

# THE AGING BRAIN AND ALZHEIMER'S DISEASE: HOW MEMORY CHANGES

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**A**ging is a natural process that occurs over time as we grow old. Everyone ages, and as we do, our bodies exhibit a variety of changes, most of which are physical changes (skin wrinkles, weaker joints, etc.). As an essential control center in our body, it is no surprise that changes also occur in our brains as we age. These changes are manifested by behavioral alterations, which stem from physiological and neurochemical changes in our brains. Among the numerous changes that can occur throughout the process of aging, memory dysfunction or impairment is a common concern in the general population as well as the scientific community.



There is a mounting interest in the scientific world in efforts to help retain memory function and/or reverse memory deficits in the aging brain. In this article, we will examine how memory changes with aging and Alzheimer's disease.

Age-related declines in memory are highly variable in rate and severity among individuals. Though most individuals go through a gradual decline in their mental agility, some retain their cognitive power throughout their life, whereas others experience severe memory impairment. Beyond individual divergence, aging affects certain domains of memory more than others. For example, working memory (a memory system that stores and manipulates information for cognitive tasks, such as memorizing names or addresses) is commonly impaired in advancing age. In contrast, procedural memory (memory that guides the tasks we perform without the involvement of consciousness, such as driving or swimming), semantic knowledge, or memory that links to emotional occasions stays intact as aging progresses [1,2].

Discernable cognitive alterations in the elderly result from the insidious structural and molecular changes in the brain. The level of dopamine in the brain, especially the prefrontal cortex (front part of the cerebral cortex that helps to improve working memory), declines dramatically with age [3]. Besides deficits of essential neurotransmitters, memory loss in the senior population can be also attributed to the deterioration of neuronal cells and their organelles. For instance, mitochondria, the powerhouse and regulator of oxidative balance in cells, demonstrate decreased production of energy and elevated generation of free radicals [4]. Free radicals are unstable and harmful molecules that cause damage to DNA and other organelles in the cells. Accumulation of these noxious substances, along with dysfunctional mitochondria, leads to weakened neurotransmission and consequent cognitive failures. On a more macroscopic level, aging is accompanied by mild shrinkage in the volume of the brain, a loss of brain weight and enlargement of the ventricles

(cavities within the brain). Loss of neurons, fragmentation of myelin that insulates nerve fibers and facilitates neural signal conduction, and declining numbers of synapses collectively contribute to the observed brain shrinkage [5].

**“BEYOND INDIVIDUAL DIVERGENCE, AGING AFFECTS CERTAIN DOMAINS OF MEMORY MORE THAN OTHERS.”**

While memory decline leaves the life quality of most old people uncompromised, a small subset of the elderly exhibits memory impairment that reaches a pathological level. Senile dementia, referred to severe mental deterioration in old age, involves progressive impairment of memory as well as other cognitive abilities. Dementia is strongly associated with myriad diseases, with Alzheimer's disease (AD) being the most prominent cause among the aged

population. Dementia corresponded to AD often foresees progressive disability throughout the disease course, with death being an almost inevitable outcome within 5-12 years of symptom onset [6].

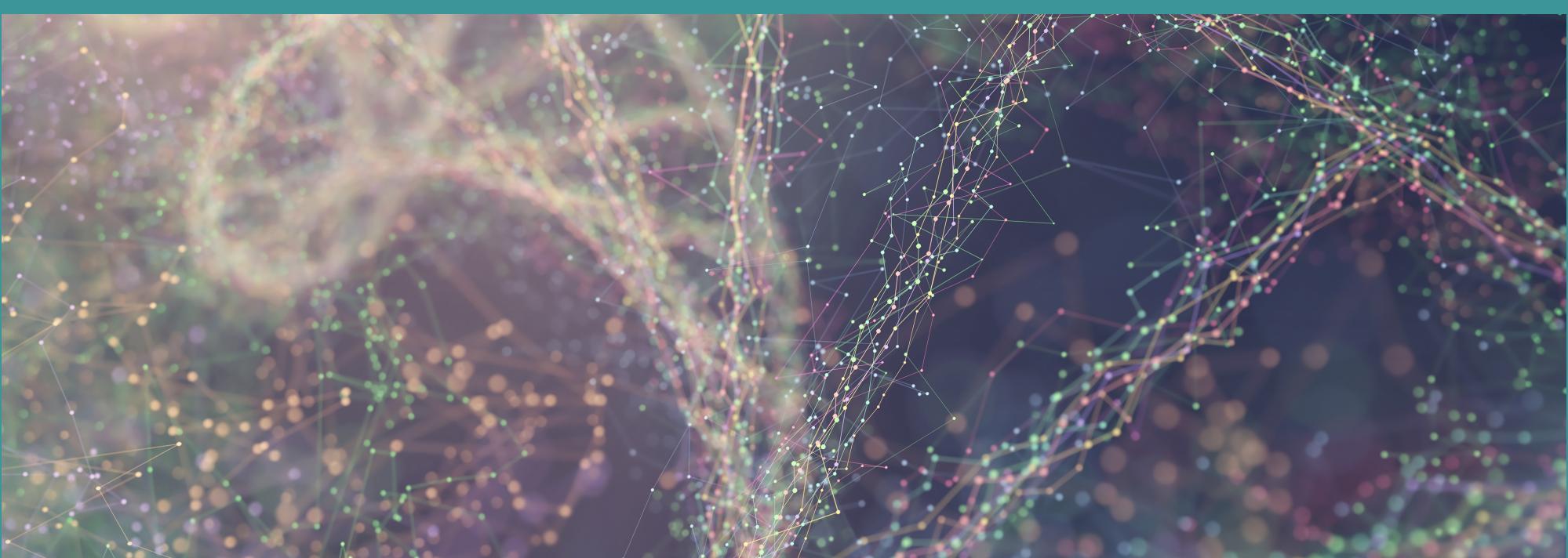
In terms of memory deficits, AD patients manifest a dramatic decline in working memory and declarative memory, a type of long-term memory involving conscious recollection of previous experiences or concepts. Alterations in hippocampus and entorhinal cortex, such as atrophy (degeneration and reduced volume of tissues) and significant neuronal loss, are likely the structural underpinnings of the aforementioned memory dysfunction [7]. The destruction of neuronal tissues in hippocampus and entorhinal cortex make the storage of new memories impossible, considering their critical role in forming, consolidating, and optimizing memory [8].

