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Physiological Basis of Memory Dysfunction in Alzheimer's Disease – An Overview

A. S. V. Prasad[1*]

[1]Department of Internal Medicine, G.I.T.A.M, Rishikonda, Visakhapatnam, India.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Alzheimer's disease (AD) is a neuro-degenerative disease, causing gradual decline in memory function in the affected patients. The loss of memory makes their existence miserable. It is first noticed and reported by the patient's care takers. The clinicians objectively assess the type and degree of the memory loss by a specific battery of tests, specially designed for the purpose (like Montreal Cognitive Assessment (MoCA) test., Mini-Mental State Exam (MMSE etc.)). Understanding the symptoms of AD, arising out of memory loss, requires deeper insights into what initiates the memory (the sensory inputs from the five sense organs), the different types of memories (explicit, implicit memories, their sub types and associative memory etc.), how the memory signals are modified at the level of the neuron, (analog to digital signals) and the synapse (sensitization, habituation and Long term potentiation / depression etc.), the processing that the inputs received , undergo (encoding, consolidation /organization, storage and retrieval) in higher brain centres (amygdala, hippocampus prefrontal vortex etc.) and also the role played by the various receptors (NMDA, AMPA and the kinase receptors), the neurotransmitters (acetylcholine, Norepineprine, Gama aminobutic acid, serotonin etc.), the central network systems involved (central executive network, salience network, and the default mode network). In short, it is the study all about, of the physiology of memory. The next step is to integrate this knowledge to interpret symptoms of patients with AD. Accordingly, the subject under discussion is dealt with in two parts. Firstly, how the memory is affected in AD and secondly the physiology behind these changes.

**Corresponding author: E-mail: drasv@ymail.com;*

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1. INTRODUCTION

Cognition and Memory:

Defective cognition is the hall mark of Alzheimer disease. Cognition is a multitasking functioning of the human brain. Cognition is "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses". The word comes from the Latin root 'cognoscer', which means "to know" Memory is but one aspect of cognition that encompasses other higher brain faculties like comprehension, contemplation, description, reasoning, judgement, planning and execution etc. There are many cognitive functions recognised like attention, perception, language and learning. Each of these cognitive functions have bearing on the memory. Leaning is a cognitive function with is the basis of forming memory. Memory is the process of acquiring new, or modifying existing, knowledge, behaviours, skills, values, or references [1]. What is thus learned is stored in the brain as *memory. Memory* defect nowadays has become synonymous to AD, though, it is a feature of other types of dementias as well. Obviously it is because AD is the foremost of the causes of dementia.

2. DISCUSSION

The discussion is considered under two parts.

- Memory changes as seen in patients of Alzheimer's disease
- The physiological basis of memory

Memory is the recording, retention and retrieval of knowledge gained from experience—facts that are known, events that are remembered, and skills that are gained and applied. Memory loss is the most conspicuous defect in AD. Alzheimer's disease (AD) typically destroys neurons and their connections in parts of the brain involved in memory, including the entorhinal cortex and hippocampus. It later affects areas in the cerebral cortex responsible for language (left inferior frontal lobe) reasoning, and social behaviour. Eventually, many other areas of the brain are damaged. (Alzheimer's Disease- NIH - National institute of aging). The initial stage of Alzheimer's is named as Minimal cognitive impairment (MCI). It causes a slight decline in cognitive abilities but the decline is not sufficient to interfere with daily activities [2]. People with MCI are more likely to develop AD or other dementias at a rate of approximately 10% to 10.5% per year [3]. It is reported. Holger Jahn et al, that even before this stage, the AD patient experiences Subjective cognitive impairment (feeling that something is not in order, without any objective evidence). The AD pt experiences inability to form new memories and Impaired retrieval of recent memories. Alzheimer's does not affect all types of memory alike. Short-term memory is the first to go; next comes episodic /autobiographical memory. Then semantic memory and finally procedural memory. As the disease advances, reasoning, attention, and language abilities are lost. Episodic memory/ executive functions in AD, like impaired planning, problem solving, and goal-directed behaviour. are associated with damage to frontal subcortical circuits (see below). Objectively speaking, Hypoosmia is the first objective sign in AD. Hypoosmia correlates with the beta amyloid (AB) plaque deposits in entorhinal cortex (EC). AD patients have impaired higher-order olfactory tasks involving specific cognitive processes [4]. In addition to subjective memory loss and hypoosmia, defective DMN & epileptic activity and sleep-wake cycle disturbances have also been reported in patients with AD by Holger Jahn et al. [5]. The memory changes can be correlated to certain anatomic structural changes in parts of the brain and metabolic changes in these areas. Even the baffling array of symptomatology is correlated to a particular type of memory.

2.1 Anatomical Correlation of Memory Changes in AD

The anatomical structures involved in AD are recently reviewed by this author [6].

Atrophy of cortical structures:

- There is loss in brain substance in regions involved in memory, emotional processing and salience brain networks, including the prefrontal, lateral temporal and parietal cortices, anterior cingulate gyrus, temporo-limbic structures and Starts in the entorhinal cortex and hippocampal formations, later spreading into other temporal, parietal, and finally frontal association cortices [7,8,9].

