அந்த பெண்ணுக்காக/ இரக்கப்பட்டு/ சிறிது பணம் கொடுத்து/ உதவி செய்தார்கள்.

(ஆ) ஜலதீபம் என்ற/ இந்திய/ கப்பல்/ திங்கட்கிழமை/ மாலை/ கன்னியாகுமரிக்கு அருகில்/ ஒரு பாறையில் மோதியது./ கடுமையான புயல்/ காரிருளும் இருந்தும்/படகுகள்/ தக்கைகளைப் போல்/ கடலில் அலகழிக்கப்பட்ட போதிலும்/ 18/ பெண்களை உள்ளிட்ட/ 60/ பிரயாணிகள் எல்லோரும்/ மீட்கப்பட்டு மறுநாட் காலை/ ஓர் இந்திய/ நீராவிக் கப்பலில்/ கரைக்குக்/ கொண்டு வரப்பட்டார்கள் .

பெற்ற எண் ----------(அ-வில் பெற்ற எண் + ஆ-வில் பெற்ற எண்) / 2

VI. பார்த்துப் பின் வரைதல்:

அ. ஆ .

பெற்ற எண் : ——

இ-1

பெற்ற எண் : ——

இ-2

பெற்ற எண் : ——

பெற்ற எண் : ——

மொத்தம் ——

VII. இணைத்துக் கற்றல்:

முதற் படைப்பு	இரண்டாம் படைப்பு	மூன்றாம் படைப்பு
(1)	(2)	(3)
உலோகம்-இரும்பு	ரோஜா -பூ	குழந்தை- அழுகிறது
குழந்தை-அழுகிறது	கீழ்ப்படி -அங்குலம்	கீழ்ப்படி-அங்குலம்
கசக்கு- இருட்டு	வடக்கு-தெற்கு	வடக்கு-தெற்கு
வடக்கு-தெற்கு	முட்டைகோஸ்-பேனா	பள்ளி-பலசரக்கு
பள்ளி-பலசரக்கு	மேலே-கீழே	ரோஜா-பூ
ரோஜா-பூ	பழம்-ஆப்பிள்	முட்டைகோஸ்-பேனா
மேலே-கீழே	பள்ளி-பலசரக்கு	மேலே-கீழே
கீழ்ப்படி-அங்குலம்	உலோகம்-இரும்பு	பழம்-ஆப்பிள்
பழம்-ஆப்பிள்	கசக்கு-இருட்டு	கசக்கு-இருட்டு
முட்டைகோஸ்-பேனா	குழந்தை-அழுகிறது	உலோகம்-இரும்பு

முதல் நினைவு கூர்வு:

	சுலபம்	கடினம்
வடக்கு	____	____
பழம்	____	____
கீழ்ப்படி	____	____
ரோஜா	____	____
குழந்தை	____	____
மேலே	____	____
முட்டைகோஸ்		____
உலோகம்	____	____
பள்ளி	____	____
கசக்கு	____	____
மொத்தம்	____	____

இரண்டாவது நினைவு கூர்வு:

	சுலபம்	கடினம்
முட்டைகோஸ்	____	____
குழந்தை	____	____
உலோகம்	____	____
பள்ளி	____	____
மேலே	____	____
ரோஜா	____	____
கீழ்ப்படி	____	____
பழம்	____	____
கசக்கு	____	____
வடக்கு	____	____
மொத்தம்	____	____

மூர்ன்றவது நினைவு கூர்வு:

	சுலபம்	கடினம்
கீழ்ப்படி	____	____
பழம்	____	____
குழந்தை	____	____
உலோகம்	____	____
கசக்கு	____	____
பள்ளி	____	____
ரோஜா	____	____
வடக்கு	____	____
முட்டைகோஸ்		____
மேலே	____	____
மொத்தம்	____	____

APPENDIX – IV TRIAL MAKING TEST A & B (TMT A & B)

Trail Making Test (TMT) Parts A & B

Instructions:

Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.

Step 1:	Give the patient a copy of the Trail Making Test Part A worksheet and a pen or pencil.
Step 2:	Demonstrate the test to the patient using the sample sheet (Trail Making Part A – *SAMPLE*).
Step 3:	Time the patient as he or she follows the "trail" made by the numbers on the test.
Step 4:	Record the time.
Step 5:	Repeat the procedure for Trail Making Test Part B.

Scoring:

Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

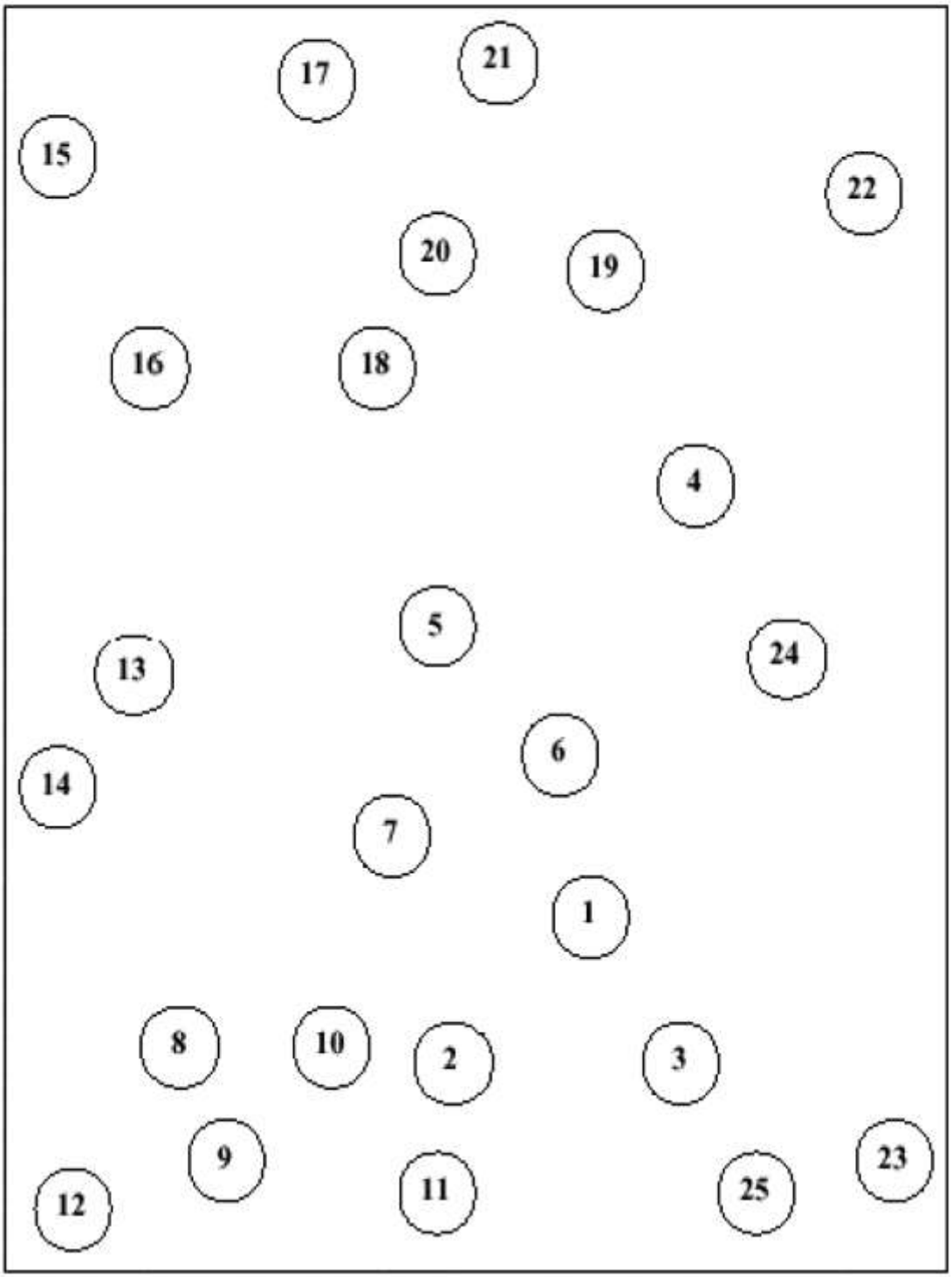
	Average	Deficient	Rule of Thumb
Trail A	29 seconds	> 78 seconds	Most in 90 seconds
Trail B	75 seconds	> 273 seconds	Most in 3 minutes

Sources:

