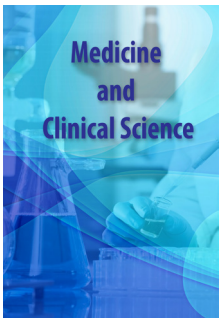
Medicine & Clinical Science

Review Article



The molecular, cellular, and biological perspectives of memory

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- Received Date: 15 Jan 2020;
- Accepted Date: 28 Jan 2020;
- Publication Date: 05 Feb 2020.

Keywords

Memory, Brain, Plasticity, Short-Term Memory, Long-Term Memory, Brain Plasticity, Neurotransmitter, Synapse

Abstract

Memory is the process that maintains the stability of intellectual, spiritual, and everyday aspects of life. Both our conscious and unconscious life depend on memory and existence would be empty and meaningless without it. The mechanism of memory formation remains one of the greatest phenomena in the fields of biology and neuroscience. Questioning the mechanism involved in memory formation roughly began a century ago with the concept of the engram, and continues to date with the advent of tools capable addressing this query and offering leading contemporary views. The present paper focuses on the way in which memory is attained or preserved and discusses the molecular biology and mechanistic function of memory. After briefly debating the mechanisms of implicit memory, the present paper will discuss the explicit memory and the complex mechanisms of neural networks required to obtain, maintain, and express learned information. The present paper gives a comprehensive review of the important literature to highlight the main issues that exist in the arena of memory science. While addressing the main contributions to the field of memory, the present paper also emphasizes studies that provide a clear description of the manner in which molecular biology has transformed our understanding of brain plasticity and memory. Moreover, the present study discusses molecular insights into implicit memory by highlighting the specific aspects that have been perceived in genetically modified laboratory animals. Finally, the present paper concentrates on the mechanisms by which the human brain encodes, consolidates, reactivates, and updates explicit memory, by discussing studies that have made a significant contribution to this knowledge..

Understanding memory organization

It has long been understood that memory is a complex process that transforms our thoughts or perceptions into durable and retrievable data, allowing us to make informed decisions. Understanding the dynamics and dependence of memory among its stages remains a fundamental challenge. Although different experimental designs and models have allowed information to be gathered regarding the nature of various events contributing to memory formation, there has been limited success in examining the outcomes. Experiencing a memory involves multiple dynamic processes that are initiated by the formation of memory and ceases at the time of the information recovery. Memory enables us to store and retrieve information after a short or long period of time and is crucial for the maintenance of our daily activities. There is no agreement to date regarding the general definition of memory; however, we consider the term as lasting changes in behavior based on prior experiences with external inputs. The present paper attempts to explain the mechanisms of implicit and explicit memory in the brain by examining the complex cellular mechanisms and neural networks required to obtain, preserve, and express saved information. The present paper discusses the manner in which simple implicit memory is attained and preserved in humans and animals and highlights the molecular biology and structural function of memory. After revealing the major contributions to the field of memory science, the present paper focuses on brain neuronal plasticity, molecular and cellular biology, and the biological mechanisms underlying memory formation and recall, which have revolutionized our understanding of brain plasticity. Finally, the paper focuses on the brain mechanisms involved in encoding, consolidating, and reactivating the explicit memory.

Declarative memory, also known as explicit memory, is the memory of information and events and is considered as form of long-term memory. Another type of long-term memory is procedural memory, which can be defined as the memory responsible for knowing how to do things such as walking, talking, or driving a car. Nevertheless, unlike declarative memory, we are not consciously aware of our procedural memories. Two major processes that characterize declarative memory are the organization of networks of memory networks maintained by the hippocampus and the encoding and retrieval of information by the prefrontal cortex. Supporters

Citation: Mallakin A. The molecular, cellular, and biological perspectives of memory. Med Clin Sci. 2020;2(3):1-5.

of modern cognitive science described the first notion as vague and proposed specific forms of systematic organization in which memories are embedded [1-4]. Offering three types of memory organizations that include associative, sequential structure, and schematic structures [3,5-8]. An associative structure involves numerous events that are connected by direct and indirect associations within a network; a sequential structure includes a chronological organization of ongoing events; and a schematic structure connects a classified or equally complex organization of items within a memory [6-8]. The brain mechanisms underlying these structures have been explained; although, there is no expectation that these organizations can be directly studied [5]. The knowledge of the existence of such organizations arises from studies identifying types of memory organization by their significance in memory judgments. A full understanding of the manner in which the brain organizes and controls memory requires further analysis in humans, with a view to characterizing these groups and recognizing the key brain areas involved in neuronal control and processing.

