

The Role of the Hippocampus in Memory Impairment: A Study of Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a continuous neurological dysfunction that can be recognized by problems in memory, thinking, and performing daily life. This paper explores the reason for memory loss in AD in hippocampal dysfunction. The hippocampus is needed to construct and organize memories of specific events and places, and also recall them. Its sub-regions, including the dentate gyrus and the CA1-CA4 regions, form an interrelated network that distinguish similar events, rebuild complete memories from partial information, and transfer processed information to other areas of the brain. At this time, there is an overgrowth of amyloid- β plaques and irregular tau proteins; as a result, there is synaptic damage, neuronal death and gradual hippocampal atrophy. CA1 and the entorhinal cortex are relatively more vulnerable in early phases of disease. Damage in these areas can disrupt memory encoding and retrieval, and could lead to rapid forgetting, confusion between similar experiences, spatial disorientation and wandering. Studies on Amyloid Precursor Protein Knock-In (APP-KI) mice have also found that, in the same circumstances, there are damaged hippocampus and entorhinal circuits, and they have impaired spatial memory. Magnetic resonance imaging (MRI) structural analysis, cognitive tests, amyloid protein and tau biomarkers may help detect these changes before severe symptoms occur. Overall, understanding hippocampal injury is helpful for early diagnosis, individualized observation, and the progression of treatment methods that protect neurons, repair neural circuits, and minimize the growth of the disease.

Keywords: Alzheimer's disease, Hippocampal atrophy, Memory disorder, Early diagnosis

1. Introduction

Memory is the mechanism of keeping knowledge for a long time that will affect one's behavior in the future [1]. There are short-term and long-term memories. The time for short-term is transient, usually lasts for 15-30 seconds, and is easy to reach and access. For example, people use it to remember the beginning of this sentence, until the end of the sentence. It is used by people in daily life to listen to, organize and produce language. All the memories that are more than 30 seconds long are classified as long-term memory [2]. Generally speaking, the size of long-term memory is fixed. People can keep the information contained for many years. Humans possess an unlimited capacity for information storage. There are two primary categories of long-term memory. First, declarative or explicit memory is the retention of facts, events and places, which people are perpetually acquiring

and remembering information. Second is non-declarative or implicit memory (procedural memory), which remembers how to do things and habits. Cleveland Clinic thinks that people can access procedural memory consciously or unconsciously. Learning is to pay attention to the relevant parts of the received information, organize them in a reasonable cognitive structure, and link them with existing relevant content in long-term memory [3]. If there is a dysfunction in the function of long-term memory, one will be unable to learn new knowledge, observe behaviors and so on [4].

Memory disorders refer to diseases that affect the memory control areas of the brain. The symptoms caused by these diseases might not be limited to memory function. Dementia refers to a general concept for diseases that influence memory, and although it is the most typical reason for dementia, about 60% to 80% cases are due to AD. According to the Alzheimer's Association, AD is characterized by memory impairment and other cognitive declines that is severe enough to affect daily life [5]. The symptoms include loss of memory, reasoning, language (aphasia), behavior and character, and spatial understanding. Patient themselves may have difficulty noticing these changes, whereas family members are often likely to observe them [6].

One component of the brain's limbic lobe is the hippocampus. However, it is the region most impacted by AD. Neuronal degeneration in AD is due to the accumulation of two abnormal proteins in the brain: amyloid- β ($A\beta$) and tau. The trait of AD is an overproduction or reduced clearance of $A\beta$. Besides $A\beta$ protein and tau protein, the new associated protein in AD that has also been found is 43 kDa TAR DNA-binding protein (TDP-43). The TDP-43 protein accumulates in the amygdala and subsequently spreads to the hippocampus, resulting in hippocampal atrophy. Consequently, one potential approach to the treatment of AD is to prevent the dissemination of this protein to the hippocampus. Microscopy and pathology have shown that, with the aggregation of neurofibrillary tangles within the cells, senile plaques are also found outside the cells [7].

The hippocampus is a role for storing memories and is damaged in AD; thus, it is necessary to know how damaging its structure can lead to cognitive decline. Therefore, the research question in this paper is as follows: In terms of Alzheimer's disease, how does hippocampal injury result in memory impairment? Through exploration of the connection between hippocampal degeneration and memory loss, this research hopes to obtain a better understanding of the reason for cognitive decline in older age and highlight the need for timely treatment of neurodegenerative disease.

