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Review

A Brief Overview of Learning and Memory

Öğrenme ve Belleğe Genel Bir Bakış

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ABSTRACT

Learning and memory occur as a result of the interaction of millions of neurons in the brain. Different types of memory are formed and stored in varying ways. So, different classifications have been made for memory. It can be divided into short-term and long-term memory, roughly. Also, long-term memory can be classified into 2 categories as explicit and implicit. Changes in synaptic plasticity are associated with learning and memory. After a neural pathway is stimulated, they begin to give higher amplitude responses to individual stimuli. So, this pathway is strengthened and potentiated. In other words, if a piece of information is learned over and over again, it makes a way for itself in the nervous system. If the information is not repeated and consolidated enough after the first path is formed, this path is lost. In other words, the connections between neurons eliminate over time. This phenomenon is called forgetting. In this way, it is interpreted as long-term changes in synaptic activity, permanent changes in behavior patterns and choices, and processing of memory into neuronal networks. This review provides a brief overview of the different types of learning and memory and their formation mechanisms.

Keywords: Learning, memory, long-term potentiation

ÖZ

Öğrenme ve hafıza, beyindeki milyonlarca nöronun etkileşimi sonucu oluşan bir süreçtir. Hafıza türlerine göre farklı çeşitlerde oluşturulur ve depolanır. Bu nedenle hafıza için farklı sınıflandırmalar yapılmıştır. Hafıza, basit bir şekilde kısa süreli ve uzun süreli hafıza olmak üzere ikiye ayrılabilir. Uzun süreli hafıza ise açık (explicit) ve örtük (implicit) olarak iki kategoride sınıflandırılabilir. Öğrenme ve hafıza sinaptik plastisitedeki değişiklikler ile ilişkilendirilir. Nöronal yolaktaki devam eden uyarıların ardından gelen tekli uyarılara artan genliklerde cevap oluşturulur. Dolayısıyla bu yolak güçlendirilir ve potansiyelize edilir. Başka bir deyişle tekrar edilen bilgi sinir sisteminde kendi yolunu oluşturur. İlk yol oluşturulduktan sonra bilgiler yeterince tekrarlanmaz ve pekiştirilmezse bu yol kaybolur. Yani nöronlar arasındaki bağlantılar zamanla ortadan kalkar. Bu fenomen unutma olarak adlandırılır. Bu şekilde, sinaptik aktivitede uzun süreli değişiklikler, davranış kalıplarında ve seçimlerde kalıcı değişiklikler ve hafızanın nöronal ağlara işlenmesi olarak yorumlanır. Bu derleme, farklı öğrenme ve hafıza türleri ve bunların oluşum mekanizmaları hakkında kısa bir genel bakış sağlar.

Anahtar Kelimeler: Öğrenme, hafıza, long term potansiyasyon

INTRODUCTION

What learning is, where memories are stored, and what kind of changes occur between neurons when memory is formed have been one of the most intriguing questions in modern neuroscience. While learning is defined as a permanent change in behavior as a result of experiences, memory is the ability to encode, store, and recall information, the trace of learning in neuronal networks.[1] Learning and memory are vital for individuals to perform their daily activities. In this review, subjects such as what are the different types of memory, how memory is stored in the brain, and what changes occur in the nervous system when memory is created are tried to be explained briefly.

Types of Memory

Memory is an important part of daily life. It allows us to interact with the environment and other people, allows experiences to be preserved, and minimizes risks. Neuroscientists have divided memory formation into 3 main processes: The first is encoding, which is initial registration and acquisition of information. The second part is the storage, that is, the preservation of information and the creation of a continuous record of the encoded