- Subcortical neuron loss occurs in the nucleus basalis of Meynert and the locus ceruleus, impairing the cholinergic and noradrenergic transmitter systems in the neocortex [10,11].
- Effect of myelinisation of neurons. Low or late myelinisation of neurons affects earlier in AD (like frontal and parietal lobes while hghly myelinated neurons are only affected in the final phases of the disease. many cognitive functions result from deficits in 3 key networks and their interactions with each other and other brain areas.

Reduction of volume of the structures of the brain:

- Reduced volume, of amygdala and hippocampus may predict which cognitively healthy elderly people will develop dementia over a six-year period [12] AMA and Archives Journals. "Reduced Brain Volume May Predict Dementia In Healthy Elderly People." Science Daily, 3 January 2006. The brain reserve hypothesis suggests that larger brain size is associated with a greater ability to tolerate pathological damage before showing any cognitive decline [13].
- AD patients with multiple neuropsychiatric manifestations showed more evident GM atrophy in the left superior temporal gyrus and insula as compared with healthy controls. In contrast, AD subjects with few neuropsychiatric symptoms displayed more GM atrophy in prefrontal regions, as well as in the dorsal anterior cingulate ad post-central gyri, as compared with healthy controls." [14].

2.2 Metabolic Correlation of Memory Loss

Individuals with insulin resistance, type 2 diabetes mellitus (T2D), hyperlipidaemia, obesity, or other metabolic disease have increased risk for the development of AD. Insulin ineffectiveness, hyperinsulinemia, insulin resistance and failure of insulin signalling system have profound effect on the memory function or dysfunction.

Obesity and memory:

1) Obesity decreases the size of the hippocampus and the decrease size of hippocampus is correlated with decline of memory.
2) The protein NLRP3 is a core component of the inflammasome complex in the fat, by promoting the production and release of interleukin-1 beta by fat cells, stokes the inflammation fire. This is confirmed in experiments on NLRP3. Knockout on mice and found the mice were protected against obesity-induced inflammation of the brain and the cognitive problems. Microglia have receptors for interleukin-1 beta, and the protein,. Which cause microglial dysfunction through the inflammatory process they cause and the microglial no longer plays the protective role.

Disturbed glucose haemostasis:

Cognitive testing revealed disturbed glucose homeostasis had significant that those with memory impairment compared to control subjects [15].

Insulin insufficiency:

This CNS insulin deficiency may potentially lead to impairments in memory, neuroprotective effects, synaptic transmission, as well as likely contributing to the development of neurodegenerative disease [16].

- **Hyperglycaemia**:

  Hyperglycaemia increases the number of mental subtraction errors in individuals with diabetes [17].
  Poor glycaemic control, as evidenced by high haemoglobin A1C levels, has been associated with low scores on neuropsychological testing [18].

- **Insulin resistance:**

  The PET scans detected, people with higher levels of insulin resistance used less blood sugar in areas of the brain most susceptible to Alzheimer's. When that happens, the brain has less energy to relay information and function, Willette said. Prolonged elevation of systemic insulin may ultimately lead to a dysfunction in insulin signalling [19]. This chronic elevation in peripheral insulin levels also impacts central insulin availability and function. Insulin's passage through the BBB is transporter-mediated (Banks et al., [20]). In a healthy state, an acute, transient rise in peripheral insulin leads to an

increase in CNS insulin, where it enters the brain. Chronic peripheral hyperinsulinemia leads to the down regulation of insulin transporters at the BBB, which in turn decreases the amount of insulin that may enter brain (Banks et al. [20]).

- **Failure of insulin signalling pathways:**

- **IRS 1, 2 Signalling pathways** connect insulin to two signal transduction pathways: The PI3K/Akt pathway, responsible for metabolic effects. The Ras/ERK pathway which modulates cell growth, survival, and gene expression (De Felice and Ferreira, 2014; Kleinridders et al., 2014). IRs are located in both neurons and glia (Abbott et al. 1999), with higher concentrations in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala, and septum—regions of strategic importance for cognition (Havrankova et al., 1978a,b)

  PI3K/Akt cascade which turn, targets multiple downstream pathways, including mTORC1, GSK3β, and the FoxO family of transcription factors

  1. **mTORC1**-mediated protein synthesis is important for synaptic plasticity (18) and the regulation of autophagy, a major mechanism to degrade misfolded proteins and damaged organelles in neurons .Dysregulation of mTORC1-dependent autophagy in neurons results in neuronal cell death and the onset of neurodegenerative diseases. **2. GSK3β** regulates neuroplasticity (GSK3β can also phosphorylate tau protein, a process involved in the pathogenesis of Alzheimer disease (AD). **3. FoxOs** controls energy homeostasis and leptin sensitivity.

- **Insulin/IGF-1 signalling:** Activates the Grb2-SOS-Ras-MAPK cascade, which contributes to the normal function and survival of neuronal cells Inhibition of MAPK has also been shown to block insulin and leptin stimulation of hypothalamic neuroprogenitor cells.

