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Essentials of Anatomy as Related to Alzheimer's disease: A Review

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Abstract

Alzheimer disease (AD) is the sixth leading cause of death, presently in America. AD is the centre of preoccupation of not only the scientific community, but also of the intelligentsia. The study of various structures of the brain, their connections and the pathways involved (anatomy), their normal functioning (physiology) and how this is subverted, leading to AD (pathology and pathogenesis), is vital to understanding comprehensively the complete gamut of clinical features of the Alzheimer disease. The anatomical structures, their connections and interplay, as implicated as having a role in AD, are briefly reviewed in this article. The functional significance with AD, of each structure is highlighted.

Keywords: Alzheimer disease; Limbic system; Hippocampal formation; Orbito-frontal cortex; Pre frontal cortex; Cingulate cortex

Introduction

Alzheimer's disease (AD) is a chronic, progressive, neuro-degenerative disease, with cognitive dysfunction and specific pathological changes, characterized by deposition of the Amyloid beta (Aβ or Abeta) and phosphorylated tau protein. Aβ is deposited in the extra cellular matrix of the nerve cells in the brain whereas the phosphorylated tau protein is deposited within the nerve cell. Being toxic, cause degeneration and death of neurons including the dendrites, axons and synapses. Gross anatomy of the structures involved shows, atrophy and loss of volume, leading to profound cognitive defect. The selectivity of involvement of the structures of the brain in AD is intriguing. While some anatomical areas are involved, the adjacent areas are spared. But, the fidelity with which these changes are reproduced in every case of AD makes the pattern, unique. This specific involvement of certain brain structures differentiates it from other neuro-degenerative diseases which also involve memory loss, like Pick's disease/Fronto-Temporal dementia (FTD), Huntington's chorea and Parkinson's disease, as well as the normal aging process. The variety of symptomatology of AD is explained by the extent, the degree of involvement of the brain structures and also is a function of time. Initially, at the stage of Mild Cognitive Impairment (MCI), the symptomatology is vague but as AD advances stage by stage, various structures are involved and a full-blown AD picture unveils itself. This article emphasises on the interconnections between the various structures Involved in AD and the contribution of each structure to the cognitive defect observed in AD.

Discussion

The structures involved in AD are shown in Table 1.

The limbic system

Location: The limbic system is located in the midbrain. It is between the neocortex and the sub-cortical lobe of cerebrum.

The parts of the limbic system: It is seen that more than half of the structures mentioned in the Table 1, belong to Limbic system. They are Hippocampus proper, Fornix, the Amygdala, the Dentate gyrus, Subicular cortex, the Septal nuclei, the Cingulate cortex, the Entorhinal cortex and the Perirhinal cortex

The hippocampus

Location: The hippocampus is located under the cerebral cortex in the allocortex [1,2].

Hippocampal Formation (HF) refers to the hippocampus proper (which includes the 4 CA fields), along with the dentate gurus, cingulate cortex and subiculum.

Functions: Consolidation of short-term memory to long-term memory and spatial memory.

The fields of the hippocampus [3]: The Hippocampus is devised into four regions called CA (Cornu Ammonis) fields. The hippocampus proper is divided into division CA1, CA2, CA3 and CA4 and is characterized by a narrow band of pyramidal cells [4].

The HC pathways

The perforant pathway: It connects the entorhinal cortex (EC) To all fields of the hippocampal formation [5].

1. **The temporo-ammonic or TA-CA1 pathway**: Connects EC directly to CA1. It mediates spatial memory and its consolidation.

S. no.	Structures in AD
1.	Hippocampus
2.	Parahipocampus
3.	Amygdala
4.	Cingulate cortex
5.	Medial septal nucleus
6.	Subiculum
7.	Nucleus basalis of Meynert
8.	Locus coeruleus
9.	Nucleus accumbens.
10.	Entorhinal cortex.
11.	Perirhinal cortex
12.	Orbito-frontal Cortex
13.	Prefrontal cortex.
14.	The raphe nuclei

Table 1: Structures involved in AD.

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2. **The mossy fibres pathway:** Connects DG (Dentate Gyrus) to CA3, pyramidal cells. CA3 is involved in encoding short-term memory [6].