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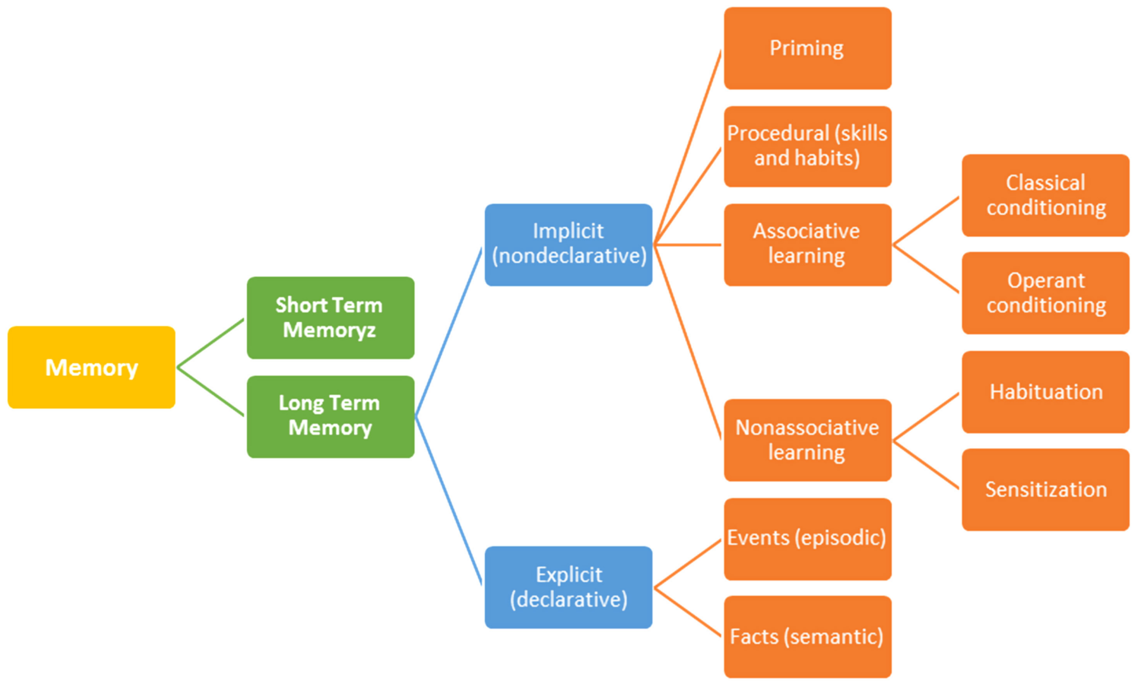

Figure 1. Memory classification (modified from Kandel, 2010).

information is the process of placing it in memory. The last stage of memory formation is retrieval, which is defined as recalling or reminding the information from the store.[2]

Memory is generally classified in 2 ways, according to time and the nature of knowledge. Depending on its duration, memory is divided into short-term and long term. The classification of memory according to duration is shown in Figure 1. Long-term memory can be divided into 2 categories: declarative and non-declarative. Declarative memory is the memory system with a component of consciousness and contains facts or events. Non-declarative memory can be examined in 4 main categories: priming, skills and habits such as riding or driving, associative learning such as classical conditioning (Pavlovian conditioning), and non-associative learning habit and sensitivity.[3]

If the information is not considered important enough it is deleted or the information reinforced in the short-term memory is transferred to the long-term memory for future recall. The storage period in long-term memory varies from days to years. In short-term memory, the stimulus between neuron groups involves chemical changes, while in long-term memory, there are permanent, structural, and functional changes such as protein synthesis.[4] In long-term memory, the sensitivity of synapses in signal transmission changes, and their physical restructuring is provided. This physical configuration includes an increase in the vesicle release region to increase neurotransmitter release, an increase in the number of neurotransmitters released in vesicles or structural changes that strengthen signal transmission in dendrite spines, and these processes are known to play a role in the long-term storage of information.[5]

MAIN POINTS

- Learning is a process that leads to permanent change in behavior as a result of experiences, and memory is the ability to encode, store, and recall information, the trace of learning in neuronal networks.
- Synaptic plasticity is the fundamental feature of memory storage.
- The hippocampus plays a crucial role in converting short-term memories to long-term memories.