- **Central insulin action is associated with alterations in cognitive function in the brain.**

  1. Patients with type 2 diabetes have a higher rate and more rapid progression of AD [21]. 2. Imaging studies have demonstrated smaller hippocampi, as well as changes in the functional connectivity between regions of the brain. 3. Multiple rodent models of diabetes have memory impairment. 4. Central insulin infusion in rats significantly improves memory tasks, including performance in the passive avoidance task and Morris water maze [22,23].

- **Biochemical pathways:** There are a number of mechanisms through which dysglycemia can lead to cognitive dysfunction. Hyperglycaemia can lead to the activation of the polyol pathway, formation of advanced glycation end products, activation of protein kinase C, increased glucose shunting in the hexosamine pathway. it is also possible that the increase in reactive oxygen species (ROS) associated with these mechanisms are then, in-part, responsible for altered brain function.

Mitochondrial dysfunction: This association between metabolic disease and AD may in part be due to the systemic mitochondrial dysfunction that is common to these pathologies. Accumulating evidence suggests that mitochondrial dysfunction is a significant feature of AD and may play a fundamental role in its pathogenesis. This association may in part be due to the systemic mitochondrial dysfunction that is common to these pathologies. Accumulating evidence suggests that mitochondrial dysfunction is a significant feature of AD and may play a fundamental role in its pathogenesis.

- **Role of neuro transmitters:** In animal models, global alterations in functional neurotransmission have also been linked to hyperglycaemia, including abnormal N-methyl-D-aspartate (NMDA), acetylcholine, serotonin, dopamine and norepinephrine neurotransmission [24,25,26,27].

2.3 Pathological Correlation

Deposits of amyloid beta or its metabolites and hyper phosphorylated Tau protein are noticed in the areas of brain that subservient memory function. The biochemical aspects of these proteins are recently reviewed by this author [28].

2.4 Symptomatic Correlation

The patient of Alzheimer's disease exhibit a variety of symptomatology which stem from

various types of memory loss, considered in more detail below. Thus the patient has difficulty in day to day tasks. Forget where he kept his keys, forgets the names of persons and the relationship with them. They fail to recollect specific events like their marriage anniversary day or the context related to a particular event, for example what happened when they visited a particular place before. They are confused about time and date and place and may not find their destination. The fail to recognises faces or pictures and the names related to them. For example they may ask his or her spouse who he or she it is. The find difficult in finding right words and may become uncommunicative. They may suffer from hallucinations and delusions at some stage. The incidents relating to past may be better remember than recent events. It is said that the grand ma suffering from AD may tell the whole process as to how to make sweet but would ask who you are and where are the sweets or who made them, after some time. The varied symptomatology is due to loss of a particular type memory. The varies types of memory are shown in table 1 and a brief description of their role in the process of memory.

2.5 Cognitive Network Systems and Memory

Thomas et al. (2005) define the CN as a network with a cognitive process that can perceive current network conditions, plan, decide, act on those conditions, learn from the consequences of its actions, all while following end-to-end goals.

- **The central executive network,**
- **The salience network, and**
- **The default mode network**

- **The Central Executive Network (CEN):** The Fronto-parietal Central Executive Network (CEN) handles inhibition, task switching, and updating. It inhibits the default mode network, engages our conscious brain to think and maintains attention on a prioritized task. It's helpful to keep our mind from wandering during a goal directed task. [29] CEN), which connects dorsolateral prefrontal cortex and the posterior parietal cortex. supports the cognitive regulation of emotion, behaviour, and thought
- **The salience network (SN)** is primarily composed of the anterior insula (AI) and dorsal anterior cingulate cortex (dACC). It is involved in detecting and filtering salient stimuli, as well as in recruiting relevant functional networks [30], the SN contributes complex functions, including communication, social behaviour, and self-awareness through the integration of sensory, emotional, and cognitive information [31,32].
- **The default Mode Network:** The default mode network (DMN) is a network of interacting brain regions that is active when a person is not focused on the outside world, measurable with the fMRI technique.(Sport and Exercise Psychology Research, 2016). Areas of the brain included in the default mode network include the medial temporal lobe, the medial prefrontal cortex, and the posterior cingulate cortex, as well as the ventral precuneus and parts of the parietal cortex. All of these regions have been associated with some aspect of internal thought. **Coordination between CEN and DMN:** The switching between the CEN and DMN are coordinated by the Salience Network which, based on the amount of relevant outside stimulus triggers a switch out of REST mode into cognitive functioning.

2.6 Defective DMN in AD

Measurements of glucose metabolism with positron emission tomography (PET), structural atrophy with MRI, and intrinsic and task-evoked brain activity with fMRI in AD all suggest an increasing disruption in the DMN [33] hypo metabolism often mirrors the same regions that belong to the posterior parts of the DMN, namely the posterior cingulate cortex, the Retrosplenial cortex, inferior parietal lobule, and the lateral temporal cortex [34]. Such hypo metabolism correlates with the mental status while AD progresses [35].

Lennart Mucke., suggest that "high levels of β-amyloid induce epileptiform activity, which triggers compensatory inhibitory responses to counteract over excitation that lead to changes in synaptic circuitry and an increase in inhibitory activity in the temporal cortex. This leads to changes in the texture of the neural networks involved and might explain disruptions of the networks as seen in the default mode network (DMN) in AD" [36,37,38].