2. Structure and function of the hippocampus

The hippocampus is an outgrowth of the temporal lobe of the cerebral brain. The hippocampus is a densely packed cluster of neurons in a C-shape situated at the terminus of the temporal lobe (Figure 1) [8]. The hippocampus comprises two components: the Cornu Ammonis (CA) and the dentate gyrus (DG). Both of these parts are divided by hippocampal sulcus and they are linked with each other. Below the subiculum is the area under the sulcus. Some anatomists have divided it into the hippocampus, subiculum and entorhinal area (EC). The whole group is named the hippocampus structure.

Head, body, and tail are the three components of the hippocampus. The expended part is called the head, and the thin curved part is called the tail (Figure 1). Based on histology analysis, the hippocampus proper is divided into CA1, CA2, CA3, and CA4 regions (Figures 2), and they are connected to form neural circuits responsible for the construction and organization of human memory [9]. The classic hippocampal pathway begins in the entorhinal cortex, continues to pass through the dentate gyrus and CA3, reaches CA1, and then sends information back to the cortex. CA2 is also connected to CA3 and CA1, while CA4 is in the dentate gyrus curve and is closely related to the function of the dentate gyrus. Given that the subfield serves different functions and

different weaknesses, they can be studied individually to enhance clinical understanding of memory loss in AD. CA1 is the main product of the hippocampus and, and together with subiculum, it is the initial areas of the hippocampus to be affected in AD, e.g., Mueller and his colleagues have shown neuronal loss in the CA1 region of AD [10, 11].

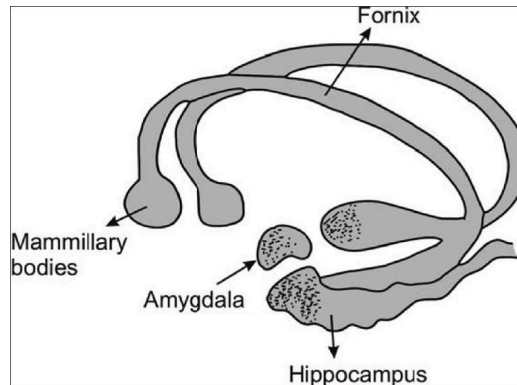


Figure 1. The limbic system and the hippocampus are connected. The hippocampus is a C-shaped structure, with the amygdaloid body situated at its anterior end, concluding deep within the mammillary bodies [8]

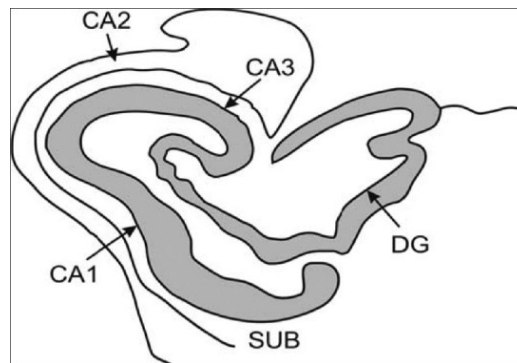


Figure 2. The microscopic structure of the hippocampus. Observe that the shaped C structure has been partitioned into distinct histological domains and CA1, which is the prominent histological region of the hippocampus, can now be demarcated radiologically [8]

Under normal circumstances, the dentate gyrus, including CA4 are responsible for encoding experiences with similar time, place or content into different memories to prevent confusion between new and old events [12]. Subsequently, CA3 links different information of the situation, enabling the brain to restore the complete event based on partial clues [13]. CA2 further incorporates information related to character identity, social relationships, etc., while CA1 integrates the content from CA2, CA3 and the entorhinal cortex, and transmits the processed memories to other brain regions for long-term storage and conscious recall [14]. When these regions are affected by tau protein deposition, synaptic loss, neuronal death or abnormal neural activity in AD, the entire memory processing process will be disrupted [10].

In Alzheimer's disease, tau protein accumulation, synaptic disruption, abnormal neural activity and neuronal loss can disrupt the communication of the entire hippocampus network. CA1 is very susceptible in the early stage of AD. Injury to the pyramidal neurons and connecting circuits in the hippocampus can impair the final integration and output of new episodic memory [15]. Patients with mild AD and amnesic mild cognitive impairment show rapid amnesia and reduced pattern

dissociation, according to behavioral studies, suggesting that the hippocampal network dysfunction has the potential to relate to similar memory confusion [16].