First, it was proven that short-term and long-term memory were formed in different ways after the surgery of a patient named Henry Gustav Molaison (HM) and that a transfer was required between them. In the epilepsy surgery that the patient had undergone, bilateral temporal lobectomy was performed, and bilaterally, the amygdala, most of the hippocampus, and part of the association areas of the temporal cortex was removed. No deterioration in vital functions was observed in the patient after the surgery, and the perception, intelligence, and personality of the patient did not change. There was no significant deterioration in the patient's working memory and preoperative long-term memory, but it was observed that the transfer of short-term memory to long-term explicit memory was completely lost. While he could not remember someone he knew a few minutes ago, he could remember his childhood memories in detail. In addition, learning motor skills, simple reflexive learning types such as habituation, sensitization, and classical and operant conditioning did not change.[6,7] This situation showed the existence of two different types of memory. Accordingly, the first type of learning is the unconscious form of memory, namely implicit memory (non-declarative or procedural memory). Implicit memory typically arises spontaneously and has different forms such as preparation, skill learning, habit memory, and conditioning. The second type of learning is the conscious recall of real information about people, places, and objects and requires reflection or conscious recall of the previous experience. This type of memory is known as explicit memory (declarative or expressive)[8] (Figure 1).

Explicit (Declarative) Memory

Explicit (declarative) memory is concerned with facts and events, and information is consciously recorded. There are 2 subtypes of declarative memory: facts (semantic) and events (episodic, memory of personal experiences, autobiographical memory). Semantic memory contains only facts, away from personal connections, for example, Ankara is the capital of Turkey. However, episodic memory contains information related to variables such as time and place, and therefore, it is a type of memory that includes feelings and opinions.[8]

Implicit (Non-Declarative or Implicit) Memory

Non-declarative (implicit) memory is a type of memory that enables the acquisition of motor skills and habits. Previously acquired knowledge and skills are called without consciousness, for example, riding a bike or driving a car. While many cognitive, perceptual, and motor skills are initially stored in explicit memory, they begin to be stored in implicit memory with trials. It has been reported that a patient whose hippocampus and temporal cortex regions are severely affected has significant losses in his memory of people and events, but he can perform the functions of reading music, playing the piano, and conducting the choir but not remember what he is doing.[9] Non-declarative memory is divided into 4 subgroups as triggering, procedural memory, associative, and non-associative learning.[10]

Triggering (priming): It is to facilitate the recognition of stimuli such as newly encountered words and objects based on past experiences. In this way, the neural pathways formed by frequently used experiences are more prominent.[11] The effect of the triggering operation on implicit memory is evaluated with the word fragment test, in which a person is asked to complete the word with the missing letters.

Procedural memory: Information is not consciously recorded; it refers to motor or sensory abilities or "habits." Functional memory is used in situations such as cycling, swimming, tying shoes, or spelling a word.[12] The ability to walk and speak is procedural and although we do not have a conscious memory of learning them as adults, these skills are easily and efficiently developed as children.[12] Motor learning is actually accomplished by creating, consolidating, and combining movement patterns for behaviors. Motor and cognitive abilities are learned through repetition.

Associative learning: It is the type of memory in which the relationship between 2 stimuli or between the stimulus and behavior is learned. Associative learning is examined in 2 groups as classical conditioning and operant conditioning.[8]

- Classical conditioning was first described by Russian physiologist Ivan Pavlov. It is the type of memory in which we learn to associate neutral stimuli (such as sound or light), that normally do not produce much of a response, with another stimulus, that produces a natural response, such as pleasure or saliva (such as food). If the conditioned stimulus is given together with the unconditioned stimulus, after a while, it can create a response to the conditioned stimulus alone. Associative memory is indicated when the conditioned stimulus (sound) begins to form the same response as the unconditioned stimulus (food) prior to learning. For example, the combination of a bell that does not produce any response and the meat that causes salivation in the dog causes the dog to give the salivation response to the bell sound (Figure 2).
- In operant conditioning, the relationship between stimulus and behavior is learned, and the relationship is controlled by the consequences that emerge at the end of the behavior. If the result of the behavior is negative, the behavior is eliminated, if it is positive, the behavior is continued. Opening the bait cover by pressing the pedal in the cage where the rat is located is positive behavior and is a good example of operant conditioning.