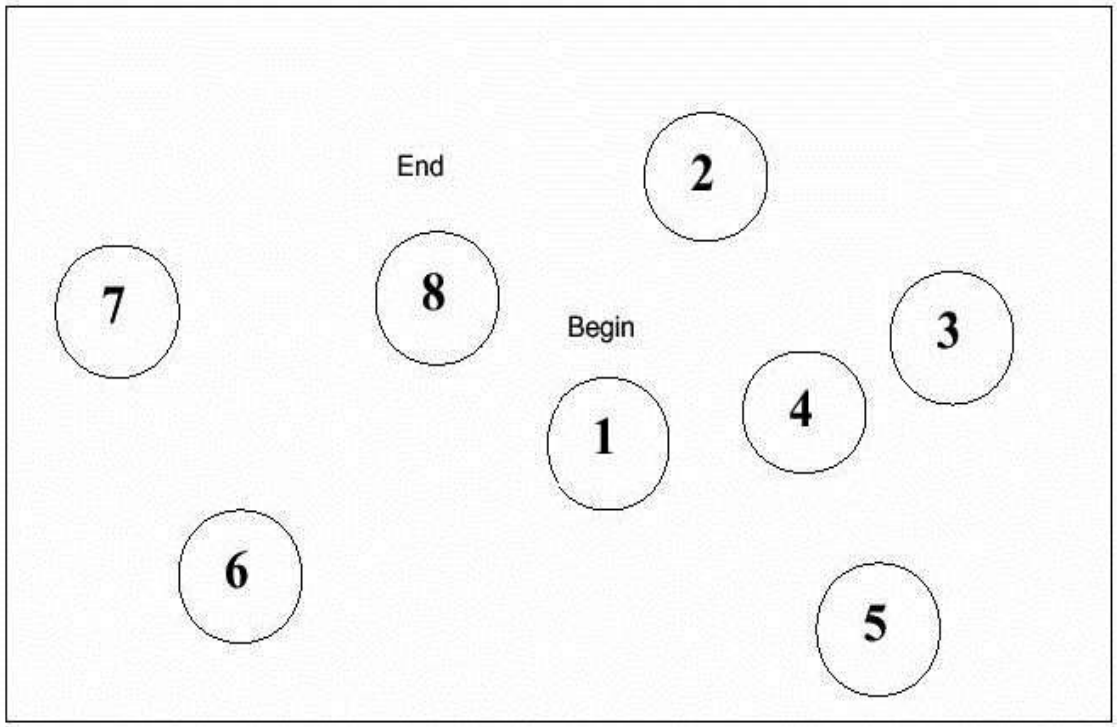
- Corrigan JD, Hinkeldey MS. Relationships between parts A and B of the Trail Making Test. *J Clin Psychol*. 1987;43(4):402–409.
- Gaudino EA, Geisler MW, Squires NK. Construct validity in the Trail Making Test: what makes Part B harder? *J Clin Exp Neuropsychol*. 1995;17(4):529-535.
- Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. 4th ed. New York: Oxford University Press; 2004.
- Reitan RM. Validity of the Trail Making test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8:271-276.

Trail Making Test Part A

Patient's Name: _____ Date: _____

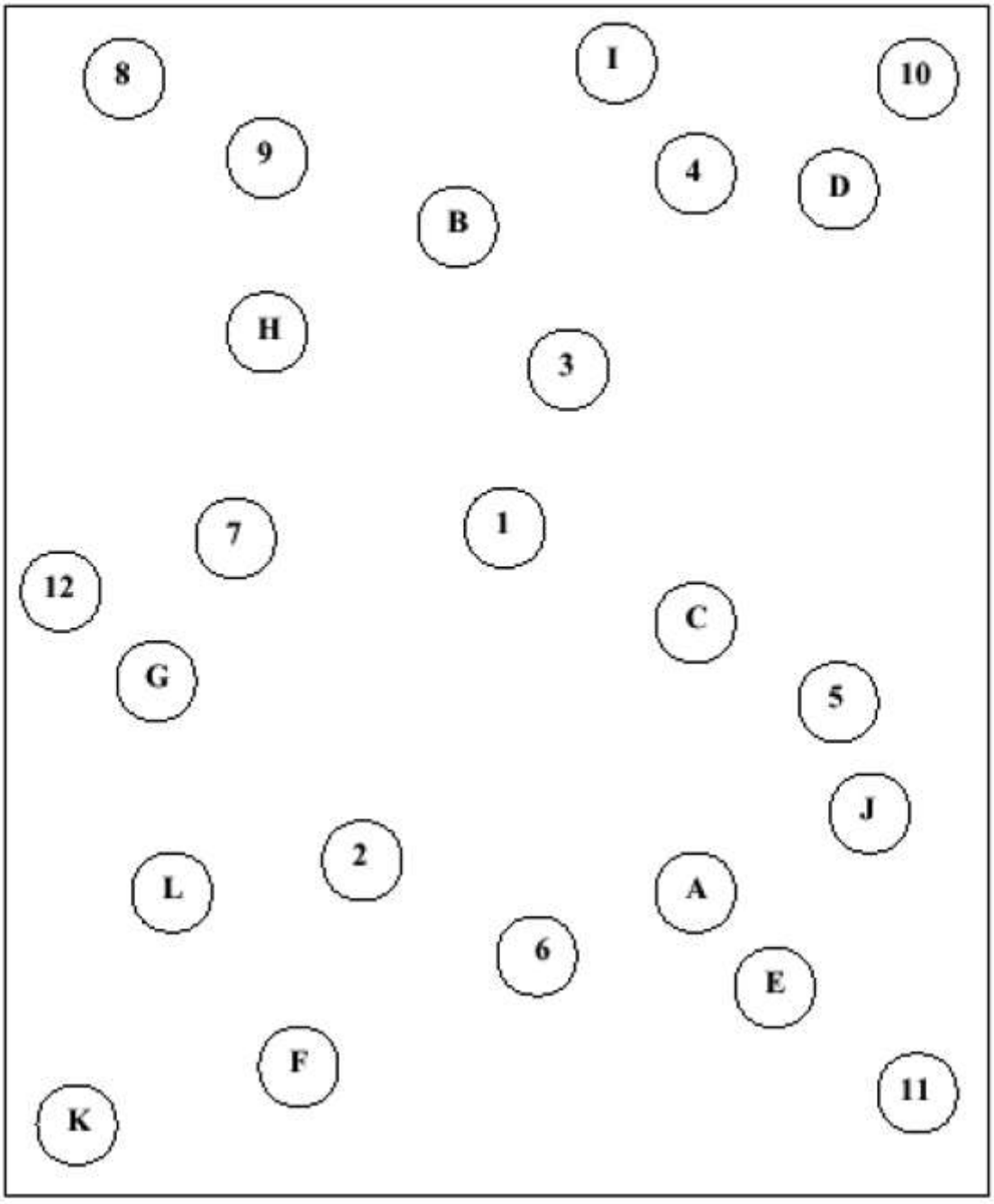


Trail Making Test Part A – *SAMPLE*

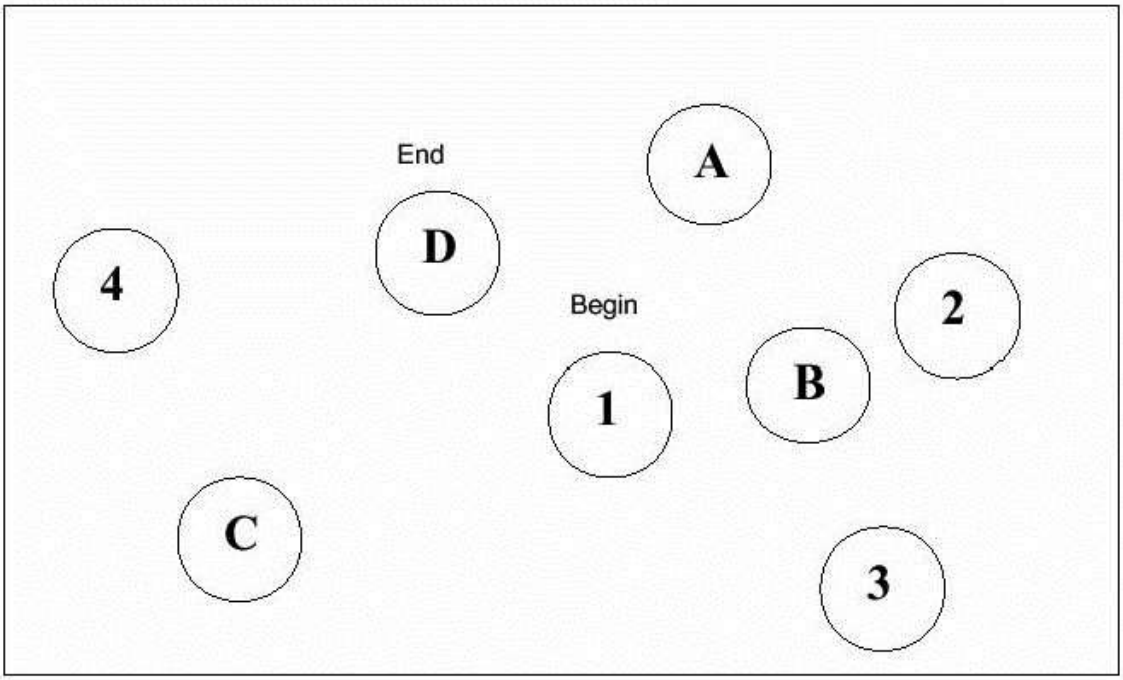


Trail Making Test Part B

Patient's Name: _____ Date: _____



Trail Making Test Part B – *SAMPLE*



APPENDIX – V AUDITORY VERBAL LEARNING TEST (AVLT)