3. **The schaffer pathway:** CA3 neurons from EC layer II send extensive connections within the region and also sends connections to Strata Radiatum and Oriens of ipsilateral and contralateral CA1, through this pathway [7].

4. **The commissural pathway:** Connects the hippocampal cortex of one lobe with the HC of the other lobe. It has role in the functions like memory integration of a variety of motor and perceptual functions and plays a significant role in the development of interhemispheric specialization.

5. **The trisynaptic pathway:** The perforant pathway -to-dentate gyrus-to-CA3-to-CA1 is called the Trisynaptic pathway or circuit. It's role is discussed elsewhere in this article.

The input HC pathways: Fibers from the cingulate cortex, Temporal lobe cortex, Amygdala, Orbital cortex and Olfactory bulb pass through the entorhinal cortex:

Fibers from Nucleus basalis of Meynert, Substantia innominata and septal nuclei. Pass through l through Pre-commissural branch of the fornix:

Fibers from the mammillary bodies of the hypothalamus. Pass through the post commissural branch.

Output paths of the HC:

- Subiculum (through Fornix and it's branch)
- Through pre commissural branch of the fornix: Septal nuclei, preoptic nuclei, ventral striatum, orbital cortex and anterior cingulate cortex.
- Anterior nucleus of the thalamus the mammillary bodies.
- Through the post commissural branch of the fornix.
- Completion of the circuit: The circuit is completed by the Papez circuit (Vide infra).

The Dentate Gyrus (DG): DG is an input part of HF. Along with Entorhinal cortex it is considered as site of neurogenesis and neural stem cell (NSC) formation. Neurogenesis contributes significantly to synaptic plasticity and cognitive function [8]. Till late in the course of the AD, DG resists plaque formation which is also attributed to NSC. DG is involved in learning and memory especially in encoding an retrieval stages.

Input: From entorhinal cortex (EC).

Output: C2 and C3 fields of HC (Mossy fibers).

Functions: It plays an important role in learning and memory as all sensory modalities, first impinge on DG.

The amygdala

Though considered as a part of HC, some researchers feel hat the amygdalae function independent of the limbic system. Major pathways and connections of Amygdala [9].

Amygdala is richly connected with many structures of the brain as listed below, but the functional significance of these connections to AD is not clear.

1. Through Ventral Amygdalo-fugal pathway**:** Nucleus accumbens, Anterior Olfactory nucleus, Orbital cortex, Cingulate Cortex, Prefrontal cortex, Septal area and the Hypothalamus.

2. Through Stria Terminalis: Septal area, Hypothalamus (Lateral & anterior) and contralateral Amygdala.

3. By direct connections to HC and EC, Thalamus ventromedial median (VM) and the brain stem.

Functions : It's role In emotions of fear and aggression and processing of related memories, is well recognised

The cingulate cortex

Cingulate gyrus (CG) over lies the corpus collosum. The cingulate cortex is divided into four functionally distinct regions [10].

- Anterior cingulate cortex (ACC)
- Midcingulate cortex
- Posterior cingulate cortex (PCC)
- Retrosplenial cortex
- Role played by the corresponding parts of CG
- Anterior CG is implicated in' reward and action' function ns. The Perigenual Anterior Cingulate Cortex (pACC) is mainly responsible for processing emotions and regulating the endocrine and autonomic responses to emotions [11].
- The posterior CG is implicated in processing of spatial orientation and memory.
- The Retrosplenial CG is implicated in memory retrieval, spatial navigation etc.

The connections of CG and their functional correlation [12].

- The CG has reciprocal connections with the structures with which it is connected.
- The projections of CG Are correlated with the known functions of the CG
- The Orbitofrontal Cortex (OFC), the basal ganglia and the insula-reward function.
- Lateral Prefrontal Cortex(LPFC)-executive control, working memory, learning and expression
- Locus Coeruleus (LC)-noradrenergic inputs to the rest of the brain
- Cortical supplementary eye fields-Attention and visual memory
- Primary and supplementary motor cortices,
- parietal premotor areas and projections to the spinal cord-control of behavior
- The posterior cingulate and retrosplenial cortex-link rewards with locations in space
- parahippocampal regions, storing and manipulating spatial representations

Afferents to the cingulate cortex: Association areas of the frontal, parietal and temporal lobes.