Non-associative learning: It is the type of memory in which the response to the same stimulus changes over time. It is divided into 2 as habituation and sensitization.[8]

- Habituation is defined as the reduction of the response to a harmless stimulus in repeated encounters with the stimulus and the disappearance of the response after a while. If stimuli do not harm the person or do not cause a sense of reward, a habituation response occurs.
- Sensitization is the intensification of the response, which becomes more sensitive in repeated encounters with a strong and harmful stimulus. A good example of sensitization is the overreaction to a light touch following an application that would hurt the rat.

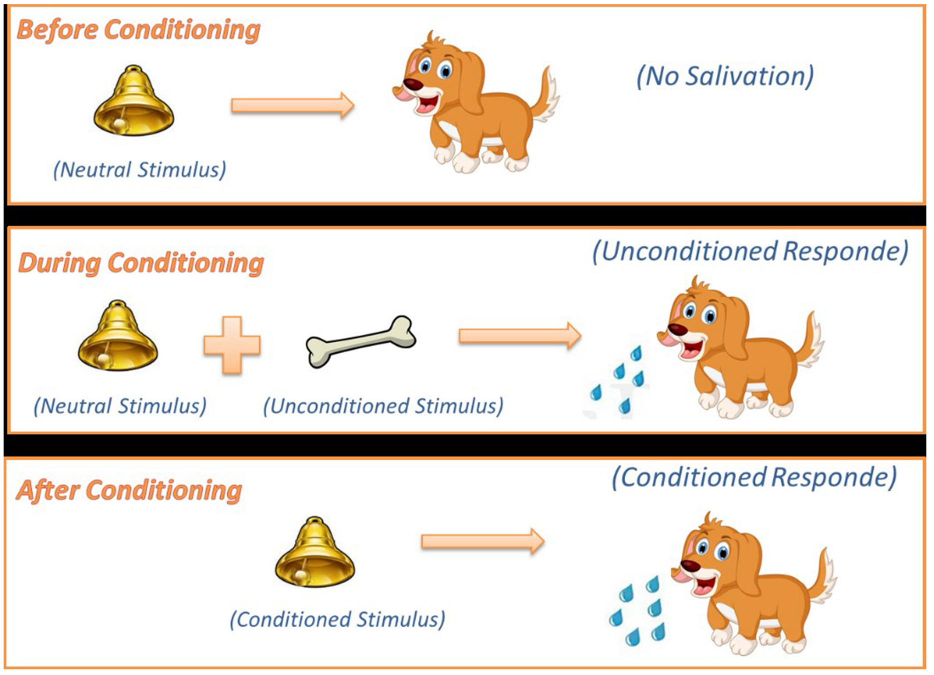

Figure 2. The classic example of Pavlov's dog.

Synaptic Plasticity

Connections between neurons change in response to experience, and this change reveals the differences between short-term and long-term memory.[13] There are many studies showing that synaptic changes play an important role in learning and memory.[13,14] In the 1940s, Hebb[15] suggested that memory is stored in synaptic connection patterns during learning, and this idea was evaluated as neurons activated simultaneously during learning strengthen synaptic connections. This simple idea is the foundation of the most effective theory of learning and memory, explaining molecular, neurophysiological, and behavioral patterns in numerous systems and organisms. Synaptic plasticity is the brain's ability to reorganize its neural circuits. Thus, structural and biochemical changes occur in the presynaptic and postsynaptic areas, forming the basis of learning and memory.[16] Synaptic plasticity controls how effectively 2 neurons communicate with each other.[5] Synaptic plasticity can be short-term or long-term. Short-term synaptic plasticity refers to changes in synaptic strength that occur in less than 2 seconds. In long-term synaptic plasticity, changes in synaptic strength persist for minutes, hours, days, or years. It is a pattern of how the brain stores information, namely, how we create and remember new memories. Different types of synaptic plasticity can be identified, depending on the type of neurons, the duration of the change, and the brain region involved. At the electrophysiological level, synaptic plasticity is divided into phenomena known as long-term potentiation (LTP) and long-term depression (LTD).[13]

