Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/63/20241585

The role of the hippocampus in memory formation and consolidation

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Abstract. The hippocampus is one of the most well-studied areas in the brain. After the studies on Henry Molaison (H.M.) and rodent model confirming its role in memory formation and consolidation, its anatomical, physiological, and psychological characteristics in memory processing have been studied for a long time. The framework of its role in memory processing is continuously building up from the synapse level to the system level. Current studies are working on enriching the detail of the blueprint and confirming whether the framework can explain results recording from new techniques. This review will introduce the physiological, theoretical mechanism of memory formation and consolidation in the hippocampus with results from current studies. In addition, it will also discuss the current process of framework, suggest some limitations that these studies face, and give a comprehensive view of the role of hippocampus' functions in memory processing after the study of H.M. Future studies should incorporate longitudinal designs to understand the developmental trajectory of hippocampus and its role in cognitive development.

Keywords: hippocampus, pattern separation and completion, system consolidation theory.

1. Introduction

The hippocampus, shaped like a seahorse, located deeply in the brain's medial temporal lobe, plays a crucial role in cognitive processing. Many studies have been conducted to understand its evolutional, physiological and cognitive roles. The famous case study of a human patient, Henry Molaison (H.M.), who surgically removed his hippocampus, evidently supports the idea that the hippocampus takes part in long-term memory formation. The study showed that after removing the medial temporal lobe (hippocampus), H.M. lost the ability to form new episodic long-term memory ("when", "where", and "what" components of the events). At the same time, he still has standard short-term memory (storage of immediate information) [1]. This highlights the role of the hippocampus in consolidating short-term memory into long-term memory. In addition, the animal study of O'Keefe and Dostrovsky on mice in maze finds that when the mice are in certain location of the maze, specific corresponding neurons would be firing in the hippocampus by using electrode recording [2]. This study highlights the role of hippocampus in encoding and forming spatial memory. However, the exact mechanism of how the hippocampus computes memory formation and consolidation remains unclear. Several theories have then been introduced to explain this process of formation and consolidation. This review will include the recent progress in these areas, from theoretical basis to the physiological mechanism of memory consolidation. Apart from building up the framework of how hippocampus encoding and consolidated

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DOI: 10.54254/2753-8818/63/20241585

memory, mostly episodic memory. There are studies working on other forms of memory which may also be processed by hippocampus, prospective memory. This form of memory would enable people to imagine things they have never seen, and therefore, they could be used for further work on other latent properties like imagination.

2. The role of hippocampus in memory formation

The study on H.M. suggested the critical role of the hippocampus in memory formation. After that, the hippocampus is extensively studied how memory is formed and consolidated into other areas. The physiology composition supports the hippocampus for its role in memory formation. Firstly, the hippocampus is one of the few brain parts that is highly plastic. To be more specific, the structure or functions of synapses in the hippocampus can be modified, and in the long term, new neurons can be generated. Synapses are the main sites where neurons or glial cells in the brain communicate with each other. According to Eric Kandel's study on sea slugs, the synapse's strength computes the memory and learning process. The synapse's high modifiability provides the physiological basis for memory formation [3].

The cellular mechanism under the synaptic plasticity is called long-term potentiation (LTP); It causes a long-lasting increase in synaptic strength. LTP is induced by high-frequency electrical stimulation (100Hz) and leads to a cascade of events, including neurotransmitter (glutamate) releasing, the opening of post-synaptic channels, induction of graded potential, the influx of calcium followed with cascades of cellular signalling pathway and new protein synthesis. In these processes, N-methyl-D-aspartate receptors (NMDAR) on the post-synaptic neurons are crucial for the LTP cellular mechanism because of their properties as a coincidence detector. NMDARs would only open their channel if the glutamates (neurotransmitters released from pre-synapses) bind to them and the post-synaptic neuron has been depolarized to remove the magnesium ion blocking in the channel. Once these two conditions are matched, calcium influxes into the post-synaptic neuron and activates calmodulin-dependent Protein Kinase II (CaMKII) to induce a series of signalling events to add and phosphorylate more α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) onto the post-synaptic cell surface to increase the conductance of AMPARs. This increase in AMPARs causes structural and functional changes in the post-synaptic neuron. The rise in the number of AMPARs causes an increase in the surface area of the post-synaptic area and, therefore, an increase in the size of the spine. The actin cytoskeleton was also developed to support the structural changes. Next time, the post-synaptic neurons would have a higher depolarization for the same level of neurotransmitters released from pre-synaptic neurons due to the higher conductance of AMPARs [3]. These structural changes make neurons which undergo LTP more resistant to depotentiation. It is also a coincidence that H.M.'s old long-term memory is not lost, and his performance on memory cognitive tests for childhood memory is better than those with undamaged brains.