3. Key features of Alzheimer's disease

There are some changes in the brain of people with AD. The initial two issues are the buildup of amyloid- β plaques outside cells and the development of intracellular neurofibrillary tangles composed of abnormal tau protein. Changes in brain cells impair communication and eventually result in synaptic loss and damage. As more and more neurons are damaged and die, the brain will begin to gradually begin to shrink; this process is called atrophy. Because the change occurs slowly, AD can gradually impair people's mind, leading to problems in memory, thinking and daily life, etc. In short, the disease is caused by the excessive growth of protein that damages neurons and brain connections. Therefore, there is brain atrophy and increase in memory loss [17-19].

Advances in imaging of brain and fluid biomarker technology indicate that the progression of AD is a gradual and organized biological process rather than affecting the entire brain simultaneously. Now, the biological definition of AD mainly focuses on amyloid- β accumulation, tau pathology and neurodegeneration, which are usually organized through the A/T/N framework. According to the biomarkers of A β deposition (A), pathological tau accumulation (T), and neurodegeneration or neuronal injury (N), a biologically classified type of AD is called the A/T/N framework [20]. Amyloid- β misfolding and aggregation are generally regarded as early pathological changes, while the later spread of abnormal tau is more closely related to neuronal damage, brain atrophy and cognitive decline. The middle part of the brain is quite far from the front and is necessary for us to form and remember things, so it will likely show some changes here.

Figure 3 shows that this pattern is the same, and tau pathology first appears in the intranasal area and then increases to the hippocampus, other limbic structures, and eventually to the neocortex. The number shows that there are not only sequential stages but also a space for diseased part of the brain and the gradual worsening of AD symptoms. Damage to the entorhinal cortex and hippocampus in the early stages may interfere with the communication and neural circuits required for memory formation; therefore, it can be known that memory loss is often the first noticeable features of AD. The timeline of biomarker in Figure 3 also shows that abnormalities in amyloid- β protein might be detected before appearance of obvious cognitive symptoms, and with the progresses of disease, synaptic dysfunction, tau-related neuronal damage, reduction in hippocampal volume, decline and impairment of cognition, etc., become more pronounced. Therefore, volumetric Magnetic Resonance Imaging (vMRI) can be employed to measure the degree of atrophy in the hippocampus and medial temporal lobe of the brain accurately and safely. The first sign of a reduction in hippocampal volume might be observed early on, and such changes in the hippocampus could indicate neurodegeneration. In conjunction with the results of vMRI and amyloid- β protein and tau biomarkers, more researchers and clinicians are able to understand the situation of AD in a particular individual more deeply. Therefore, Figure 3 is not only a description of the stage of pathology; the evidence it provides shows that early biomarker changes and regional atrophy of hippocampus can be used to understand disease progression, explain early memory impairment, and evaluate the possible effect of disease-modifying treatment [21].