3. THE PHYSIOLOGICAL BASIS OF MEMORY

It is proposed to discuss here the various type of memory, the loss of which accounts for the varied symptomatology observed above. Also how the memory is initiated and processed, stored and retrieved. The role of neurons, synapse, various receptors as well as neurotransmitters is briefed.

Types of memory: These are presented in Table 1.

3.1 The Long-term Memory (LTM)

The long-term memory (LTM) refers to the unlimited capacity memory store that can hold information over lengthy periods of time. The way long-term memories are stored is similar to a **digital compression**. This means that information is filed in a way that **takes up the least amount of space**. The way long-term memories are stored is similar to a digital compression. This means that information is filed in a way that takes up the least amount of space. There are **three types of memories that can be stored** in LTM: **Procedural memory**, **semantic memory,** and **episodic memory.** The mode of encoding LTM is semantic and visual and to less extent acoustic. It's retrieval is slow and may not be accurate. Long term memory is generally well preserved in early and mid-stage Alzheimer's disease. It loss is a sign of aging. Sort term memory is converted to LTM memory through a memory process called **consolidation**.

3.2 Declarative Memory

Declarative memory is the conscious storage and recollection of data [39]. It is also called **explicit memory.** Declarative memories are encoded by the **hippocampus**, **entorhinal cortex and perirhinal cortex** (all within the medial temporal lobe of the brain), but are **consolidated and stored** in the temporal cortex.

- **It is devised into 2 types, the episodic and semantic memories.**
- **Episodic memory: It is** remembrance of an event or episode or personal experiences that took place at a particular place and time like the first kiss, or marriage anniversary day.
- **Autobiographical memory:** The memory of personal episodic details constitutes the "The information is encoded along a spatial and temporal plane in the brain [40]".
- **Flash bulb memory: It is a type of autobiographical memory.** These memories are so emotionally important to us that they are laid down as vividly, completely and accurately as a photograph.

3.3 Semantic Memory

Semantic memory is a type of long-term **memory** that processes ideas and concepts that contributes to our knowledge, not the time and place where we acquired the knowledge as is the case with episodic memory. It includes things that are common knowledge, such as the names of colours, the sounds of letters, the capitals of countries and other basic facts acquired over a lifetime.

To be more clear, when you have first visited a zoo, the details are engraved in memory as episodic. Conscious recollection brings out all

Table 1. Types of memory

Regular memory				Associate & Non associative memory	
Long term memory		**Short term memory**		Associate memory	Non-associative memory
Declarative / Explicit memory	Non declarative / Implicit memory	Working / Executive memory	Sensory memory		
Episodic memory	Procedural memory –		Iconic memory - Vision	Classical conditioning	Habituation
Semantic memory	perceptual, motor and cognitive skill learning		Echoic memory – Hearing Haptic memory -- Touch	Operant Conditioning	Sensitisation

these details in episodic memory. The knowledge of how a lion looks like might have been gained at the event of going to zoo, but when recollecting how a lion looks like calls for the semantic memory (knowledge about details of the lion, rather than the event that hat is responsible (the visit to zoo). Over time the event fades but not the knowledge. It is suggested that semantic memory starts as episodic and gradual attenuation of the episode retains only the knowledge in the form of semantic memory. The implications are that semantic memory out lives episodic memory and the site, storage and retrieval mechanisms for both are different.

3.4 Non Declarative or Implicit Memory

Non declarative or implicit memory is the unconscious storage and recollection of information. it is a long term memory. These forms of memory guide current behavior on the basis of past experiences unrelated to any conscious awareness of those experiences and therefore are referred to as *implicit* memory. An example of a non-declarative process would be the unconscious learning or retrieval of information by way of procedural memory, or a priming phenomenon [41].

Priming: Implicit memory can also come about from priming. You are "primed" by your experiences; if you have heard something very recently, or many more times than another thing, you are primed to recall it more quickly.

Procedural memory: This is an explicit type memory that does not involve consciousness in encoding or retrieval. They relate to procedures like how to tie the shoes or drive a cat. They involve both continue and motor skills. This memory also requires a repetition of motor skill but once it is learnt, it's retrieval is automatic. In car driving, you repeat until you a quire the skill and after words, the retrieval of the skill is automatic. Procedural memories, do not involve the hippocampus and are encoded and stored by the **cerebellum, putamen, caudate nucleus and the motor cortex,** all of which are involved in motor control. **Learned skills** such as riding a bike are stored in the **putamen**; **instinctive actions** such as grooming are stored in the **caudate nucleus**; and the **cerebellum** is involved with timing and coordination of body skills.

3.5 Implicit Forms of Memory Include Perceptual, Motor and Cognitive Skill

learning (sometimes referred to as procedural memory), which is the increased accuracy, speed, or skill acquired for a given task during multiple training sessions in the absence of conscious awareness, Procedural memory involved in motor learning depends on the cerebellum and basal ganglia.

3.6 Associative Memory

Associative memory is a memory unit whose stored data can be identified for access by the content of the data itself rather than by an address or memory location. Associative memory is often referred to as Content Addressable Memory (CAM).