LIST A	LIST B
DRUM	DESK
CURTAIN	RANGER
BELL	BIRD
COFFEE	SHOE
SCHOOL	STOVE
PARENT	MOUNTAIN
MOON	GLASSES
GARDEN	TOWEL
HAT	CLOUD
FARMER	BOAT
NOSE	LAMB
TURKEY	GUN
COLOR	PENCIL
HOUSE	CHURCH
RIVER	FISH

14. TABLES

14. TABLES

Table 1: Various Cognitive Domains studied and Neuroradiological correlates.

Domains	Voxel Based Morphometry	FDG PET	Diffusion Tensor Imaging (FA, ADC, MD, RD)
Attention	Dorsolateral Prefrontal Cortex Frontal eye field Occipital Eye Field Cingulum Posterior parietal gyrus	Frontal Association Anterior cingulate Posterior cingulate Parietal Association Caudate	Superior Longitudinal Fasciculus Inferior Longitudinal Fasciculus Cingulate Fasciculus
Language	Broca's area Wernicke's area Geschwind area (Inferior Parietal Lobule)	Frontal Association Temporal Association Parietal Association	Arcuate fasciculus Superior Longitudinal Fasciculus Inferior Longitudinal Fasciculus Inferior Fronto-occipital fasciculus
Memory	Uncus Hippocampus Nucleus Accumbens	Anterior Cingulate	Uncinate fasciculus Cingulate Fasciculus Fornix

Table 2: Comparisons between Patients and Controls in Demographics

		Group				Mann Whitney U Test	
		Patients		Control			
		n	%	n	%	U Value	P – Value
Age	≤ 45 Years	9	15.00	5	16.67	895.000	.965
	46 - 55	11	18.33	5	16.67		
	56 - 65	16	26.67	8	26.67		
	66 - 75	18	30.00	9	30.00		
	> 75 Years	6	10.00	3	10.00		
Gender	Male	42	70.00	19	63.33	840.000	.526
	Female	18	30.00	11	36.67		
Education	Illiterate	21	35.00	0	.00	369.500	.000
	Primary	5	8.33	2	6.67		
	High School	24	40.00	8	26.67		
	Hr. Sec.	2	3.33	5	16.67		
	Graduate	4	6.67	10	33.33		
	Post Graduate	1	1.67	4	13.33		
	Professional	3	5.00	1	3.33		
Demography	Chennai	49	81.67	27	90.00	827.500	.324
	Other Districts in Tamilnadu	9	15.00	2	6.67		
	Other States	2	3.33	1	3.33		

Table 3: Comparisons between Patients and Controls in Neuro-Psychological Aspects

	Group				Independent Samples t-test	
	Patients		Control			
	Mean	SD	Mean	SD	t-Value	P-Value
MOCA (30)	15.25	7.26	28.27	.98	-13.638	**<0.001**
Addenbrooke's (100)	55.33	25.85	95.23	2.87	-11.809	**<0.001**
Attention (18)	10.77	5.75	17.70	.88	-9.130	**<0.001**
Memory(26)	10.80	6.80	24.13	1.38	-14.603	**<0.001**
Fluency (14)	6.92	3.67	12.33	1.03	-10.629	**<0.001**
Language (26)	18.47	6.99	25.83	.46	-8.125	**<0.001**
Visuo-spatial (16)	8.38	5.12	15.23	1.07	-9.944	**<0.001**
WMS	78.98	21.76	125.27	11.65	-13.137	**<0.001**
AVLT (15)	3.67	2.42	10.63	2.19	-13.281	**<0.001**
Digit span (15)	5.22	2.89	10.93	1.70	-11.768	**<0.001**
Story recall (24)	11.93	7.35	22.92	1.19	-11.279	**<0.001**
Complex figure (14)	2.52	2.79	9.83	2.60	-11.992	**<0.001**

Table 4 : Neuro Psychological Data of All Subjects - Correlations

	Adden brooke's	Attention	Memory	Fluency	Language	Visuo-spatial	WMS	AVLT	Digit span	Story recall	Complex figure
Adden brooke's	1										
Attention	**.955****	1									
Memory	**.958****	**.912****	1								
Fluency	**.937****	**.864****	**.882****	1							
Language	**.909****	**.823****	**.794****	**.847****	1						
Visuo-spatial	**.936****	**.882****	**.877****	**.847****	**.804****	1					
WMS	**.912****	**.880****	**.924****	**.836****	**.762****	**.859****	1				
AVLT	**.853****	**.799****	**.881****	**.815****	**.709****	**.787****	**.903****	1			
Digit span	**.880****	**.844****	**.857****	**.824****	**.780****	**.821****	**.880****	**.834****	1		
Story recall	**.887****	**.862****	**.898****	**.829****	**.742****	**.820****	**.898****	**.826****	**.801****	1	
Complex figure	.795**	**.716****	**.821****	**.735****	**.661****	**.779****	**.850****	**.830****	**.776****	**.753****	1

Note: *. Correlation is significant at the 0.05 level (2-tailed);**. Correlation is significant at the 0.01 level (2-tailed).

Table 5 : Neuro Psychological Data of Patients and Controls - Correlations

Group		Control										
		Adden brooke's	**Atten tion**	**Memory**	**Fluency**	**Lang uage**	**Visuo-spatial**	**WMS**	**AVLT**	**Digit span**	**Story recall**	**Complex figure**
Patients	Addenbrooke's	1	.439*	.738**	.580**	.551**	.575**	.370*	.486**	.201	.268	.176
	Attention	.943**	1	.063	-.076	.725**	.040	.484**	.641**	.472**	.537**	.174
	Memory	.933**	.903**	1	.380*	.144	.211	.133	.165	.121	.154	.035
	Fluency	.901**	.811**	.801**	1	.048	.146	.211	.225	-.223	-.019	.073
	Language	.884**	.751**	.721**	.799**	1	.221	.349	.450*	.381*	.351	.264
	Visuo-spatial	.901**	.832**	.811**	.766**	.725**	1	.072	.155	.047	-.052	.101
	WMS	.884**	.876**	.883**	.744**	.698**	.824**	1	.712**	.537**	.288	.270
	AVLT	.828**	.790**	.828**	.762**	.667**	.740**	.785**	1	.521**	.484**	.183
	Digit span	.831**	.806**	.742**	.763**	.734**	.756**	.766**	.640**	1	.483**	.270
	Story recall	.805**	.790**	.825**	.723**	.623**	.716**	.864**	.761**	.660**	1	.090
	Complex figure	.694**	.618**	.679**	.577**	.560**	.728**	.737**	.666**	.547**	.607**	1

Note: Correlations for Controls are shaded in yellow and Patients are shaded in Grey

Note: *. Correlation is significant at the 0.05 level (2-tailed); **. Correlation is significant at the 0.01 level (2-tailed).