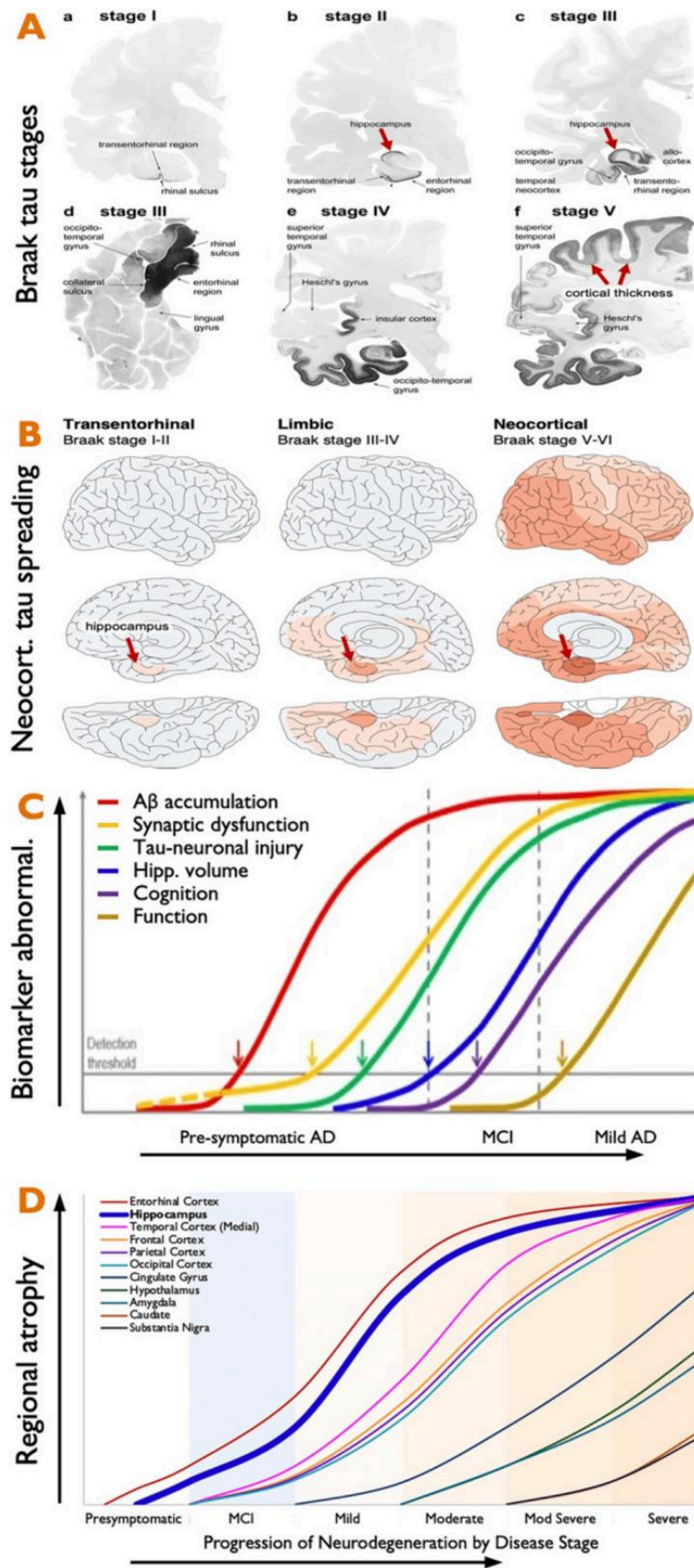


Figure 3. The typical progression of AD, which includes early amyloid accumulation, spread of tau from the entorhinal cortex and hippocampus to the neocortex, increased neurodegeneration, and progressive brain atrophy. It also indicates that hippocampus atrophy may commence prior to the manifestation of overt symptoms and will persist as the disease advances from light cognitive disorder to dementia [21]

4. Episodic memory

Episodic memory is the recall of events and experiences that can be retrieved in connection with a specific time and in order. The primary components of episodic memory are the "what" and "who" of a previous experience, as well as the "when" and "where". The episodic memory of a person can be assessed through interviews or self-reports; however, due to the considerable amount of detail that needs to be remembered, this method is impractical for individuals with memory disorders or speaking disorders [22]. Encoding, storage, and retrieval are the three periods of episodic memory. Encoding is the initial stage of concentrating, perceiving, and organizing information for learning. Storage is the potential to keep new material for a long time; retrieval is the capacity to recall this exact information intentionally. Retrieval is generally considered a person's ability to rapidly recall new knowledge, and recognition memory is often tested by a yes/no forced-choice test to see if one can distinguish between old and new knowledge; thus, it involves storing [23].

5. Spatial memory deficits

People with AD usually have space memory issues and are disorientated. They cannot remember where they have put their things. They often exhibit wandering behavior, and this is also one of the signs of spatial memory impairment [24]. Spatial memory and navigation are essential functions of the neural circuit. It is made up of grid cells in the medial entorhinal cortex (MEC) and place cells in the hippocampus in both human and animal brains. MEC neurons layer 2 and 3 and grid cells both send their axons to the CA1 region of the hippocampus, where spatially tuned place cells are located in the circuit. Remapping is a function that allows grid cells and place cells to retain a variety of firing patterns that correspond to different environments. Remapping of grid cells and place cells can offer subjects a variety of integrative codes for diverse circumstances. Consequently, spatial memory is believed to be containing a circuit mechanism for pattern separation through remapping. To study the problem of spatial memory deficits in AD, the researchers used a context discrimination experiment with APP-KI mice, which develop amyloid- β plaques similar to those found in AD. The mice were divided in two groups, Context A and Context B, which looked similar but had different spatial features. In Context A, the mice received a mild foot shock, while no shock was given in Context B. The researchers then measured how much the mice froze in each environment. Freezing showed whether the mice remembered which location was dangerous. Young APP-KI mice were still able to distinguish the two environments, as shown in Figure 5. However, older APP-KI mice froze at similar levels in both contexts and had a lower discrimination index than healthy wild-type mice, as shown in Figure 4. A discrimination index with the same sized high-scoring group and the low-scoring groups in the test. In this context it measures how well mice distinguish the shock-associated context from the safe context. A higher index indicates better contextual discrimination, whereas an index closes to zero indicates similar freezing in both environments and impaired spatial-contextual memory. This means that they could not clearly remember which environment was connected to the shock. The experiment demonstrates that deficits in spatial memory associated