Long-Term Potentiation

It is a form of activity-induced plasticity where high-frequency stimulation (HFS) causes a permanent increase in synaptic transmission.[17] Short-term high-frequency stimuli in the hippocampus lead to LTP. For a stimulus to generate LTP, it must meet 2 important conditions: excitatory and high frequency. Long-term synaptic plasticity was first described in 1973. Bliss and Lømo[5] discovered that rapid and repeated activation of synapses makes them stronger in rabbit hippocampus and they named it LTP. Different cellular and molecular mechanisms are active in different temporal phases of LTP. The early phase is independent of protein synthesis and lasts up to 30 minutes. The later stage is called persistent synaptic plasticity or long-term memory and is characterized by rapid transcription of mRNA genes into proteins and longer (≥ 1 day) synaptic efficiency. Gene transcription and translation make new-growing synaptic connections between nerve cells.[4,5] Repetitive presynaptic stimulation or synchronized input in the LTP increases sensitivity and enhances the postsynaptic response. Long-term synaptic changes are not only high input-specific but also synapse-specific.[1] Repetitive activation of excitatory synapses in the hippocampus is shown to result in increased synaptic connectivity, that is, LTP formation, which continues for hours or even days.[18]

Long-Term Depression

Decreases in synaptic activity are called long-term depression and are produced by low-frequency stimulation.[13] Theoretical studies predict the existence of LTD because without a mechanism to stabilize LTP, synapses in neuronal circuits will become increasingly saturated and thus unable to store new information. When the synaptic connection reaches its maximum activity level as a result of LTP and it gets hard to code new information, LTD selectively attenuates such synapse clusters to maintain synaptic strength.

Neuronal Mechanism of Learning and Memory

When the action potential reaches the presynaptic neuron, glutamate was released and binds to its receptors, the α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) and kainic acid (KA) receptors, on the postsynaptic membrane, and then the permeability of the postsynaptic membrane to Na^{+} ions increases. This strong depolarization causes the repulsion of magnesium (Mg^{2+}) ions that block the NMDA receptor (NMDAR) at its resting potential and the removal of the blockage, and calcium (Ca^{+2}) and Na^{+} ions flow into the cell via NMDAR (Nowak et al., 1984). Ca^{2+} influx into the postsynaptic cell activates several signaling pathways, including calcium/calmodulin kinase II, protein kinase C (PKC), and tyrosine kinase. These signaling pathways both increase the response in the postsynaptic cell and cause more glutamate release from the presynaptic cells. Calcium/calmodulin kinase II enzyme activated by Ca^{+2} entry increases the permeability of AMPA receptors.[8] Intracellular fusion of vesicles with AMPA receptors to the plasma membrane is triggered by PKC phosphorylation of the cytoplasmic tail of the endosomal AMPA receptor. Increasing intracellular Ca^{2+} activates nitric oxide synthase enzymes and induces nitric oxide synthesis, which is an important retrograde messenger. The changes that occur up to this stage are biochemical changes and constitute the early phase of LTP. Early LTP persists for 1-3 hours and does not require protein synthesis.

In the late phase of LTP, it has been shown that there is an enlargement in the presynaptic area and an increase in AMPA receptors in the postsynaptic area. It has also been reported that new dendritic spines and new excitatory synaptic areas are formed (Figure 3).[8]

The enzyme adenylate cyclase (AC), which is activated by the increasing Ca^{+2} concentration in the postsynaptic neuron, converts intracellular ATP to cyclic adenosine monophosphate (cAMP). Increasing intracellular cAMP activates protein kinase A (PKA), and phosphorylation of PKA translocates to the nucleus and phosphorylates cAMP-responsive element binding protein, mitogen-activated protein kinase activation. Cyclic adenosine monophosph ate-responsive element binding protein, a potent transcriptional coactivator, initiates protein synthesis in the cell nucleus and activates the transcription of targets (including the CRE promoter) thought to lead to the growth of new synaptic junctions. Thus, the increased synaptic strength due to the formation of new receptors and synapses mediates the storage of memories in long-term memory.[8]

Role of the Hippocampus in Learning and Memory

Neuropsychological and neuroanatomical studies show that the hippocampus and temporal lobe structures are important for declarative/associative memory.[18] The hippocampus is an important part of the limbic system located in the temporal lobe and plays an important role in the formation, consolidation, and recall of episodic memories.[18] The hippocampus consists of a trisynaptic loop containing the dentate gyrus (DG), cornu ammonis 3 (CA3), and CA1 parts. Cajal[19] published his famous