Table 6: Comparison of Patients and Controls in DTI Metrics on Right and Left hemispheres of Brain

RIGHT SIDE OF BRAIN			LEFT SIDE OF BRAIN		
White matter tract	**DTI parameter**	**Patients and Controls**	**White matter tract**	**DTI parameter**	**Patients and Controls**
SLF	NO DIFFERENCE		SLF	RD	P↑
ILF	MD	P ↑	ILF	FA	P↓
	RD	P ↑		RD	P ↑
IFO	FA ADC MD RD	P↓ P↑ P↑ P↑	IFO	FA ADC	P↓ P↑
ARCUATE	ADC AD MD RD	P↑ P↑ P↑ P↑	ARCUATE	ADC AD MD	P↑ P↑ P↑
UNCINATE	MD	P↑	UNCINATE	ADC MD RD	P↑ P↑ P↑
FORNIX	FA ADC MD RD	P↓ P↑ P↑ P↑	FORNIX	FA ADC AD MD RD	P↓ P↑ P↑ P↑ P↑
CINGULUM	ADC MD RD	P↑ P↑ P↑	CINGULUM	NO DIFFERENCE	

Table 7 : Comparisons of DTI Metricsbetween Patients and Controls in All White Matter Tracts

DTI WITH AVERAGE OF BOTH THE SIDES

WHITE MATTER TRACT	DTI PARAMETER	PATIENTS AND CONTROLS LEVEL
CINGULUM	ADC	P↑
	MD	P↑
ILF	FA	P↓
	MD	P↑
	RD	P↑
SLF	NO DIFFERENCE	
IFO	FA	P↓
	ADC	P↑
	MD	P↑
	RD	P↑
ARCUATE	ADC	P↑
	AD	P↑
	MD	P↑
	RD	P↑
UNCINATE	ADC	P↑
	MD	P↑
	RD	P↑
FORNIX	FA	P↓
	ADC	P↑
	AD	P↑
	MD	P↑
	RD	P↑

Table 8: Summary table of Neuro-Psychiatric domains and Diffusion Tensor imaging

Domains	Right side brain			Left Side Brain		
	WMT	**DTI**	**Groups**	**White Matter Tract**	**DTI**	**Groups**
Attention	**Cingulum**	ADC	2 Groups, PL ↑, CON↓, [PH-(PL,CON)]	Cingulum	ADC	Nil
		MD	2 Groups- PH+CON↓ , PL↑		MD	Nil
		RD	2 Groups- PH+CON↓, PL↑		RD	2 groups- (PL↑, CON+PH↓)
		FA	Nil		FA	2 groups- PL↓,PH↑, [CON- (PL,PH)]
		AD	Nil		AD	Nil
	ILF	ADC	Nil	ILF	ADC	Nil
		MD	2 groups- PL+PH↑, CON↓		MD	2 groups- PL↑,CON↓, [PH-(PL,CON)]
		RD	2 groups- PL↑+PH, CON↓		RD	2 groups- PL↑,CON↓, [PH-(PL,CON)]
		FA	Nil		FA	2 groups- PL↓,CON↑, [PH-(PL,CON)]
		AD	Nil		AD	Nil
	SLF		Nil	SLF		Nil
Language & Fluency	**SLF**	FA	Nil	SLF	FA	2 Groups: PL+PH↓, Con↑
	ILF	FA	2 Groups : PL↓ , PH ↑, Con(PL, PH)	ILF	FA	2 Groups: PL↓, Con↑,PH(PL, Con)
		ADC	2 Groups, Con+PL↓, PH↑		ADC	2 Groups: Con, PH↑, PL↓ (Con, PH)
		RD	2 Groups: Con↓, PL↑, PH (Con, PL)		RD	2 Groups Con, PL↑, PH(PL,Con)
	IFO	FA	2 Groups: PL, Con.↑ PH (PL,Con)	IFO	FA	2 Groups: PL, Con↑,PH(PL, Con)
		ADC	2 Groups, Con, PL↑, PH (Con, PL)		ADC	2 Groups: Con, PL↑, PH (PL, Con)
		MD	2 Groups: Con, PL↑, PH(Con, PL)		MD	2 Groups: Con, PL↑, PH (Con, PL)
		RD	2 Groups:Con, PL↑, PH(Con, PL)		RD	2 Groups Con, PL↑, PH(PL,Con)

Domains	Right side brain			Left Side Brain		
	WMT	**DTI**	**Groups**	**White Matter Tract**	**DTI**	**Groups**
	Arcute Fasciculus	FA	Nil	Arcute Fasciculus	FA	Nil
		ADC	2 Groups:Con, PL+PH↑		ADC	2 Groups: Con, PL↑, PH (Con, PL)
		AD	2 Groups: Con, PL+PH↑		AD	2 Groups: Con, PL+PH↑
		MD	2 Groups: Con, PL + PH↑		MD	2 Groups Con, PL↑, PH(PL,Con)
		RD	2 Groups:Con, PL↑, PH(Con, PL)		RD	2 Groups Con, PL↑, PH(PL,Con)
Memory	**Uncinate**	ADC	Nil	UNCINATE	ADC	2 groups- PL↑, PH↓+CON
		MD	Nil		MD	2 groups- PL↑, PH+CON↓
		RD	2 groups- PL↑,CON↓, [PH-(PL,CON)]		RD	2 groups- PL↑, PH+CON↓
		FA	Nil		FA	2 groups- PL ↓, CON ↑ +PH
		AD	Nil		AD	Nil
	Fornix	ADC	2 groups- PL↑+PH, CON↓	FORNIX	ADC	2 groups- PL↑+PH, CON↓
		MD	2 groups- PL↑,CON↓, [PH-(PL,CON)]		MD	2 groups- PL↑+PH↓, CON↓
		RD	2 groups- PL↑+PH, CON↓		RD	2 groups- PL↑+PH, CON↓
		FA	2 groups- PL↓+PH, CON↑		FA	2 groups- PL↓+PH, CON↑
		AD	Nil		AD	2 groups- PL↑+PH, CON↓
	Cingulum	ADC	2 groups- PL↑, PH+CON↓	CINGULUM	ADC	2 groups- PL↑,PH↓, [CON- (PL,PH)]
		MD	2 groups- PL↑, PH↓+CON		MD	2 groups- PL ↑;CON↓, [PH-(PL,CON)]
		RD	2 groups- PL↑, PH↓+CON		RD	2 groups- PL ↑, PH↓+CON
		FA	Nil		FA	2 groups- PL↓, PH+CON↑
		AD	Nil		AD	Nil

Note: PL – Patient with low score, PH – Patient with high score, CO – Control
[ ]– Group that has been split

Table 9: Summary of significant findings noted in either low score patient group or high score patient group in comparison to controls

DOMAIN	WHITE MATTER TRACT	R/L	FA	AD	RD	MD	ADC
Attention	CINGULUM	R L			↑ ↑	↑	↑
	ILF	R L	↓		↑ ↑	↑ ↑	
	SLF	R L					
Language and Fluency	IFO	R L	↓ ↓		↑ ↑	↑ ↑	↑ ↑
	ARCUATE	R L		↑ ↑	↑ ↑	↑ ↑	↑ ↑
	ILF	R L	↓ ↓		↑ ↑	↑ ↑	↑
	SLF	R L					
Memory	UNCINATE	R L	↓		↑ ↑	↑	↑
	FORNIX	R L	↓ ↓	↑	↑ ↑	↑ ↑	↑ ↑
	CINGULUM	R L	↓		↑ ↑	↑ ↑	↑ ↑

Table 10: Percent of Patients having Hypometabolism in various cortical regions studied.