with AD involve difficulty recognizing and forming separate memories of similar places, which could help explain why patients can become confused or lost even in familiar environments [25].

6. Clinical and real-world implications

Early detection of AD is necessary, as cognitive changes could have begun several years before significant memory loss appears in people with disease. The Hippocampus is a good object of early research. For a long time, doctors and researchers have employed MRI to measure hippocampal volume. A small hippocampus is a sign of neuronal loss in AD. According to the research "Early Detection of Alzheimer's Disease Using MRI Hippocampal Texture", one can determine the beginning of AD through changes in the internal structure of the hippocampus before any reduction in total volume is observed. Hippocampal Texture is the detailed structure of light and pixel arrangements shown in an MRI image. These patterns are not always obvious in the scan pictures. Therefore, computer-based image analysis and machine learning technology have been employed in the measurement process. Researchers have utilized T1-weighted MRI images from the AD Neuroimaging Initiative (ADNI) to create a hippocampal texture marker, which has subsequently been applied to independent datasets from the Australian Imaging, Biomarkers and Lifestyle study (AIBL), the Danish aging study, and the Metropolitan cohort, among others. The results showed that hippocampus texture was more predictive of the onset of AD in people with mild cognitive impairment (MCI) than hippocampal volume. In the ADNI dataset, 0.74 was texture analysis value of Area Under the Curve (AUC); it is a measure that indicates how well a test or model can distinguish between two groups, such as people who will develop AD and those who will not, and hippocampal volume was 0.67. The AUC of Texture Analysis in the independent Australian dataset was 0.83. Based on the above, it can be determined that some structural changes in the hippocampus have already occurred before substantial atrophy. A patient with progressive amnesia will be examined cognitively in the clinic to assess their memory, attention, language, sense of time and place, thinking abilities, etc. According to the above research, an abnormal structure of the hippocampus was associated with lower scores in the Addenbrooke's Cognitive Examination; however, only the size of the hippocampus was not correlated with the Metropolitan group. Cognitive assessment combined with MRI texture analysis can help us better know about a person's condition. Physicians can also periodically carry out cognitive tests and MRIs to check for any changes in memory or in the shape of the hippocampus. As MRI texture shows changes in the structure of the hippocampus and glucose metabolism indicates how active the hippocampus is, both types of data can help us better understand the extent of early brain injury. In the FDG-PET (positron emission tomography) pictures, a texture marker was likewise linked to decreased glucose metabolism in the hippocampus. Active and healthy neurons are generally glucose-dependent for energy, so reduced glucose metabolism may be a sign of impaired hippocampal function. Therefore, MRI texture, cognitive tests and other biomarkers can be used together in the examination of patients by doctors. Many research groups around the world have set up ADNI in the United States and AIBL in Australia to collect brain scan data, cognitive test results, other health indicators, etc., for the development and assessment of early-detection technologies. In the future, hospitals will be able to automatically analyze the texture of the hippocampus in regular MRIs and recommend further examinations or closer observation of some patients with the help of software. Early discovery will help to make adjustments to one's daily life, learn new ways to remember, take care of health and other measures before cognitive decline is severe, etc. It can help researchers find suitable volunteers for the clinical trials of interventions to slow the development of AD. However, for the diagnosis of patients, texture analysis of the hippocampus should not be used alone due to

other reasons such as aging, other neurological diseases and differences among individuals. Considering the patient's medical conditions and cognitive tests, neurological examinations, blood or cerebrospinal fluid tests, PET scans, etc., need to be conducted to determine whether it is indeed AD. Based on the above research, it is proposed that general analysis of hippocampal MRI images can help in the management of AD after diagnosis, early detection of severe memory decline, precise monitoring of changes, and the development of personalized treatment plans [26].