**“DEMENTIA IS STRONGLY ASSOCIATED WITH MYRIAD DISEASES, WITH ALZHEIMER'S DISEASE (AD) BEING THE MOST PROMINENT CAUSE AMONG THE AGED POPULATION.”**

Though the exact cause of AD remains poorly understood since first proposed by Alois Alzheimer in 1907, scientists have made considerable progress in elucidating the pathogenic mechanism of neural degeneration, atrophy, and other molecular abnormalities observed in the AD patients. One predominant characteristic of the AD pathology is the presence of insoluble sheets of beta-amyloid proteins ( $A\beta$ ) called amyloid plaques.  $A\beta$ , a natural product in healthy human bodies, originates from amyloid precursor protein (APP), a protein widely present in the nervous system and can be cleaved into shorter segments like  $A\beta$  molecules [9]. The amyloid hypothesis that connects APP or  $A\beta$  with the debilitated memory function of AD is supported by converging lines of evidence [10].

For example, synthetic  $A\beta$  demonstrates toxicity to hippocampal and cortical neurons [11]. Furthermore, the gene that encodes APP presents in three copies (normally two) on Chromosome 21 in people with Down Syndrome, causing APP to be excessively expressed; and AD will be inevitably triggered among Down Syndrome patients in their early 40s [12]. This association is consistent with the idea that excessive expression of APP precipitates  $A\beta$  and consequent AD symptoms. The assemblage of  $A\beta$  into amyloid fibrils contributes to neuronal injury, synaptic loss, and disruption of synaptic plasticity (a function critical to memory formation), which strongly correlate with severity of dementia and memory loss in AD [13,14].

Another hallmark of AD pathology is the neurofibrillary tangle (NFT), an insoluble associate of dysfunctional tau protein. Tau, a normally soluble protein, plays a key role in intracellular transport by binding to and stabilizing microtubules (principle component of the cytoskeleton, or skeleton of cell). A compelling model that tries to explain the initiation of disease cascade, the tau hypothesis, attributes the main cause of NFT formation to hyperphosphorylation of tau (all sites are saturated with phosphate groups). As tau loses its function in assembling and stabilizing microtubules, it starts to pair with other tau proteins to form tangles and gain toxicity, dismantling the cytoskeleton of cells and consequently destroying the neurons’



transportation pathway [15]. The progressive accumulation of NFTs is strongly correlated with the staging of this progressive disease—for instance, NFTs first aggregate in the hippocampus, which is responsible for memory complaints at an early stage. The spatial distribution of tau is also closely linked to specific cognitive domain performance and the pattern of AD's clinical symptoms [16]. Overall, tau pathology is intimately tied to cognitive impairment like memory deficits.

With the number of AD patients reaching 50 million worldwide and is expected to be projected to 152 million by 2050 [17], developing proper prevention, treatment, and prognosis strategies becomes urgent in the public health realm. There are miscellaneous risk factors involved in the onset and progression of AD. Age is undeniably a major trigger of AD, since the aging brain undergoes functional decline likely driven by decreased synaptic density and altered metabolism like more inflammation occurrences [18].

Another major risk factor is genetics: for instance, mutations in genes that encode APP (main cause of familial AD) increase the production of A $\beta$  protein and in turn give rise to amyloid plaques [19].

Though AD can be diagnosed well with advanced imaging and intellectual assessment, available treatments or prognosis that aim to restore cognitive function remain poor. However, new medications and therapeutic measures are emerging everyday, with some proven to be effective. For example, researchers have employed a neurosurgical method called deep brain stimulation (DBS) to modulate human memory. By implanting electrodes in the brain's major memory hub, the entorhinal-hippocampal system, memory function can be potentially edited through electrical stimulations. Several studies have addressed the hope of ameliorating memory impairment through applying DBS to the memory domain [20]. This kind of research is remarkably promising for patients long suffering from memory loss.

With the advent of new technology and medicines, hopefully, one day we no longer have to link aging to a dreadful process that inevitably triggers AD or wipes out the valuable memory imprinted in our mind.

**“THOUGH ALZHEIMER'S DISEASE (AD) CAN BE DIAGNOSED WELL WITH ADVANCED IMAGING AND INTELLECTUAL ASSESSMENT, AVAILABLE TREATMENTS OR PROGNOSSES THAT AIM TO RESTORE COGNITIVE FUNCTION REMAIN POOR.”**