Neuroscience research has revealed that the hippocampus is at the center of a brain system supporting memory organization [9,10]. Recent analyses of hippocampal neuronal activity patterns have provided insights into the nature of memory organizations supported by the hippocampus. Further evidence has shown that the prefrontal cortex actively controls memory organization by means of interactions with the hippocampus [11,12]. Similarities between behavioral and physiological data in humans and animals and the resulting discoveries regarding the organization and control of memory by these brain areas have been reported by different researchers.

In describing the type of memory that is supported by the hippocampus, researchers have reported important features of memory impairment in humans with hippocampal damage. Declarative memory, which is dependent on the hippocampal region, is considered the capacity to remember specific events and facts through direct access to memories by conscious recollection. The cognitive process involves the ability to recognize a previously acknowledged stimulus via reminiscence of the stimulus within the framework of other information connected to the experience independent of the context in which it was experienced [13,14]. Furthermore, we should distinguish this cognitive behavior from episodic memory, accumulated knowledge about the world that is comprised of many experiences and is not dependent on any specific event during which the information was obtained. Episodic memory can be severely impaired following hippocampal damage [15,16]. Research in animals demonstrated the properties of memory that are dependent on the hippocampus. Conscious recollection, typically observed through subjective reports in humans, is beyond direct access in animals. One approach to identifying such memory experience is to study the recognition memory through an examination of receiver operating characteristics (ROCs), in which subjects study a list of objects and are subsequently tested to remember them on a larger list. The ROC function is typically characterized by two main dimensions that distinguish recollection and familiarity [17]. The main difference between these two dimensions is that familiarity occurs through the integration of featural elements that compose a particular perception, whereas recollection occurs via the elaboration of its association within their organizational structure [3]. Research has demonstrated that the ROC function for recognition memory in certain laboratory animals is similar to that observed in humans [18,19]. Furthermore, the ROCs favor recollection in rats under the same conditions that favor recollection in humans [20]. Importantly, considerable evidence indicates that the recollection component of the ROCs is differentially impaired by hippocampal damage in humans [13,14]. Damage to the hippocampus in laboratory animals selectively impairs the recollection-based performance, confirming the importance of the medial temporal lobe in the process of memory [20,21]. These and other observations support the view that the fundamental mechanisms of cognitive processes underlying recollection and its dependence on the hippocampus are conserved across species.

Communication within the hippocampus and prefrontal cortex

The hippocampus plays an essential role in memory, since it encodes associations among events through a framework, sequential associations of episodes, and complex organizations of related memories. On the other hand, the prefrontal cortex supports the cognitive control of memory by developing representations that use existing relative signals to select context-appropriate memory, mainly by suppressing context-inappropriate memories [22]. A dialog between the hippocampus and prefrontal cortex may reinforce context-appropriate memory retrieval, such that the ventral hippocampus sends contextual information to the prefrontal cortex, which subsequently identifies contextual rules that guide the retrieval of specific memory representations in the hippocampus. The prefrontal cortex itself controls the recovery of detailed memories in the hippocampus by suppressing of context-inappropriate memories. The inclusion of mistakes in recognition memory results in a selective increase in incorrect signals from previously learned memory in laboratory animals performing a recognition task. Further evidence for the suppression of context-inappropriate memories arises from studies in which subjects used either of two distinctive spatial contexts differing in multiple features to allow the recovery of opposing object–reward associations [23]. This observation indicates that the hippocampus can retrieve memories even in the absence of prefrontal involvement; nevertheless, the function of the prefrontal cortex is to select a suitable memory for each context by suppressing alternative representations.

Considerable evidence indicates that the prefrontal cortex contributes to the development of memory by controlling the memory recovery processes within different brain areas [24-28] via selection memories pertinent to the existing context and the suppression of irrelevant memories [29]. In humans, certain parts of the prefrontal cortex are involved in establishing the organization of relationships among memories and in monitoring retrieval. The memory impairment caused by damage to the prefrontal cortex can be characterized as a deficit in the suppression of interfering memories. Consistent with this view, patients with injury to the prefrontal cortex do not have severe losses in their memory of events. However, discrepancies caused by prefrontal cortex injury can be seen when memories of specific information must be obtained under circumstances of memory interference or distraction.