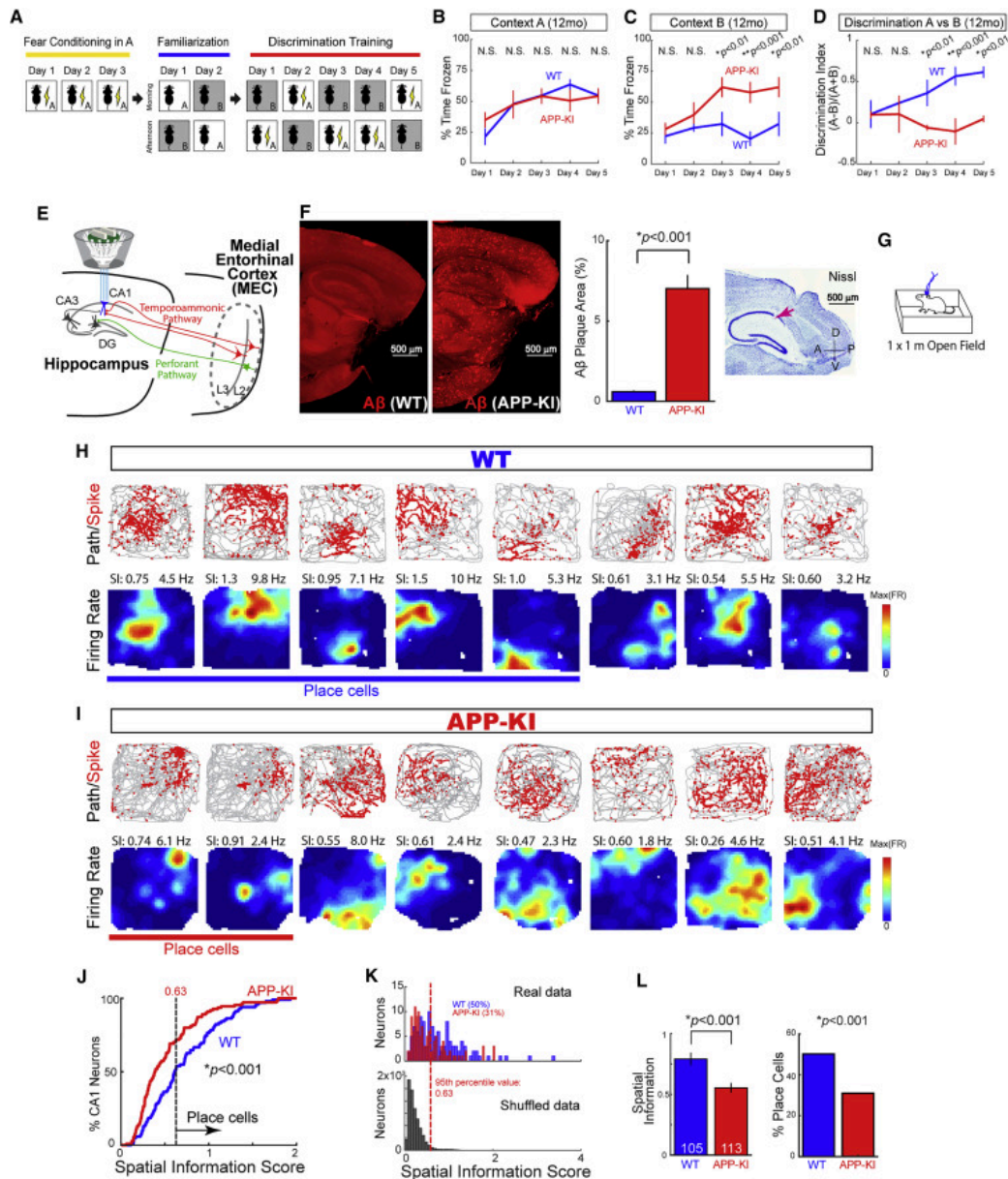


Figure 4. Shows how old APP-KI mice's hippocampal CA1 neurons had somewhat diminished spatial tuning and impaired spatial memory [25]