Secondly, the hippocampus comprises place and grid cells essential for space navigation and coordination. The place cells encode the location information. The grid cells integrate spatial information and are responsible for spatial navigation; they also work coherently to form a cognitive map. Ohn O'Keefe and Lynn Nadel suggest this cognitive map theory. It is considered to give out the spatial representation for episodic memory, which is considered encoding at the hippocampus. Episodic memory is considered to be made up of many different components [4].

Apart from spatial content, other abstract contextual details of episodic memory, like temporal context, are also considered integrated in the hippocampus. For example, Fortin's study on rodents showed that the hippocampus encodes the sequence of events by lesion studies [5]. There are many types of representations of experience encoding in the hippocampus [4]. From the structure view, the hippocampus receives input from several sensory centres into the dentate gyrus (DG) and then projects to the Cornu Ammonis 1 (CA1) region [6]. These detailed sensory components enable the hippocampus to memorize many detailed episodic memories, including distinguishing similar memories by minor differences known as pattern separation and quickly retrieving the whole memory based on incomplete or partial abstract cues called pattern completion. CA1 then project to the CA3 region, a self-loop

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structure that facilitates pattern separation by amplifying and stabilizing similar but distinct memories and helps retrieval by reactivating whole memory traces by incomplete cues. It takes part in linking pattern completion and separation. Studies that damage the CA3 area also support this correlation; pattern separation and pattern completion impairs after the lesion.

A recent study looks at the properties of these sub-regions in the hippocampus. Studies conducted by the research group of Allegra and her colleagues, using two-photon calcium imaging techniques on DG and CA1 areas of rodents whose heads are restricted in movement, investigated behaviour differences between these recorded areas [7]. They present several sets of designed virtual reality environments with minor differences in spatial pattern and context of pattern. By recording the firing properties of the neurons in DG and CA1, they found that DG works better in selectivity of minor differences in spatial, contextual, or non-spatial visual stimuli than CA1. This confirms that DG plays a vital role in pattern separation compared to CA1. Moreover, when more significant differences occur, the neuronal activity in CA1 is more significant than that of DG [7]. However, the mechanism of pattern separation and completion is still unclear. Evidence using the whole-cell patch clamp on the granule cells in the DG shows that pattern separation is due to the inhibition signals from neighbouring cells.[7] All cells receive the signal sent from the sensory areas; they all activate at first, but some of them turn to send inhibitory information to neighbouring cells.

At the system level, hippocampal sub-regions connect different brain areas. Each sub-region may have its distinct connectivity, which directly correlates with the different memory outcomes they correspond to. The area they connected to gives properties of the types of memory they encoded for. For example, the posterior part of the hippocampus connects with the retrosplenial, which encodes for spatial navigation, and the other posterior part of the hippocampus encodes for spatial-related memory [8]. An area, the medial prefrontal lobe (mPFC), which is also crucial for memory formation and memory improvement, shows a clear trend of age-relating behaviour of memory improvement. However, unlike mFPC, there is no significant relationship between the layout of hippocampal sub-areas and the age. The recent neuroimaging study, using fMRI on samples ranging from 8 to 25 years old human participants, shows the hippocampus exhibits an increasing trend in functional connection with mPFC along the long axis of the hippocampus (from anterior to posterior) [8]. This may suggest that the hippocampus would involve some age-related properties for memory formation.