Cortical Area	Hypometabolism (%)
ATTENTION DOMAIN	
Frontal Association - Right	79.63
Frontal Association –Left	88.89
Anterior Cingulate– Right	88.89
Anterior Cingulate–Left	85.19
Posterior Cingulate– Right	70.37
Posterior Cingulate- Left	75.93
Parietal Association – Right	81.48
Parietal Association –Left	90.74
Caudate – Right	90.74
Caudate –Left	92.59
LANGUAGE DOMAIN	
Frontal Association – Right	79.63
Frontal Association –Left	88.89
Temporal Association – Right	77.78
Temporal Association –Left	79.63
Parietal Association – Right	81.48
Parietal Association –Left	90.74
MEMORY DOMAIN	
Anterior Cingulate - Right	88.89
Anterior Cingulate - Left	85.19

Table 11 (a): Table showing Hypometabolism in low attention score and high attention score patient groups in attention domain

Cortical Areas studied in attention	Low Attention Score Patient Group (% showing Hypometabolism)	High Attention Score Patient Group (% showing Hypometabolism)
Frontal Association Right	87.88	66.67
Frontal Association - Left	93.94	80.95
Anterior cingulate - Right	90.91	85.71
Anterior cingulate - Left	87.88	80.95
Posterior cingulate - Right	72.73	66.67
Posterior cingulate- Left	81.82	63.63
Parietal Association - Right	84.85	76.19
Parietal Association - Left	96.97	80.95
Caudate - Right	87.88	95.24
Caudate - Left	93.94	90.48

Table 11 (b): Table showing Hypometabolism in low attention score and high attention score patient groups in Language and Fluency domain

Cortical Areas studied in Language and Fluency Domain	Low Language & Fluency Score Group (% showing Hypometabolism)	High Language & Fluency Score Group (% showing Hypometabolism)
Frontal Association - Rt	84.09	60.00
Frontal Association - Lt	93.18	70.00
Temporal Association - Rt	75.00	90.00
Temporal Association - Lt	77.27	90.00
Parietal Association – Rt	79.55	90.00
Parietal Association – Lt	93.18	80.00

Table 11 (c): Table showing Hypometabolism in low attention score and high attention score patient groups in Memory domain

Cortical Areas studied in Memory	Low Memory Score Patient Group (% showing Hypometabolism)	High Language Score Patient Group (% showing Hypometabolism)
Anterior Cingulate – Rt - Grp	90.32	86.96
Anterior Cingulate – Lt - Grp	87.10	82.61

Table 12: ROI Areas and comparisons between patients and controls on the two sides of hemisphere

ROI	Left/Right	Peak-level (T- Value)	Peak-level (P Uncorr)	MNI Coordinates		
				x	y	z
Brocas Area	Left	9.65	<0.001	-32	24	6
	Right	8.3	<0.001	33	24	6
Cingulate gyrus	Left	8.06	<0.001	-3	-26	42
	Right	7.59	<0.001	2	-51	27
DLPFC	Left	6.92	<0.001	-42	2	30
	Right	4.83	<0.001	8	45	18
Frontal Eye Fields	Left	4.27	<0.001	-5	35	54
	Right	4.1	<0.001	26	21	53
Hippocampus	Left	7.24	<0.001	-33	-14	-12
	Right	7.74	<0.001	20	-33	-2
Inferior ParietalLobule	Left	6.29	<0.001	-51	-24	14
	Right	6.92	<0.001	56	-47	24
Nucleus Accumbens	Left	7.01	<0.001	-18	6	-15
	Right	7.39	<0.001	15	6	-15
Occipital Eye Fields	Left	6.7	<0.001	-15	-56	0
	Right	5.35	<0.001	14	-56	3
Superior ParietalLobule	Left	6.75	<0.001	-2	-54	35
	Right	6.5	<0.001	3	-69	30
Uncus	Left	7.45	<0.001	-26	6	-21
	Right	7.95	<0.001	26	8	-21
Wernicke's Area	Left	6.26	<0.001	-53	-30	5
	Right	7.79	<0.001	62	-27	-2

15. BIBILOGRAPHY

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1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013
2. Alzheimer's Disease International. Policy Brief for G8 Heads of Government. The Global Impact of Dementia 2013-2050. London: Alzheimer's Disease International; 2013.
3. Das SK, Pal S, Ghosal MK. Dementia: Indian scenario. Neurology India. 2012 Nov 1;60(6):618.
4. Mesulam M. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Annals of neurology. 1990 Nov 1;28(5):597-613.
5. Grossman M, Irwin DJ. The mental status examination in patients with suspected dementia. CONTINUUM: Lifelong Learning in Neurology. 2016 Apr;22(2 Dementia):385.
6. Catani M, Ffytche DH. The rises and falls of disconnection syndromes. Brain. 2005 Sep 1;128(10):2224-39.
7. Catani M, Howard RJ, Pajevic S, Jones DK. Virtual in vivo interactive dissection of white matter fasciculi in the human brain. Neuroimage 2002; 17: 77–94.
8. Wernicke K. Some new studies on aphasia. Fortschr Med 1885; 824–30. Translated in: Eling P, editor. Reader in the history of aphasia. Vol. 4. Amsterdam: John Benjamins; 1994. p. 90–98.
9. Wernicke K. The aphasia symptom-complex. 1874. Breslau, Cohn and Weigert. Translated in: Eling P, editor. Reader in the history of aphasia. Vol. 4. Amsterdam: John Benjamins; 1994. p. 69–89.
10. Lissauer H. Ein Fall von Seelenblindheit nebst einem Beitrage zur Theorie derselben. Arch Psychiat Nervenkr 1890; 21: 222–70.
11. Liepmann H. Das Krankheitsbild der Apraxie (motorische Asymbolie) auf Grund eines Falles von einseitiger Apraxie. Monatssch Psychia Neurol 1900; 8: 15–44, 102–32, 182–97.

12. Déjerine J. Sur un cas de cécité verbale avec agraphie suivi d'autopsie. Mémoires de la Société de Biologie. 1891;3:197-201.

13. Déjerine J. Contribution à l'étude anatomopathologique et clinique des différents variétés de cécité verbale. Mémoires de la Société de Biologie. 1892;4:61-90.

14. Luria AR. Higher cortical functions in man. New York: Basic Books Inc.; 1980.

15. Geschwind N. The paradoxical position of Kurt Goldstein in the history of aphasia. Cortex 1964; 214–224. Reprinted in: Devinsky O, Schacter SC, editors. Norman Geschwind: selected publications on language, behavior and epilepsy. Boston: Butterworth–Heinemann; 1997. p. 53–61.

16. Geschwind N. Disconnexion syndromes in animals and man. I. Brain 1965a; 88: 237–94.

17. Geschwind N. Disconnexion syndromes in animals and man. II. Brain 1965b; 88: 585–644.

18. Damasio AR, Damasio H. The anatomic basis of pure alexia. Neurology 1983; 33: 1573–83.

19. Damasio AR, Geschwind N. The neural basis of language. Annu Rev Neurosci 1984; 7: 127–47.

20. Damasio AR, Galaburda A. Norman Geschwind. Arch Neurol 1985; 42: 500–4.

21. Mesulam MM. A cortical network for directed attention and unilateral neglect. Ann Neurol 1981; 10:309–25.

22. Mesulam MM. Human brain cholinergic pathways. Prog Brain Res 1990a; 84: 231–41.

23. Mesulam MM. From sensation to cognition. Brain 1998; 121: 1013–52. Mesulam MM. Primary progressive aphasia. Ann Neurol 2001; 49: 425–32.

24. Catani M, Mesulam M. The arcuate fasciculus and the disconnection theme in language and aphasia: history and current state. cortex. 2008 Sep 1;44(8):953-61.

25. Welch K, StucervilleP. Experimental production of unilateral neglect in monkeys. Brain 1958;81:341-347

26. Heilman KM, Pandya DN, Geschwind N. Trimodal inattention following parietal lobe ablations. Trans Am Neurol Assoc 1970;95:259-261

27. Daffner K, Ahern G, Weintraub S, Mesulam M-M. Dissociated neglect behavior following sequential strokes to the right hemisphere. Ann Neurol 1990;28:97-101

28. Spiers P, Schomer D, Blume H, et al. Visual neglect during intracarotid Amytal testing. Neurology 1990; (in press)

29. Mesulam M-M, Van Hoesen GW, Pandya DN, Geschwind N. Limbic and sensory connections of the inferior parietal lobule (Area PG) in the rhesus monkey: a study with a new method for horseradish peroxidase histochemistry. Brain Res 1977; 136:393-414

30. Wurtz RH, Goldberg ME. Activity of superior colliculus in behaving monkey. 111. Cells discharging before eye movement. J Neurophysiol 1972;35:575-585

31. Barbas H, Mesulam M-M. Organization of afferent input to subdivisions of area 8 in the rhesus monkey. J Comp Neurol 1981;200:407-43 1

32. Seltzer B, Pandya D N . Converging visual and somatic sensory input to the intrapariecal sulcus of the rhesus monkey. Brain Res 1980;192:339-3 51

33. Wise SP, Desimone R. Behavioral neurophysiology: insights into seeing and grasping. Science 1988;242:736-741

34. Selemon LD, Gohhnm-Rakic PD. Common cortical and sub- cortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distrib- uted neural network subserving spatially guided behavior. J Neurosci 1988;8:4049-4068

35. Geschwind N. Language and the brain. Sci Am 1972;226: 76-83.

36. Lichtheim L. On aphasia. Brain, 7: 433–484, 1885.

37. Kljajevic V. White matter architecture of the language network. Translational Neuroscience. 2014 Dec 1;5(4):239-52.

38. Rauschecker J.P., Tian B., Mechanisms and streams for processing of “what“ and “where” in auditory cortex, Proc. Natl. Acad. Sci USA, 2000, 97, 11800-11806