3.6.1 Associative vs regular memory

Regular memory is a set of storage locations accessed through an address. Associative memory is a set of storage locations accessed through their contents. You would use associative over regular memory when doing a lot of pattern matches or lookups. In these situations, associative memory is faster.

3.6.2 Classical conditioning

The classical example is 'Pavlov experiments on dog. In his experiments, he found that the very sight of an at tendentious bring food (Conscious stimulus) evoked saliva in the mouth of the dog (an unconscious response.

A conscious stimulating of an unconscious response is called classical conditioning. Saliva secretion is conditioned to sight of the food here.

3.6.3 Operant conditioning

Operant conditioning (sometimes referred to **instrumental conditioning**) is a method of **learning** that occurs through rewards and punishments for behavior [42]. Through **operant conditioning**, an association is made between a behavior and a consequence for that behaviour. An example is that a mouse that learn to get a food pellet by pressing a blue button presses the same for reward and avoids pressing the red bottom that gives it an electric shock punishment. An example is th at a car driver is conditioned to stop when red signal appears and start when green signal is flashed.

The linking of the stimulus to the operant occurs in Hippocampus and Amygdala and integration **occurs in OFC.**

3.7 Non Associative Learning/ Memory

3.7.1 Habituation

It is a type of non associative Learning:

In habituation, behavioural responsiveness to a test stimulus decreases with repetition. It has the important function of enabling us to ignore repetitive, irrelevant stimuli so that we can remain responsive to sporadic stimuli, typically of greater significance (International encyclopaedia of learning and behavioural Science, 2001). For example, a ring tone of a mobile may distract our attention at first, but on reputed exposures fails to draw the same attention i.e. the response to repetition has diminished [43].

3.7.2 Sensitization

Sensitization refers to a non-associative learning process through which repeated exposure to a stimulus results in the progressive amplification (increasing strength) of the reaction to the stimulus [44]. The organism is becoming more sensitive to the stimulus as time progresses. It is opposite of habituation (American Psychology Association, *Alleydog.com's online glossary*). For example repeated blurting on a loudspeaker may increase your annoyance.

3.8 Short Time Memory (STM)/ Executive or Working Memory

The unit of the sensory input to the brain receives is called a '**bit'**.
The rate of sensory input to the brain is - **50 bits/ second.**
The total capacity of the brain is **2×10^8;**
Reading -24 bits/ sec;
Calculation-12 bits/ se

Total number of bits needed **for learning a language**- 40- 50 million bits/ sec
The number of neurons needed. To o **store 1 bit – 10.**
Counting - **3 bits / sec.**

The speed of flow of information to the brain is **20 bit/ sec**

Short-term memory is the capacity for holding, but not manipulating, a small amount of information in mind in an active, readily available state for a short period of time. For example, short-term memory can be used to remember a phone number that has just been recited.

Durations: Minutes to hours.
Capacity: Millers magic number 7 plus or minus 2 chunks.
Mechanism: By forming temporary memory traces.
Area of brain concerned: -PFC.

3.9 Sensory Memory

The memory built upon the sensory inputs by the 5 special senses. They are –

- **Iconic memory (vision)**
- **Echoic memory** (**hearing)**
- **Olfactory memory (smell)**
- **Gustatory memory (taste) and**
- **Haptic memory (touch)**

Some features of sensory memory:

Short memory time.
Speed – very short. Decays within 5 seconds.
Capacity: 15- 20 bits
Entry into data storage: Automatic.
Recovery from data storage: Very rapid.

Mechanisms:

Stimulation of reverberating circuits.
Synaptic sensitisation.
Post synaptic potentiation..

Short time memory (STM)/ Executive or working memory:

The unit of the sensory input to the brain receives is called a ' **bit'**.
The rate of sensory input to the brain is - **50 bits/ second.**
The total capacity of the brain is **2×10^8;**
Reading -24 bits/ sec.
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4. THE MEMORY FORMATION

4.1 The Role of Neuron

The neuron is likened to a microchip processor, receiving inputs and delivering out puts. Neurons are either connected directly to other neurons forming a continuous network or connect indirectly through a synapse. The Synapse s a junction between two axons of two neurons separated by a synaptic cleft. The presynaptic axon secretes a neurotransmitter which generates an action potential in the post synaptic axon which is an **'analog signal'** were as when neurons receives sensory input via the dendrites, the stimulus generates an action potential which is like a **"digital signal".** The post synaptic axon which generates the analog signal converts into digital signal for the next neurone to receive, which is propagated. The monosynaptic transfer mission of sensory input digital signal) is short lived and so subservient sort time memory or working memory. The Analog signal lasts longer for hours to days and is the preferred mode used in long term memory. The conversion of long time memory from short time memory is done by hippocampus.

4.2 The Role of Synapse

Synapse is the junction place where f the axons of the information sending neurons(pretty synaptic fibers) and the dendrites of the information receiving next neurons(post synaptic fibers) communicate through a small space called synaptic cleft. The information is transmitted by a neurotransmitter. The electrical to chemical impulse at the synapse and the same is converted again to electrical impulse. Synapses are affected in AD, as well as the neurons, axons and the dendrites as well causing direction of impulse transduction.