- The subiculum
- The septal nuclei
- The thalamic nuclei

Para Hippocampal Cortex (PHC): PHC is situated at the junction of hippocampus and fusiform cortex. It surrounds the hippocampus. Atrophy in the parahippocampal gyrus is suggested as an early biomarker of Alzheimer's disease [13].

Functions memory encoding and retrieval, Spatial navigation and attention.

The Parahippocampal Place Area (PPA) is responsible for encoding the memory of senes. Electrical stimulation of this place lead to visual hallu cinations of scenes [14].

The Entorhinal Cortex (EC)

The entorhinal cortex is a small structure embedded in the anterior temporal lobe. It is considered a gateway between HF and Neo Cortex. Entorhinal cortex is a site of early pathology in Alzheimer's Disease [15]. It's involvement is earlier than the involvement of the hippocampus, even at the stage of MCI. i t is implicated in memory, navigation and the perception of time. EC-hippocampus system plays an important role in declarative memories and in particular spatial memories.

The connections of EC: EC is divided into two divisions, lateral and medial EC. The lateral entorhinal Cortex, is strongly connected to the perirhinal Cortex, olfactory and insular Cortex and the amygdala [16]. The medial entorhinal Cortex preferentially connects with the Post-rhinal cortex, the pre-subiculum, visual association (occipital), Retr-splenial cortices.

The subiculum: It is the major output structure of the hippocampus.

Connections: Projections to various subcortical structures.

Divisions: It is divided into dorsal and ventral parts by some and as proximal and distal subiculum by others. Proximal subiculum receives, input from C3 area of HC and distal subiculum from the C1 area.

Functions of subiculum: Among the recognised functions are spatial navigation and in mnemonic processing. Also belied to play a role in temporal reinforced behaviour.

The perirhinal cortex

It is a medial temporal lobe structure represented by Brodmann areas 35 and 36. Perirhinal cortex is involved In declarative memory concerned with recognition of objects. for example AD patients fail to recognise even known faces which is thought to be due to involvement of Perirhinal cortex. The perirhinal cortex is involved in both visual perception and memory [17].

The perirhinal cortex is also involved in item memory, especially in coding familiarity or recency of items [18].

The Raphe nuclei: These are serotonergic neurons found at all levels of brainstem. They contain the neuro transmitter, serotonin. Through their projection to the fore brain structures, they influence the mood, emotion and behaviour of an individual. These changes as seen in some AD patients, is attributed to the malfunctioning of these nuclei.

The nucleus basalis (nucleus basalis of Meynert, nbM, nucleus basalismagnocellularis): They are basal forebrain brain Structure found in substantia innominata. The nuclei are rich in NT acetyl choline. They are implicated to have role in arousal, sustained attention and. Virtual visual perception They have widespread projection to the neocortex and other brain structures. The nbM was then found to be a cholinergic centre, with neurons providing cholinergic afferents to the entire neocortex [19,20]. The decrease in cortical acetylcholine levels seen in dementing disorders was thought to relate to cell death within the nbM.

The nucleus accumbens septi (NAcc)

These are a group of neurons present in the striatum. It is the source of important NTs like GABA, Glutamate, dopamine and serotonin. GABAB receptors have inhibitory control over turning behavior mediated by acetylcholine [21].

Glutamate: Studies have shown that local blockade of glutamatergic NMDA receptors in the NAcc core impaired spatial learning [22]. The dopamine and serotonin are involved in reward crcuit.

The connections of NAcc

Inputs pathways: It receives the Glutaminergic inputs are from prefrontal (PFC), basal amygdala, thalamus nuclei, Ventral Tegmental Area (VTA).

Output pathways: Basal ganglia and ventral pallidum(VP). The VP, in turn, projects to the medial dorsal nucleus of the dorsal thalamus, which projects to the prefrontal cortex as well as the striatum.

Functions: The NAcc is believed to influence the reward circuit through dopamine and serotonin, the former promoting the desire and the later, the inhibition of the desire and satiety.