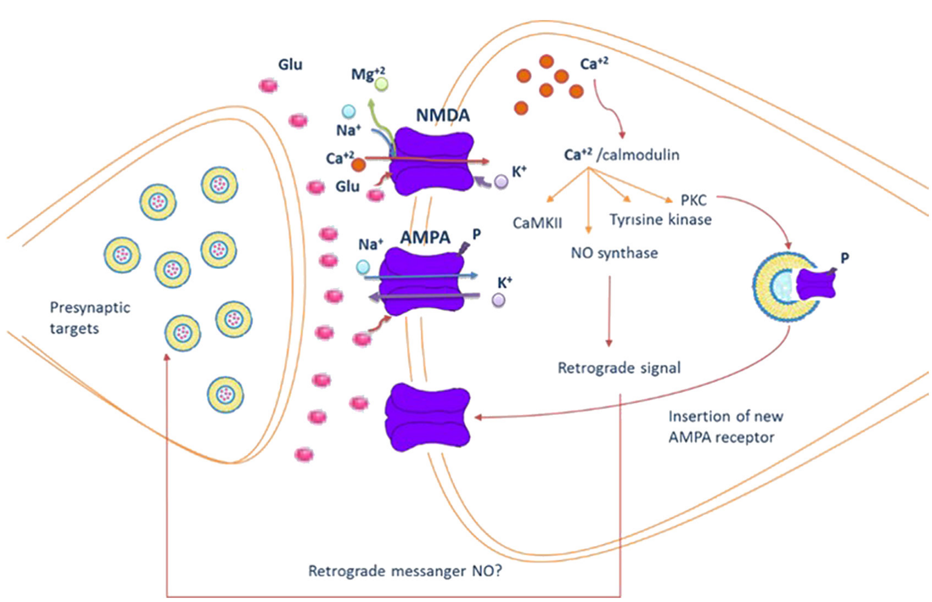

Figure 3. A model for the induction of long-term potentiation (modified from Kandel, 2013).

drawing showing the main cells, connections and flow of impulse traffic in the hippocampal formation. There are 3 main pathways in the trisynaptic loop: perforant pathway extending from the entorhinal cortex to the DG, which provides input to the hippocampal formation, mossy fibers projecting from the granular cell layer of the DG to the CA3 pyramidal cells, and Schaffer collaterals extending from the CA3 region to the CA1 region.[20]

Discovered by O'Keefe[21] in 1976, he introduced the idea that place cells in the hippocampus are a cognitive map that constitutes the representation of the environmental map in the nervous system. Place cells are nerve cells in the hippocampus that are activated (generating action potentials) only when an individual passes through a familiar place. The functional roles of neurons in the hippocampus of free-moving rodents have been characterized by spatial activation (firing) patterns. When exploring the rodent environment, neurons in the hippocampus increase their activation rate at certain locations.[21]

Field potentials, which are tens or hundreds of microvolts in normal cortical recordings, are measured in millivolts in the hippocampus.[24] Such potentials arise from the uniform parallel alignment of the soma and dendrites of pyramidal and granule cells and hippocampal afferents that trigger nearly simultaneous activation of a large population of hippocampal neurons.[22] In the hippocampus, rhythmic activities and interactions at θ (5-10 Hz) and γ (40-120 Hz) frequencies are critical for encoding and storing information.[23] θ increases during attention and is necessary for memory formation[24]; hippocampal γ activity facilitates memory encoding.[25] These 2 types of oscillatory activity often coexist, and θ-γ coupling is seen as a correlation of memory formation.[26] Thus, such oscillatory activities are likely to trigger long-term synaptic modifications that underlie learning and memory. A short stimulation or repeated HFS at the γ frequency (100 Hz) results in LTP,[27] and this protocol is widely used to elicit LTP in multiple neuronal networks.

CONCLUSION

In this review, different types of learning and memory have been described. Studies have shown great progress in recent years in understanding learning, which is a process that operates in every moment of our lives, even while we sleep. New studies on the relationship between learning and memory will provide a better understanding of this complex process.

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