3. The role of hippocampus in memory consolidation

3.1. Memory consolidation in neuroimaging and animal model studies

Consolidation refers to the process of stabilization and storage of the newly formed memory. The Study of H.M. also suggested that the hippocampus is critical for memory consolidation. The consolidation process of the hippocampus requires the connection between the hippocampus and other brain areas in the system, known as systems consolidation. The cooperation within these areas highlights the time-limit properties of hippocampal memory. A theory on memory formation called the dual-processing theory suggests that memory formation and consolidation would be slow or fast. The hippocampus is responsible for the quick step; It takes part in the initial encoding of memory and temporarily stores memory for weeks to months. The study using functional Magnetic Resonance Imaging (fMRI) could support the idea that the activity of the hippocampus increases when the participants memorize new information. The slow steps may take place at the neocortex [9]. The temporarily stored memory transfers to the neocortex, which means these sorts of memories would not be lost due to the damage to the hippocampus after transfer. This theoretical process also coincides with the study of H.M.; new memory cannot be formed due to the loss of the hippocampus, leading to the inability to encode new long-term memory; the old long-term memory remains because they are already transferred to the neocortex. However, evidence suggests increased hippocampus activity using fMRI while retrieving long-term or detailed memory. This is explained by the multiple tracing theory, which suggests that new memory tracing will be formed when memory is retrieved. In addition, this memory will be strengthened after retrieval [10].

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The possible molecular mechanism for memory formation and consolidation has been introduced by studying the engram neurons resulting from memory encoding and retrieval. Memory consolidation requires the change of synapse's structure in the long term; as mentioned above, the long-term potentiation would increase the level of actin skeleton around the synapses. The study of Marco and his colleagues used a technique called Targeted Recombination in Active Recombination (TRAP), which could be used to monitor the gene expression of the targeted cells' cytoskeleton activation; fluorescence tags are applied as well [11]. The activity levels of two groups of mice are compared; one group has reactivation stimuli, and the other group is unchanged. The activities of the reactivated group are significantly higher than that of the unchanged group, confirming that the memory would strengthen after retrieval. In addition, the study found a population of enhancers that would increase activity by increasing chromatin accessibility and, therefore, increase interaction between enhancers and premotor, which may stand as the critical component for the early memory formation processes because the level of promoters remains stable and sufficient during the process of synthesizing new neurons of the memory formation. Moreover, similar chromatin accessibility behaviour was observed during early memory consolidation. This suggests that this chromatin accessibility correlated mechanism may contribute to the molecular mechanism of memory encoding and stabilization.

In addition, although many experiments have been conducted to boost the efficiency of learning and memorizing, the mechanism for accelerating memory formation still needs to be determined. For example, the study of McGaugh suggests that the arousal system and emotion affect memory consolidation [12]. Plenty of factors affecting the brain state also contribute to memory consolidation, like stress and sugar uptake levels. The number and the complexity of factors involved make building a computation model of memory consolidation even harder. Apart from that, the molecular basis of the memory process is not fully understood because the existing experimental tools could not provide detailed and precise recordings, including the temporal and spatial dimensions. In addition, the molecular mechanism underneath is complex and dynamic. Plenty of cascades occurred at different stages of memory consolidation, including many different kinases, functional proteins and their associated protein during transcriptions and translation. For example, the LTP is considered to happen roughly minutes to hours after the events, right after the synaptic tagging, which refers to the initial marking of the changes for the synapses that happened at the second-to-minute level after the events happened [13]. The consolidation period in which LTP happened is known as Intermediate Consolidation. During this period, only the structure of the synapses is changed by using the extra AMAPRs stored on the vesicles within the cells; no new protein is synthesized. Flexner's study can support this. After using protein synthesis inhibitors, the short-term memory remained while the long-term memory was not formed.