The Locus Coeruleus (LC)

LC is a pontine nucleus that produces the stress hormone, norepinephrine(NE). NE has a priming action on neurons of reticular activating system, during stress. Arousal, sleep-wake cycle, memory, emotions and stress are all influenced by by the locus coeruleus [23]. LC together with it he target organs of NE it produces, is called locus coeruleus-noradrenergic system or LC-NA system [24]. NE that binds to alfa 2 receptors, increases the working me memory, but in excess, amounts it binds to alfa 1 receptors, it is inhibitory [25].

LC connections: projections of LC, include the following connection to Amygdala and Hippocampus, Brain stem and Spinal cord Cerebellum, Cerebral cortex Hypothalamus Tectum Thalamus,Ventral tegmental area [26].

LC receives input connections from The Medial Prefrontal Cortex (MFC) and Output connections to hippocampus and amygdala.

Functions of LC-NA System: Arousal, Cognitive control, behavioural flexibility and inhibition, attention and memory emotions, neuroplasticity, posture and balance [27,28].

The septal nuclei

These are subcortical nuclei. The septal nuclei are believed to play role in in behaviours (emotional, sexual and aggressive) and memory functions.

The afferents are from the HC, amygdala, the VTN, i and hypothalamic nuclei.

The efferents to the hippocampus and dentate gyrus, the medial dorsal nucleus of the thalamus and several hypothalamic nuclei.

The septo-hippocampal-septal pathway: Fbres of the medial septal/diagonal band of Broca's (MS/DB) area project to the hippocampus to form this pathway. These contain both Cholinergic and GABAergic fibres.

The hippocampus and the septum are reciprocally innervated The hippocampus receives both cholinergic and GABAergic fibers located in the MS/DB complex through the fimbria-fornix and terminate on the GABAergic fibres of the medial and the glutamatergic neurons of the lateral septum. It has a role in learning and memory.

The neurotransmitters influencing MS/DB area are shown in Table 2.

Area.	NT neurons
EC	Glutamatergic.
RN	Serotonergic
VTA	Dopaminergic
TMN	Histaminergic
LC	Adrenergic
EC: Entorhinal Cortex; RN: Raphe Nuclei; VTA: Ventral Tegmental Area; TMN: Tubulo-Mamiliary Nuclei; LC: The Locus Coeruleus	

Table 2: Neurotransmitters influencing MS/DB area.

The Prefrontal Cortex (PFC)

The front portion of frontal lobe is called PFC. PFC controls the short term memory especially, the executive functions like memory, attention, flexibility, planning, problem solving and decision making. Inferior PFC is the part most commonly effected in AD.

The Orbitofrontal Cortex (OFC)

The part of PFC above the orbital sockets is called OFC. It is implicated in impulse control and response inhibition as is the case with the PFC

Afferents of OFC: The PFC receives the afferents from the medial dorsal nucleus, insular cortex, entorhinal cortex, perirhinal cortex, hypothalamus and amygdala [16].

Efferents of OFC: The orbitofrontal cortex is reciprocally connected with the perirhinal and entorhinal cortices, the amygdala, the hypothalamus and parts of the medial temporal lobe [29].

Functions: It is implicated in impulse control and inhibition of behaviour. By virtue of its connection with amygdala, it plays important role in emotions.

Altered connectivity of OFC systems in the later stages of Alzheimer's Disease is suggested.

The Papez circuit

The Papez circuit goes through the following neural pathways:

Hippocampal formation(subiculum) → fornix → mammillary bodies → mammillothalamic tract → anterior thalamic nucleus → cingulum → entorhinal cortex → hippocampal formation.

The role of Papez circuit in AD: Alzheimer's disease patients have impaired memory and inability to learn new things. They recall the names of people, objects, etc. Problems with episodic memory are linked to damage in the Papez circuit. As a result of these adverse effects on episodic memory, damage to the Papez circuit can not only indicate/predict amnesia but also Alzheimer's in a patient.

Conclusion

The anatomy of all structures implicated in AD are discussed. Some of these structures have received more importance than others, at present. It is hoped that more research will throw light on some of the less understood structures as to their role in AD, in future.

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