39. Hickok G., Poeppel D., Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language, Cognition, 2004, 92, 67-99

40. Damasio H , Damasio AR. The anatomical basis of conduction aphasia. Brain 1980;103:337-350

41. Naeser MA. Quantitative approaches to computerized tomog- raphy in behavioral neurology. In: Mesulam M-M, ed. Principles of Behavioral Neurology. Philadelphia: FA Davis, 1985: 363-383

42. Mesulam M-M. Patterns in behavioral neuroanatomy. In: Mesulam M-M, ed. Principles of Behavioral Neurology. Philadelphia: FA Davis, 1985:l-70

43. Mohr JP, Pessin MS, Finkelstein S, et al. Broca aphasia:patho- logical and clinical. Neurology 1978;28:311-324

44. Goodglass H. Linguistic aspects of aphasia. Trends Neurosci 1983;6:241-243 ,

45. Lesser RP, Luders H, Dinner DS, et al. The location of speech and writing functions in the frontal language area. Brain 1984;107:275-291

46. Oishi K., Faria A., van Zijl P.C.M., Mori S., MRI atlas of human white matter, Elsevier, Amsterdam, The Netherlands, 2011

47. Schmahmann J.D., Pandya D.N., Wang R., Dai G., D'Arceuil H.E., de Crespigny A.J. et al., Association fiber pathways of the brain: parallel observation from diffusion spectrum imaging and autoradiography, Brain, 2007, 130, 630-653

48. Makris N., Pandya D.N., The extreme capsule in humans and rethinking of the language circuitry, Brain Struct. Funct., 2009, 213, 343-358

49. Petrides M., Pandya D.N., Neural circuitry underlying language, In: Marie□n P., Abutalebi, J. (Eds.), Neuropsychological research, Psychology Press, New York, NY, USA, 2008, 25-50

50. Petrides M., Pandya D.N., Association ber pathways to the frontal cortex from the superior temporal region in the rhesus monkey, J. Comp. Neurol., 1988, 273, 52-66

51. Schmahmann J.D., Smith E.E., Eichler F.S., Filley C.M., Cerebral white matter. Neuroanatomy, clinical neurology, and neurobehavioral correlates, Ann. NY Acad. Sci., 2008, 1142, 266-309

52. Makris N., Preti M.G., Asami T., Pelavin P., Campbell B., Papadimitriou G.M., et al., Human middle longitudinal fascicle: variations in patterns of anatomical connections, Brain Struct. Funct., 2013, 218, 951-968

53. Turken A.U., Dronkers N.F., The neural architecture of the language comprehension network: converging evidence from leasion and connectivity analyses, Front. Syst. Neurosci., 2011, 5, 1-20

54. Gil-Robles S., Carvallo A., del Mar Jimenez M., Caicoya A.G., Martinez R., Ruiz-Ocana C., et al., Double dissociation between visual recognition and picture naming: a study of the visual language connectivity using tractography and brain stimulation, Neurosurgery, 2013, 72, 678-686

55. Mandonnet E., Nouet A., Gatignol P., Cappelle L., Du au H., Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study, Brain, 2007, 130, 623-629

56. Kier L.E., Staib H.L., Davis L.M., Bronen R.A., MR imaging of the temporal stem: anatomic dissection tractography of the uncinate fasciculus, inferior occipito-frontal fasciculus, and Meyer's loop of the optic radiation, Am. J. Neuroradiol., 2004, 25, 677-691

57. Duffau H., Gatignol P., Mandonnet E., Peruzzi P., Tzourio-Mazoyer N., Capelle L., New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations, Brain, 2005, 128, 797-810

58. Duffau H., The anatomo-functional connectivity of language revisited. New insights provided by electrostimulation and tractography, Neuropsychologia, 2008, 46, 927-934

59. Duffau H., Moritz-Gasser S., Mandonett E., A re-examination of neural basis of language processing: proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming, Brain Lang., 2014, 131, 1-10

60. Dick A.S., Bernal B., Tremblay P., The language connectome: new pathways, new concepts, Neuroscientist, 2013, Epub ahead of print, DOI: 10.1177/1073858413513502

61. Lemaire J.-J., Golby A., Wells W.M.3rd, Pujol S., Tie Y., Rigolo L., et al., Extended Broca's area in the functional connectome of language in adults: combined cortical and subcortical single- subject analysis using fMRI and DTI tractography, Brain Topogr., 2013, 26, 428-441

62. Kinoshita M., Shinohara H., Hori O., Ozaki N., Ueda F., Nakada M., et al., Association fibers connecting the Broca center and the lateral superior frontal gyrus: a microsurgical and tractography anatomy, J. Neurosurg., 2012, 116, 323-330

63. Gloor P, Olivier A, Quesney LF, et al. The role of the limbic system in experiential phenomena of temporal lobe epilepsy. Ann Neurol 1982;12:129-144

64. Halgren E, Babb TL, Crandall P H . Activity of human hip- pocampal formation and amygdala neurons during memory testing. Electroencephalogr Clin Neurophysiol 1978;45:585- 601

65. Bauer RM. Autonomic recognition of names and faces in prosopagnosia: a neuropsychological application of the guilty knowledge test. Neuropsychologia 1984;22:457-469

66. Tranel D, Damasio AR. Autonomic recognition of familiar faces by prosopagnosiacs: evidence for knowledge without awareness. Neurology 1985;35:119- 120

67. Catani M, Jones DK, ytche DH (2005) Perisylvian language networks of the human brain. Ann Neurol 57: 8–16

68. Fernandez-Miranda JC, Rhoton AL Jr, Alvarez-Linera J, Kakizawa Y, Choi C, de Oliveira EP (2008) three-dimensional microsurgical and tractographic anatomy of the white matter of the human brain. Neurosurgery 62 (Suppl 3): 989–1026

69. Glasser MF, Rilling JK (2008) DTI tractography of the human brain's language pathways. Cereb Cortex 18: 2471–2482

70. Powell HW, Parker GJ, Alexander DC, Symms MR, Boul- by PA, Wheeler-Kingshott CA, Barker GJ, Noppeney U, Koepp MJ, Duncan JS (2006) Hemispheric asymmetries in language-related pathways: a combined functional MRI and tractography study. Neuroimage 32: 388–399

71. Catani M, Jones DK, Donato R, Ffytche DH (2003) Occipito-temporal connections in the human brain. Brain 129: 2093–2107

72. Fernandez-Miranda JC, Rhoton AL Jr, Kakizawa Y, Choi C, Alvarez-Linera J (2008) e claustrum and its projection system in the human brain: a microsurgical and tractographic anatomical study. J Neurosurg 108: 764–774

73. Wu Y, Sun D, Wang Y, Wang Y. Subcomponents and connectivity of the inferior fronto-occipital fasciculus revealed by diffusion spectrum imaging fiber tracking. Frontiers in neuroanatomy. 2016 Sep 23;10:88.

74. Ebeling U, von Cramon D (1992) Topography of the uncinate fascicle and adjacent temporal ber tracts. Acta Neurochir (Wien) 115: 143–148

75. Rhoton AL Jr (2002) The cerebrum. Neurosurgery 51(Suppl 1): 1–51

76. Tu□re U, Yasargil MG, Friedman AH, Al-Mefty O (2000) Fiber dissection technique: lateral aspect of the brain. Neurosurgery 47: 417–426

77. Y Yu C, Zhou Y, Liu Y, Jiang T, Dong H, Zhang Y, Walter M. Functional segregation of the human cingulate cortex is confirmed by functional connectivity based neuroanatomical parcellation. Neuroimage. 2011 Feb 14;54(4):2571-81.

78. Miller BL, Cummings JL, editors. The human frontal lobes: Functions and disorders. Guilford Publications; 2017 Oct 4.

79. Kiernan JA. Anatomy of the temporal lobe. Epilepsy research and treatment. 2012;2012..

80. Vingerhoets G. Contribution of the posterior parietal cortex in reaching, grasping, and using objects and tools. Frontiers in psychology. 2014 Mar 5;5:151.

81. Shomstein S. Cognitive functions of the posterior parietal cortex: top-down and bottom-up attentional control. Frontiers in integrative neuroscience. 2012 Jul 4;6:38.