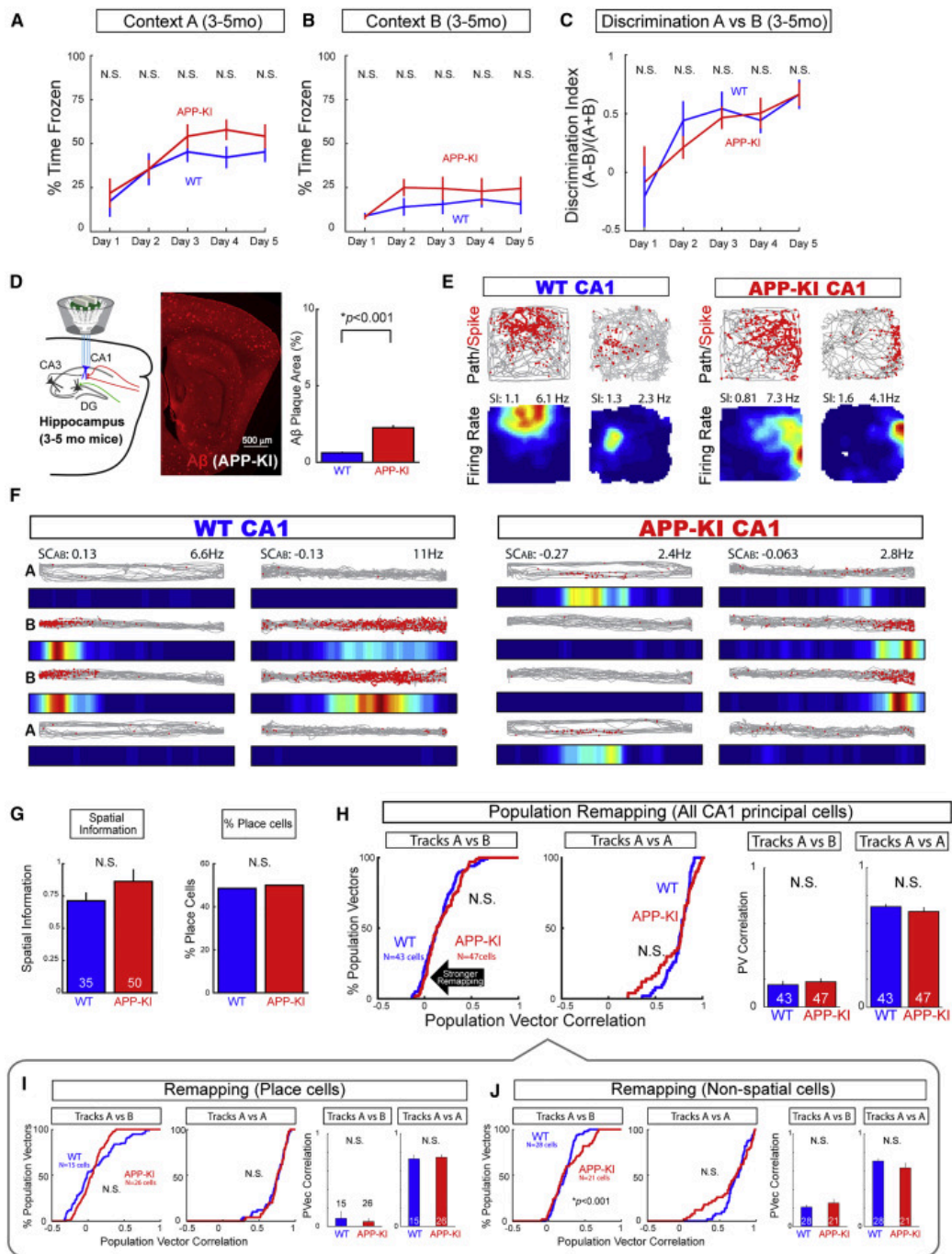


Figure 5. Young mice with APP-KI demonstrate intact spatial memory and intact remapping in their CA1 neurons [25]

7. Implications for Alzheimer's treatment and research

The three sections of this part are: protection of early-stage AD, understanding the progression process of the disease, and future treatments and plans.

7.1. Aiming at early hippocampal damage

One way to deal with AD is to protect or repair the damaged hippocampus before it is too far gone. The hippocampus is needed to store memories, but it is also one of the areas in the brain that is damaged early in AD. Shetty thinks that neural stem cells (NSCs) are kind of regenerative cells capable of turning into various kinds of brain cells, and they may help repair damage to the hippocampus. Transferring NSCs to the hippocampus shortly after the injury could prevent the memory problems that would develop in the later, chronic stage of the injury in animals. Cells can protect the hippocampus in the following ways: they release neurotrophic factors to promote the growth and survival of neurons, reduce inflammation, create new gamma-aminobutyric acid (GABA)-producing interneurons to help regulate brain activity and maintain a balance in the brain, repair damaged myelin, and keep neurogenesis in good condition. It is the generation of new neurons [27]. Based on the above analysis, it is proposed that future Alzheimer's therapy will target the prevention of damage to brain cells in the hippocampus and the reconstruction of damaged neural networks. However, NSC transplantation is still in the experimental stage, and most of the evidence presented in this paper is based on animal studies, not human Alzheimer's patients.