4.3 Neuroplasticity (of Brain and Synapse) [45]

The **brain's** ability to reorganize itself by forming new **neural** connections throughout life. **Neuroplasticity** allows the neurons (nerve cells) in the **brain** to compensate for injury and disease and to adjust their activities in response to new situations or to changes in their environment. **Neuroplasticity** is the change in neural pathways and synapses that occurs due to certain factors, like behaviour, environment, or neural processes. During such changes, the brain engages in synaptic pruning, deleting the neural connections that are no longer necessary or useful, and strengthening the necessary ones.

4.4 Modification of the Strength of the Sensory Signal: He LTP

The LTP and The LTD

If the post synaptic nerve fiber is repeatedly stimulated, the strength of the synoptic potential may increase in strength which persist for long duration. This enhanced synaptic signal strength is called **Long Term Potentiation (LTP)** which is considered the basis of long term memory. The signal strength if decreased on repeated stimulation of the presynaptic axon, it is called **long-time depression** (**LTD**). Again whether the post synaptic fibre is stimulated or inhibited depends on whether the transmitting neuro hormones (NH) is excitatory or inhibitory. LTP could be recorded in the hippocampal synapses *in vivo* [46].

4.5 The Hebb Rule: [47]

How the synaptic signal potential is strengthened or diminished is explained by Donald Hebb in 1949. Supposing neuron A is connected to neuron B by synapse-

1) If A fires repeatedly and B fires after it, strengthen g of the potential occurs.
2) If B fires before A or if A doesn't fire at all, the synaptic potential strength decreases.

5. ROLE OF RECEPTORS IN SIGNAL TRANSDUCTION

The receptors are classified as

- **NMDA**
- **Non NMDA receptors:**
- **AMPA receptors.**
- **Kinase receptors**

5.1 NMDA Receptors (*N*-methyl-D-aspartate Receptor)

It's rare glutamate neurotransmitter receptor located in the cell membrane of the post synaptic

(signal receiving) neuron. These receptors play an important role in neuroplasticity and memory function. The receptor has 3 binding sites, one each for glutamine and glycine and an allosteric binding site. NMDARs require the binding of two molecules of glutamate or aspartate and two of glycin. Glutamate is the fast acting excitatory neurotransmitter especially implicated in the learning and memory processes. It is secreted by the presynaptic neuron's axon (signal sending). The NMDA receptors are both voltage gated and ligand gated. These are functional only when the membrane is depolarised and glutamine and glycine are attached to the receptors. How the post synaptic membrane is depolarised is seen below when AMPA receptors are considered. In nondepolarised state the NMDA channel pores don't open due to blockage by intracellular Mg ions. They are extruded into extracellular space consequent to the depolarised ion of the post synaptic neuron. Thus the ion channels open and positive ions of calcium especially and in addition to sodium and potassium ions enter the cell. These calcium ions help phosphorylation of AMP receptors where by the later become more responsive to the neurotransmitter and also increase quantitatively. This helps perpetuation of depolarisation of the post synaptic NMDA receptors producing LTP. The LTP requires two thing, secretion of glutamate at the presynaptic nerve ending and depolarisation of the post synaptic membrane. Over activation of NMDA receptors, relieving the Mg^{2+} block and causing excessive influx of Ca^{2+} can lead to excitotoxicity. Excitotoxicity is implied to be involved in some neurodegenerative disorders such as Alzheimer's disease. Blocking this excitotoxicity is a theoretical consideration as a therapeutic target in A D [48,49].

5.2 AMPA (The α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor)

These are also glutamate receptors, distributed all over the brain and are involved in fast exaction nerve conduction in CNS. They are involved in synaptic plasticity and LT necessary for the memory and learning.

AMPARs are composed of four types of subunits, designated as GluA, GluA2, GluA3, and GluA4, each which combine to form tetramers. [50] each having one receptor binding site. Two sites need to be occupied for opening of the transmembrane ionic channels they contain. More the number of lands attached, stronger is the stimulus for opening the ion channel. The opening of the ion channels permits the entry of positive ions (Na and K) inside the cell which has a me membrane resting potential of -70 mV. The entry of positive ions brings down this membrane potential to zero, equipotential to that of NMDA receptors.. So an electric gradient is developed across the cell membrane and the resulting action potentials set in membrane depolarisation of the NMDA receptors. Consequently the Mg ions blocking the ion channels NMDA receptors are extruded out and calcium enters in to the post synaptic cell. Rest of the events are already seen under rge heading, NMDA receptors above. The prevention of calcium entry into the cell on activation of GluA2 (important of the 4 sub units of AMPA receptor mentioned above) -containing AMPARs is proposed to guard [51] against excitotoxicity.

5.3 The Trafficking of the AMPA Receptors into the Premicellar Space

Once AMPA receptors are transported to the peristaltic region through PKA or SAP97 phosphorylation, receptors are then trafficked to the postsynaptic density (PSD). This is belied to occur by a process called **'lateralisation' or 'exocytosis'** of the receptor.