82. Salgado S, Kaplitt MG. The nucleus accumbens: a comprehensive review. Stereotactic and functional neurosurgery. 2015;93(2):75-93

83. Snell RS. Clinical neuroanatomy. Lippincott Williams & Wilkins; 2010: Page 292

84. Freitas S, Simoes MR, Alves L, Vicente M, Santana I. Montreal Cognitive Assessment (MoCA): validation study for vascular dementia. Journal of the International Neuropsychological Society. 2012 Nov;18(6):1031-40.

85. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005 Apr 1;53(4):695-9.

86. Tsai CF, Lee WJ, Wang SJ, Shia BC, Nasreddine Z, Fuh JL. Psychometrics of the Montreal Cognitive Assessment (MoCA) and its subscales: validation of the Taiwanese version of the MoCA and an item response theory analysis. International Psychogeriatrics. 2012 Apr;24(4):651-8

87. Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR. Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. Dementia and geriatric cognitive disorders. 2013;36(3-4):242-50.

88. Matias-Guiu JA, Cortés-Martínez A, Valles-Salgado M, Rognoni T, Fernández-Matarrubia M, Moreno-Ramos T, Matías-Guiu J. Addenbrooke's cognitive examination III: diagnostic utility for mild cognitive impairment and dementia and correlation with standardized neuropsychological tests. International psychogeriatrics. 2017 Jan;29(1):105-13.

89. Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. Neurology. 2000 Dec 12;55(11):1613-20.

90. W Wechsler, David (1939). The measurement of adult intelligence. Baltimore: Williams & Wilkins. p. 229

91. Gonçalves C, Pinho MS, Cruz V, Gens H, Oliveira F, Pais J, Rente J, Santana I, Santos JM. Portuguese version of Wechsler Memory Scale–3rd edition's utility with demented elderly adults. Applied Neuropsychology: Adult. 2017 May 4;24(3):212-25.

92. Adishesa MS, Halim MS. Diagnostic Utility of the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV) Among Elders with Alzheimer's Dementia. ANIMA Indonesian Psychological Journal. 2015 Oct 25;31(1):14-21.

93. CANGÖZ B, Demirci S, Uluc S. TRAIL MAKING TEST: PREDICTIVE VALIDITY STUDY ON TURKISH PATIENTS WITH ALZHEIMER DEMENTIA. Turkish Journal of Geriatrics/Türk Geriatri Dergisi. 2013 Jan 1;16(1)

94. Campanholo KR, Romão MA, Machado MD, Serrao VT, Coutinho DG, Benute GR, Lucia MC. Performance of an adult Brazilian sample on the Trail Making Test and Stroop Test. Dementia & Neuropsychologia. 2014 Mar;8(1):26-31.

95. Powell JB, Cripe LI, Dodrill CB. Assessment of brain impairment with the Rey Auditory Verbal Learning Test: A comparison with other neuropsychological measures. Archives of Clinical Neuropsychology. 1991 Jan 1;6(4):241-9.

96. Catani M, Dell'Acqua F. Mapping white matter pathways with diffusion imaging tractography: focus on neurosurgical applications. In Brain Mapping 2011 (pp. 61-75). Springer, Vienna.

97. L e Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S et al (2001) Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging 13: 534–546

98. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics. 2007 Jul 1;4(3):316-29.

99. Meyer P, Feldkamp H, Hoppstädter M, King AV, Frölich L, Wessa M, Flor H. Using voxel-based morphometry to examine the relationship between regional brain volumes and memory performance in amnestic mild cognitive impairment. Frontiers in behavioral neuroscience. 2013 Jul 23;7:89.

100. Head D, Buckner RL, Shimony JS, et al. Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. Cereb Cortex. 2004;14(4):410–23.

101. Tighe SK, Oishi K, Mori S, et al. Diffusion tensor imaging of neuropsychiatric symptoms in mild cognitive impairment and Alzheimer's dementia. J Neuropsychiatry Clin Neurosci. 2012;24(4):484–8.

102. Gold BT, Powell DK, Andersen AH, Smith CD. Alterations in multiple measures of white matter integrity in normal women at high risk for Alzheimer's disease. NeuroImage. 2010;52(4):1487–94.

103. Salat DH, Tuch DS, van der Kouwe AJ, et al. White matter pathology isolates the hippocampal formation in Alzheimer's disease. Neurobiol Aging. 2010;31(2):244–56.

104. Rogalski E, Stebbins GT, Barnes CA, et al. Age-related changes in parahippocampal white matter integrity: a diffusion tensor imaging study. Neuropsychologia. 2012;50(8):1759–65.

105. Agosta F, Pievani M, Sala S, et al. White matter damage in Alzheimer disease and its relationship to gray matter atrophy. Radiology. 2011;258(3):853–63.

106. Mahoney CJ, Simpson IJ, Nicholas JM, Fletcher PD, Downey LE, Golden HL, Clark CN, Schmitz N, Rohrer JD, Schott JM, Zhang H. Longitudinal diffusion tensor imaging in frontotemporal dementia. Annals of neurology. 2015 Jan 1;77(1):33-46.

107. Galantucci S, Tartaglia MC, Wilson SM, Henry ML, Filippi M, Agosta F, Dronkers NF, Henry RG, Ogar JM, Miller BL, Gorno-Tempini ML. White matter damage in primary progressive aphasias: a diffusion tensor tractography study. Brain. 2011 Jun 11;134(10):3011-29.

108. Kljajevic V. White matter architecture of the language network. Translational Neuroscience. 2014 Dec 1;5(4):239-52.

109. Kantarci K, Senjem ML, Avula R, Zhang B, Samikoglu AR, Weigand SD, Przybelski SA, Edmonson HA, Vemuri P, Knopman DS, Boeve BF. Diffusion tensor imaging and cognitive function in older adults with no dementia. Neurology. 2011 Jul 5;77(1):26-34

110. Posner MI, Sheese BE, Odludaş Y, Tang Y. Analyzing and shaping human attentional networks. Neural networks. 2006 Nov 1;19(9):1422-9.

111. Petersen SE, Posner MI. The attention system of the human brain: 20 years after. Annual review of neuroscience. 2012 Jul 21;35:73-89

112. Niogi SN, Mukherjee P, Ghajar J, McCandliss BD. Individual differences in distinct components of attention are linked to anatomical variations in distinct white matter tracts. Frontiers in neuroanatomy. 2010 Feb 22;4:2.

113. McDonald CR, Ahmadi ME, Hagler DJ, Tecoma ES, Iragui VJ, Gharapetian L, Dale AM, Halgren E. Diffusion tensor imaging correlates of memory and language impairments in temporal lobe epilepsy. Neurology. 2008 Dec 2;71(23):1869-76.

114. Douet V, Chang L. Fornix as an imaging marker for episodic memory deficits in healthy aging and in various neurological disorders. Frontiers in aging neuroscience. 2015 Jan 14;6:343.

115. Brown RK, Bohnen NI, Wong KK, Minoshima S, Frey KA. Brain PET in suspected dementia: patterns of altered FDG metabolism. Radiographics. 2014 May;34(3):684-701.

116. Kawasaki K, Ishii K, SaitoY, Oda K, KimuraY, Ishiwata K. Influence of mild hyperglycemia on cerebral FDG distribution patterns calculated by statistical parametric mapping. Ann Nucl Med 2008;22(3):191–200

117. Brown, Richard KJ, et al. "Brain PET in suspected dementia: patterns of altered FDG metabolism." *Radiographics* 34.3 (2014): 684-701.

118. Shivamurthy, Veeresh KN, et al. "Brain FDG PET and the diagnosis of dementia." *American Journal of Roentgenology* 204.1 (2015): W76-W85.

119. Kawasaki K, Ishii K, Saito Y, Oda K, Kimura Y, Ishiwata K. Infuence of mild hyperglycemia on cerebral FDG distribution patterns calculated by statistical parametric mapping. Ann Nucl Med 2008;22(3):191–200.

120. Foster NL, VanDerSpek AF, Aldrich MS, et al. The effect of diazepam sedation on cerebral glucose metabolism in Alzheimer's disease as measured using positron emission tomography. J Cereb Blood Flow Metab 1987;7(4):415–420.

121. Del Sole A, Clerici F, Chiti A, et al. Individual cerebral metabolic deficits in Alzheimer's disease and amnestic mild cognitive impairment: an FDG PET study. Eur J Nucl Med Mol Imaging 2008;35 (7):1357–1366

122. Ishii K, Kono AK, Sasaki H, et al. Fully automatic diagnostic system for early- and late-onset mild Alzheimer's disease using FDG PET and 3D-SSP. Eur J Nucl Med Mol Imaging 2006;33(5):575–583.