7.2. Slowing the disease progression

Even if the treatment of NSC transplantation is safer and more effective in the future, doctors will still need to decide when to start the treatment based on the speed of disease progression for each individual patient. To slow the progression of AD, it is necessary to know that different people have different speeds of disease development. Thalhauser and Komarova studied the medical records of 648 Alzheimer's patients to determine how long they were in different stages of the Functional Assessment Staging (FAST) procedure. FAST is a way to judge the level of function for people with dementia. It is a simple and general way to determine a person's present level of function and how that function changes over time [28]. The two kinds of results are as follows: A group of fast-rising and a group of slow-developing. The average duration of a period in the three stages could be as long as two years. It was also found that patients in the early stages were likely to continue to decline at the same rate afterwards [28]. Although this study is not a drug that directly treats AD, it will still offer some therapeutic effects. Doctors can observe the change in cognitive functions, daily life, brain atrophy and biomarkers, etc., over time, to find out which patients are likely to decline more rapidly. These patients will be able to get timely treatment. People should also divide the rapid-progressors and the slow-progressors in the clinical trials, otherwise, a treatment group with a relatively high proportion of naturally slow-progressing patients might seem to have achieved success falsely. Therefore, by learning about the different speeds at which people change, people can better test various drugs and develop individualized anti-aging plans for the brain.

7.3. Future therapies

Future Alzheimer's therapies will likely aim to change the disease process instead of only reducing symptoms. Current symptomatic drugs discussed in the article, including cholinesterase inhibitors, which increase the activity of a brain chemical complexed in memory and learning, and memantine, may produce modest improvements in memory, daily functioning, or general condition, but they do not stop the underlying neurodegeneration. Researchers are therefore studying disease-modifying treatments that target A β and tau, the two abnormal proteins strongly connected to Alzheimer's pathology. Possible approaches include reducing the production of these proteins, preventing them

from forming toxic aggregates, removing harmful forms from the brain, or combining several approaches. Other possible targets include inflammation, oxidative stress, and vascular risk factors. Most importantly, future treatment may need to begin during the presymptomatic or very early stage, when neurons are damaged but have not yet been lost permanently. MRI scans, amyloid- β and tau levels in the cerebrospinal fluid (CSF), PET imaging, and sensitive cognitive tests can be employed to select suitable patients and determine whether the treatment is protective of the brain. The authors conclude that further investigations must concentrate on the neuroprotective effects of disease-modifying drugs before obvious dementia develops. Overall, the most promising strategy has the potential to combine early diagnosis, protection of the hippocampus, careful monitoring of each patient's progression rate, and treatments that target several disease mechanisms at the same time [29].

8. Conclusion

One area of the brain where AD causes memory loss is the hippocampus. Overall, the dentate gyrus and the CA1-CA4 subregions usually work together to retain new experiences and are not very similar. It can also complete the missing parts of an event based on the available clues and pass this information to different parts of the brain for long-term storage. If the above connected network is damaged, then not only will but also many parts of the memory processing will fail. In AD, there are A β plaques and abnormal tau accumulation, synaptic loss, inflammation and neuronal death; gradually, there is damage to the hippocampus and entorhinal cortex. CA1 is more susceptible and may change early in the course of the disease. Changes in the dentate gyrus and CA3 can also interfere with a person's ability to differentiate between analogous experiences or remember the whole event after only keeping some of it. As a result, the patient has suffered from short-term memory loss, disorientation, difficulty learning new knowledge, etc. The evidence in this paper also shows that damage to the hippocampus may occur before the appearance of dementia symptoms. However, a single test should not be used alone because of ageing and other neurological diseases, memory and brain structure can also be impaired. In the future, researchers should try to protect the hippocampus before too many neurons are lost. The possible way is to reduce the amount of harmful A β and tau proteins and repair damaged neural circuits, etc. Currently, timely diagnosis and ongoing management of all pathogenic mechanisms in disorders can mitigate cognitive decline and preserve an individual's memory and self-care capabilities.

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