5.4 The Kainite Receptor

This is another NONNMDA receptors that responds to the neurotransmitter glutamate. It has action on both pretty synaptic ally and post synaptic effects. Postsynaptic kainite receptors are involved in excitatory neurotransmission. Presynaptic kainate receptors have been implicated in inhibitory neurotransmission by modulating release of the inhibitory neurotransmitter GABA through a presynaptic mechanism.

6. THE ROLE OF ASTROCYTES –The GLUTANERGIC CONCEPT OF TRISYNAPTIC PATHWAY

Pereira et al. [52] contend that cognitive processing is not only done by the neuronal action vita as cited above, but in addition to this, astrocyte network also play a part in it. The devised a model of Trisynaptic working model to explain their concept.

Glutamatergic tripartite synapses (composed by functional units of two neurons and one astrocyte. Astrocyte terminations wrap the synaptic cleft. In some brain regions, each

astrocyte can contact up to 140,000 synapses (Agulhon et al. 2008) Neighbouring astrocytes are coupled by gap junctions forming a functional syncytium.

Neighbouring astrocytes are coupled by gap junctions forming a functional syncytium .The glutamate released by presynaptic terminal stimulates metaballotropic receptors on a single astrocyte of the tripartite sy naps. Synchronization of such stimuli from other astrocytes raises threshold to a level when it elicits coherent, amplitude- and/or frequency-modulated calcium waves with the potential of integrating local information.

When global brain synchronisation occurs, calcium waves integrate sensory, cognitive and affective/emotional patterns from distinct neuronal populations; Glutamate released from astrocytes to postsynaptic neurons in tripartite synapses binds to extra synaptic NMDA receptors of the NR2B subtype, which drives slow inward calcium currents, causing a delayed depolarization and an increase of CaMKII phosphorylation and AMPA excitability, a process called “meta-potentiation” (Pereira Jr and Furlan, 2007) and reinforces long-term potentiation, (LTP) or alternatively triggers a process of long-term depression.(LTD).

7. THE PROCESSING OF MEMORY

It involves 4 stages.

Encoding.
Consolidation
Storage
Retrieval

7.1 Encoding

It is classification and placing of the information items in their proper storage places in the brain. The parts of brain involved in encoding are;

1) Hippocampus (principal site. All bits of sensory information reach it first)
2) Amygdala (Emotional information)
3) Mammillary bodies of thalamus
4) Prefrontal cortex.
5) Nucleus of Myenert
6) Neo Cortex.

Mechanism of encoding:

Bits from sensory organs flow through a closed circuit consisting of Hippocampus to mammillary bodies to OFC to Myenert nucleus back to Hyppocampus. Also from Myenert nucleus the information passes to the Amygdala and the Neocortex. The pathways leading from the Myenert nucleus to Hippocampus, Amygdala and the neocortex through cholinergic projections.

7.2 Consolidation

It is a process by which the brain converts short time memory to long time memory.

The structures involved in consolidation.
Hippocampus (main)
Anterior and lateral temporal cortex.
Medial temporal cortex

Amygdala

The connection of the circuit:

The circuit is completed by 3 pathways.

1) Perfont pathway: Which connects para hippocampus to the granular layer of Amygdala.
2) Mossy fibers: Connect the i layer of dental nucleus to the C3 layer of hippocampus.
3) Scaffers fibers: Connect C3 layer of hippocampus to its C 1 layer

7.3 Storage

Storage sites of different memories:

Executive memory: PFC
Long term memory: Mainly Hippocampus.
Emotional memory: Amygdala
Explicit memory: Hippocampus
Implicit memory: Basal ganglia and Cerebellum
Neocortex: Some information from Hippocampus is transferred to the Neo Cortex and is stores general knowledge

Memory Trace: A memory trace, also know as an **engram**, is a theoretical means by which memories are physically stored in the brain The actual method of storage of memory, whether by biophysical or biochemical means, is still being debated

7.4 Retrieval

The two main methods of accessing memory:

Recognition
Recall.

Recognition is the association of an event or physical object with one previously experienced or encountered, and involves a process of comparison of information with memory, e.g

Recall involves remembering a fact, event or object that is not currently physically present (in the sense of retrieving a representation, mental image or concept), and requires the direct uncovering of information from memory, e.g. remembering the name of a recognized person, fill-in the blank questions, etc. **Types** of **recall;**

Free real: The events are recalled in any order.

Cued recall: The real of event occurs when a cue is given but not otherwise.

Serial real: Recollection of events in the same chronological order in which they are presented.

8. THE ROLE OF NEUROHARMONES IN COGNITIVE PROCESSING

Glutamate and Glutanergic pathways: The role of glutamate In neuroplasticity and LTP etc. are all ready seen below

Table 2. Neurotransmitters involved in cognitive processing

Glutamate.
Dopamine
GABA
Acetyl choline
Serotonin
Adrenaline and Noradrenaline.

8.1 The Glutamate Transporters

There are two types ie. EAST (excitatory amino acid transporters) and VGLUT (vesicular glutamate transporters). Both of the most remove excess glutamate from the synapse and perisynaptic area and cause reuptake by the nuroglial cells and nurons and thus prevent excitotoxicity which can cause neuronal death.