123. Diehl-Schmid J, Grimmer T, Drzezga A, et al. Decline of cerebral glucose metabolism in fronto-temporal dementia: a longitudinal 18F-FDG-PET study. Neurobiol Aging 2007;28(1):42–50.

124. Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, Barbas NR, DeCarli CS, Scott Turner R, Koeppe RA, Higdon R, Minoshima S. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain. 2007 Aug 18;130(10):2616-35.

125. Imamura T, Ishii K, Sasaki M, et al. Regional cerebral glucose metabolism in dementia with Lewy bodies and Alzheimer's disease: a comparative study using positron emission tomography. Neurosci Lett 1997;235(1-2):49–52.

126. Black S, Gao F, Bilbao J. Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. Stroke 2009;40 (3 suppl):S48–S52.

127. Herholz K, Carter SF, Jones M. Positron emission tomography imaging in dementia. Br J Radiol 2007;80(Spec No 2):S160–S167.

128. Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. NeuroImage, 38, 95–113.

129. Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—The methods. NeuroImage, 11, 805–821.

130. Ashburner, J., & Friston, K. (1997). Multimodal image coregistration and partitioning—A unified framework. NeuroImage, 6, 209–217.

131. Ashburner, J., & Friston, K. J. (1999). Nonlinear spatial normalization using basis functions. Human Brain Mapping, 7, 254–266.

132. Rajapakse, J. C., Giedd, J. N., & Rapoport, J. L. (1997). Statistical approach to segmentation of single-channel cerebral MR images. IEEE Transactions on Medical Imaging, 16, 176–186

133. Hartley T, Harlow R. An association between human hippocampal volume and topographical memory in healthy young adults. Frontiers in human neuroscience. 2012 Dec 31;6:338.

134. Leube DT, Weis S, Freymann K, Erb M, Jessen F, Heun R, Grodd W, Kircher TT. Neural correlates of verbal episodic memory in patients with MCI and Alzheimer's disease—a VBM study. International journal of geriatric psychiatry. 2008 Nov 1;23(11):1114-8.

135. Taylor, M. J. & Heaton, R. K. (2001). Sensitivity and specificity of WAIS–III / WMS–III demographically corrected factor scores in neuropsychological assessment. Journal of the International Neuropsychological Society, 7, 867–874

136. Mathew G, Thomas S, Pretesh RK, Arvind K. Screening for dementia using picture memory impairment screen among older adults in an urban underprivileged area of Bangalore city, India. International Journal Of Community Medicine And Public Health. 2018 Mar 23;5(4):1575-9.

137. De Jager CA, Joska JA, Hoffman M, Borochowitz KE, Combrinck MI. Dementia in rural South Africa: A pressing need for epidemiological studies. SAMJ: South African Medical Journal. 2015 Mar;105(3):189-90.

138. Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. New England Journal of Medicine. 2016 Feb 11;374(6):523-32.

139. Doblhammer G, Fink A, Zylla S, Willekens F. Compression or expansion of dementia in Germany? An observational study of short-term trends in incidence and death rates of dementia between 2006/07 and 2009/10 based on German health insurance data. Alzheimer's research & therapy. 2015 Dec;7(1):66.

140. Matthews FE, Stephan BC, Robinson L, Jagger C, Barnes LE, Arthur A, Brayne C, Collaboration AS, Comas-Herrera A, Wittenberg R, Dening T. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. Nature communications. 2016 Apr 19;7:11398.

141. Lobo A, Saz P, Marcos G, Dia JL, De-la-Camara C, Ventura T, Montañes JA, Lobo-Escolar A, Aznar S, ZARADEMP Workgroup. Prevalence of dementia in a southern European population in two different time periods: the ZARADEMP Project. Acta Psychiatrica Scandinavica. 2007 Oct;116(4):299-307.

142. Rodriguez FS, Aranda MP, Lloyd DA, Vega WA. Racial and Ethnic Disparities in Dementia Risk among Individuals with Low Education. The American Journal of Geriatric Psychiatry. 2018 May 23.

143. Xu W, Tan L, Wang HF, Tan MS, Tan L, Li JQ, Zhao QF, Yu JT. Education and risk of dementia: dose-response meta-analysis of prospective cohort studies. Molecular neurobiology. 2016 Jul 1;53(5):3113-23.

144. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, Weintraub D. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2009 Nov 24;73(21):1738-45.

145. Matías-Guiu JA, Valles-Salgado M, Rognoni T, Hamre-Gil F, Moreno-Ramos T, Matías-Guiu J. Comparative diagnostic accuracy of the ACE-III, MIS, MMSE, MoCA, and RUDAS for screening of Alzheimer Disease. Dementia and geriatric cognitive disorders. 2017;43(5-6):237-46.

146. Tierney MC, Moineddin R, McDowell I. Prediction of all-cause dementia using neuropsychological tests within 10 and 5 years of diagnosis in a community-based sample. Journal of Alzheimer's Disease. 2010 Jan 1;22(4):1231-40.

147. A Ashendorf L, Jefferson AL, O'Connor MK, Chaisson C, Green RC, Stern RA. Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. Archives of Clinical Neuropsychology. 2008 Mar 1;23(2):129-37.

148. Zhao Q, Guo Q, Liang X, Chen M, Zhou Y, Ding D, Hong Z. Auditory verbal learning test is superior to rey-osterrieth complex figure memory for predicting mild cognitive impairment to Alzheimer's disease. Current Alzheimer Research. 2015 Jul 1;12(6):520-6.

149. French BM, Dawson MR, Dobbs AR. Classification and staging of dementia of the Alzheimer type: a comparison between neural networks and linear discriminant analysis. Archives of Neurology. 1997 Aug 1;54(8):1001-9.

150. Fletcher JM, Rice WJ, Ray RM. Linear discriminant function analysis in neuropsychological research: Some uses and abuses. Cortex. 1978 Dec 1;14(4):564-77.

151. Corballis,M.C.(2009).Theevolution and genetics of cerebral asymmetry. *Philos.Trans.R.Soc.Lond.BBiol.Sci.* 364,867–879.

152. Hardyck C, Petrinovich LF, Goldman RD. Left-handedness and cognitive deficit. Cortex. 1976 Sep 1;12(3):266-79.

153. Aggleton,J.P.,Vann,S.D.,Oswald,C.J.,andGood,M.(2000).Identifying cortical inputs to the rat hippocampus that subserve allocentric spatial processes: a simple problem with a complex answer. *Hippocampus* 10, 466–474. doi:10.1002/10981063(2000)10:4<466::AID-HIPO13>3. 0.CO;2-Y

154. Zahr,N.M., Rohlfing,T.,Pfefferbaum,A.,and Sullivan,E.V.(2009). Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study. *Neuroimage* 44,1050 1062.doi:10.1016/j.neuroimage.2008.09.046

155. Fletcher,E.,Raman,M.,Huebner,P.,Liu,A.,Mungas,D.,Carmichael,O.,etal. (2013). Loss of fornix white matter volume as a predictor of cognitive impairment in cognitively normal elderly individuals. *JAMANeurol*.70,1389–1395. doi:10.1001/jamaneurol.2013.3263

156. Douet V, Chang L. Fornix as an imaging marker for episodic memory deficits in healthy aging and in various neurological disorders. Frontiers in aging neuroscience. 2015 Jan 14;6:343.

157. Salmon E, Collette F, Degueldre C, Lemaire C, Franck G (2000) Voxel-based analysis of confounding effects of age and dementia severity on cerebral metabolism in Alzheimer's disease. Hum Brain Mapp 10:39–48

158. Rabinovici GD, Jagust WJ, Furst AJ, Ogar JM, Racine CA, Mormino EC, O'Neil JP, Lal RA, Dronkers NF, Miller BL, Gorno-Tempini ML (2008) A beta amyloid and glucose metabolism in three variants of primary progressive aphasia. Ann Neurol 64:388–401

159. Schroeter ML, Stein T, Maslowski N, Neumann J (2009) Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. Neuroimage 47:1196–1206

160. Frisch S, Dukart J, Vogt B, Horstmann A, Becker G, Villringer A et al (2013) Dissociating memory networks in early Alzheimer's disease and frontotemporal lobar degeneration—a combined study of hypometabolism and atrophy. PLoS One 8:e55251. doi:10.1371/journal.pone.0055251