3.2. Sleep as a crucial factor

Sleep is suggested as the other crucial brain state for memory consolidation. Diekelmann and his colleague show that sleep is crucial for declarative memory (factual and episodic memory) [14]. In addition, according to the wave recording using EEG (electroencephalography), sleep has been divided into different sub-stages, such as non-rapid eye-movement sleep (NREM) and rapid eye movement sleep (REM). The NERM includes several stages; among these, slow-wave sleep (SWS), characterized by slow brain waves and slow oscillations (4-8Hz, known as delta waves), is crucial for memory consolidation, especially for episodic memory. Research conducted by Wilson and McNaughton (1994) shows that the hippocampus would replay the neuron activities learned during the awake state, which is considered part of the mechanism of consolidation [15]. It hypothesized that the hippocampus reactivates recent experiences through sharp-wave ripples, synchronizing them with sleep spindles and slow oscillations in the neocortex to transfer memories to long-term storage.

A recent study using the real-time closed-loop electrode (RTCL) implanted deep inside the brain of epilepsy patients supports that the synchronised wave would increase the accuracy of memory formation [16]. The cognition tasks are taken twice, 30 minutes after learning and after 10 hours of sleeping with or without the RTCL stimulus. The test results show that the number of people who sleep under the

DOI: 10.54254/2753-8818/63/20241585

RTCL stimulus exceeds those without RTCL. This finding consists of Wilson and McNaughton's study; enhanced synchronised stimulation would improve memorisation accuracy compared with control. In addition, the study also suggests that despite the increase in memorising accuracy, the reaction time decreases; this suggests that not all aspects of the cognitive ability of a task would be improved by sleep. Furthermore, they also record the exact neuron firing pattern; the phase-locking of the spikes is more profound and the proportion of phase-locking increases.

Moreover, Schabus and his colleague's study shows that people with more sleep spindles will have a better memory. These synchronized spindles are considered underlying in the induction of LTP. A recent study using optogenetic techniques investigated the relationship between LTP and sleep [17]. It monitors the genes of mice to make the LTP under light. After learning that no synchronized sharp-wave ripple pattern is observed while light is applied. However, synchronized patterns are observed 2 hours after learning while the light turns off. This indicated that LTP may contribute to the basis of synchronized activity during sleep, which is essential for consolidation. REM also contributes to memory consolidation. However, it contributes more towards procedural memory, which is unconscious memory essential for learning a new skill.

4. Conclusion

In summary, after H.M.'sH.M. study, theoretical frameworks for memory formation and consolidation are approaching completion. These theories for formation covered the synaptic level, LTP; cellular level, place cells and grid cells in cognitive map theory; connectivity level; pattern completion and separation in D.G., CA1 and CA3; and system level; hippocampus connect with multiple sensory centres and other areas in the brain essential for planning and memory storage. In addition, memory consolidation includes sleep, a brain state showing the pattern of repeated sleep spindle and synchronized activities, which can indicate the replay of activity that will be memorized. The study uses optogenetics by blocking the process of LTP to see the pattern of the sleep spindle, which connects the activity of formation and consolidation in the hippocampus. Moreover, the molecular mechanism, chromatin accessibility, would influence the enhancer level during memory formation, suggesting that memory consolidation theory occurs at an early stage of memory formation and memory consolidation process, which may suggest they are using a similar molecular mechanism. More and more studies are being conducted to fill the gaps between the physiological structure mechanism of the hippocampus and its function to form and consolidate memory. Moreover, these results can be used to mimic the framework for studies of other latent properties.

However, there are still some unsolved questions. The primary controversial topic on the system consolidation theory mentioned above is the precise consolidation timeline. The rate at which memory is formed and consolidated may vary by individual differences. The neuropharmacological experiment cannot provide the mechanism for this short-term, long-term memory transaction over time and space. Moreover, most experiments are conducted on animals, so some results cannot be fully translated for human use. Translating the findings for clinical use is still challenging.

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