8.2 Metaballotropic Receptors

In addition to the AMP, pK and NMDA receptors which are ionotropic receptor (the last one being voltage fared also) the rest are 3 groups of metabolloreceptor which function with the help of a second messenger like C amp.

They are G protein linked receptors.

Group 1: The inhibit adenyl cycle through stimulating phosphorus lipase C.
Group 2 and 3: They inhibit C amp.

8.3 GABA

These are inhibitory neurotransmitters .The are ion channelled and make the nerve hyperpolarised by transporting either cloud ions inside the cell or letting out positively charged potassium ions there by increasing the electro negativity of the cell. Their concentration is found to be lower in Schizophrenia and depression. GABAergic neurons exert a presynaptic action via $GABA_A$ and $GABA_B$ receptors and presynaptically inhibit D_2 dopaminergic neurons located in the hippocampus.

8.4 Acetylcholine and Cholinergic Pathways

The source of this neurotransmitter is the Nucleus of Myenert of basal brain. The fibers that connect with the other brain structures are called cholinergic projections important of them are to the neocortex of the forebrain, the limbic system, MS/DB region to hippocampus. Other subcortical inner at ions are from the basal ganglia to Ponto mesencephalic areas. This acts on both presynaptic and post synaptic fibers in the CNS. It is synthesised by an enzyme called cholineacetylasetransfarease (CAT) and is destroyed by another enzyme, cholinesterase. Of the two types of receptors ie. Nicotinic and muscarinic , the later are important in CNS Muscarinic receptors, in contrast, are important mediators of behavior in the CNS. One example is their role in modulating motor control circuits in the basal ganglia. A second example is their participation in learning and memory. The latter is inferred from two types of observations: 1) muscarinic antagonists are amnesic agents, and 2) deterioration of the cholinergic innervation of the neocortex is associated with memory loss in Alzheimer's disease.

Mechanism of action:

Muscarinic receptors are G protein couple receptors (GPCR). We stimulated these produce conformational changes in the G protein which converts GDP to GTP which inhibits adenylyl cycle. The concentration of C amp is reduced and C amp dependent pkA is inhibited with failure of phosphorylation of proteins concerned. The muscarinic receptor activates phosphoinositide-specific phospholipase C

($PLC_ß$) through interaction with a GTP-binding protein. The hydrolysis of **phosphatidylinositol bisphosphate** yields two second messengers; **inositol trisphosphate** (IP_3) and **diacylglycerol** (DAG). The DAG activates **protein kinase**). Cellular responses are influenced by PKC's phosphorylation of target proteins the **IP_3** diffuses to the **smooth endoplasmic reticulum**(ER) where it interacts with IP_3receptors to increase Ca^{2+} release from the intracellular storage site. 5 **IP_3**plase Ca^{2+} release from the intracellular site.

8.5 Dopamine and Dopaminergic Pathways

Dopamine and Dopaminergic Pathways are involved in many functions such as executive function, learning, reward, motivation, and neuroendocrine control. The functions of the DA pathways are divided broadly into three categories: motor control (nigrostriatal system), behavioural effects (mesolimbic and neocortical systems), and endocrine control (tuberohypophyseal system; Bridge, 2002. The dopamine receptors are grouped into two main families, D1 and D2, whose actions linked to stimulation and inhibition of adenylate cyclase, respectively.

8.6 The Main Dopamergic Pathways: [53]

VTA → Amygdala
VTA → Hippocampus.
VTA → Cingulate cortex
VTA → Olfactory bulb.
SNc → Sub thalamic nucleus.

The neocortical and mesolimbic pathways are sometimes referred to simultaneously as the **Mesocorticolimbic projection**, system, or pathway.

Mesocorticolimbic pathways.

VTA → Prefrontal cortex
VTA → Ventral striatum(nucleus accumbens and olfactory tubercle)
Serotonin pathways:

8.7 Serotonin and Pathways

Serotonin and pathways are thought to be involved in regulation of mood, feeding behavior, sleep/wakefulness, control of sensory **pathways** including nociception, control of body temperature, vomiting and emotional behaviours such as aggression. Low levels of serotonin are observed in pts of AD.

Of 5-HT neurons are located in the caudal raphe nuclei and the rostral raphe nuclei. Of these two nuclei, the rostral one (in the region of the midbrain and pons [hindbrain]) is of relevance to abuse liability as these neurons project (via the MFB [as the DA neurons]) to almost the entire cortex (including the **PFC**) as well as the **hippocampus** and **thalamus**.

8.8 Adrenergic Receptors

Norepinephrine (NE) is synthesized in the Locus Coeruleus (LC) of the brainstem, They are coupled to G proteins (metaballotropic) that control the production of second messengers. Adrenergic receptors are both excitatory and inhibitory. The α1 receptors produce a slow depolarizing (excitatory) effect on the postsynaptic membrane, while α2 receptors produce a slow hyperpolarization (inhibitory) effect.

9. CONCLUSION

The memory changes in AD and the relevant physiological background of memory are reviewed in this article. Better understanding the physiology of memory and how memory is affected in AD, it is hoped might help the quest in finding a solution to decline of memory in AD patients.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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