There exist substantial evidence for the importance of the prefrontal cortex in the control of memory across different species. Studies have shown that prefrontal cortex injury can result in severe loss of memory in animals when switching between learned perceptual sets [30,31]. Several studies have also demonstrated that the prefrontal cortex is important in rule-guided switching between memory strategies [32-34]. Further studies have revealed that the prefrontal cortex attains representations of behavioral settings that determine appropriate memory retrieval, acquiring prefrontal neural representations that guide perceptions, actions, and cognitive rules [28,35]. Neuronal bundle in the prefrontal cortex fire in different behavioral contexts and patterns of neural activity are altered following a change in contingencies [32,36,37]. These and other results have led to the view that the hippocampus creates organizations of memories, whereas the prefrontal cortex summaries task rules that govern the selection of memories within the hippocampal organization. Consolidation of certain memories involves the appropriate transfer of information from the hippocampus to the medial prefrontal cortex, which seems necessary for memory representations that confer the ability to resolve distinctions between new events and old memories [38]. These activities occur at varying degrees and in numerous levels of brain neuronal organizations, from simple to complex memory systems. They start with molecular and cellular changes at the synaptic level, followed by wide changes distributed throughout multiple synaptic connections of many neurons rooted in extensive neuronal networks that function at the communicative level.

Biological mechanisms of memory

The main question in the biology of memory is the degree to which mechanisms of memory processing are common across species, the answer to which appears to be a significant degree, since the fundamental molecular and cellular mechanisms of memory have been conserved during evolution. One example of such conservation can be seen during vernalization, a memory-like phenomenon observed in certain plants. Through this process exposure of a plant to prolonged cold temperature accelerates its flowering following its subsequent exposure to warm conditions; this is the phenomenon we observe during the spring season. Vernalization can be accomplished by an increase in the expression of the floral repressor gene, during which the expression of flowering locus C gene is slowly downregulated through epigenetic repression in cold temperatures, which continues when warmer temperatures return [39].

Another case of memory preservation occurs with N-methyl-D-aspartate (NMDA) receptors. Activation of postsynaptic NMDA receptors as the main component of the synaptic function of memory provides prolonged strength of synapses between nerve cells [40]. While all animals appear to have shared molecular and cellular aspects of memory, the extent to which these are common among various species has remained undetermined. Memory consolidation in animals includes two major levels; the cellular or synaptic level and the systems level [41]. The first level involves gene transcription followed by protein synthesis or repression, which mediates the association with fading and retraction of synapses, resulting in the continuous alteration of neural circuits in the nervous system and the creation of a memory. These mechanisms appear to be common among different classes, since activation of the transcription factor cyclic AMP response element-binding protein (CREB) is an essential step in the cellular level consolidation of memory in many species [42]. The second level, systems-level memory consolidation, assumes that hippocampal-dependent memories are reinforced in widely distributed brain circuits.

Humans are the main model that can provide numerous forms of higher-order learning and memory; nevertheless, it has been shown that significant elements of episodic memory, the memory system known to retain past experiences, are shared by humans and certain animals [43]. Studies have revealed an active isoform of protein kinase C (PKMζ) that may play an important role in maintaining memory. PKMζ mRNA is created by the splicing of the atypical PKCζ gene and subsequently transported to neuronal dendrites, where its translation initiates learning-related synaptic stimulation, inducing long term potentiation (LTP). PKMζ cannot be typically inhibited, but pharmacological inhibition can impede its expression, and consolidated memories and LTP can be erased [44]. Non-traumatic and traumatic memories can be extensively erased by inhibiting the activity of PKMζ in the brain; nonetheless, not all types of consolidated memories are prone to disruption by the inhibition of PKMζ [45].

The challenge in understanding the biological mechanisms of memory involves a deep consideration of these processes using sophisticated models of human perception. For example, there is evidence that certain characteristics of human memory can be modeled in animals, including such processes as declarative, episodic, and prospective memory. Novel findings related to the biological aspects of memory have not only increased our knowledge of the cognitive processes but also advanced the development of therapeutic approaches to treat different mental disorders. Another success is the rapid improvements in experimental procedures that allow the in-situ observation of neuronal activity while laboratory animals are learning or recollecting learned experiences. Soon after acknowledging the association of certain types of long-term memory with the hippocampus and the medial temporal lobe for data acquisition, it quickly became apparent that the brain has two main types of memory: explicit (declarative) memory, for facts, events, places, and items; and implicit (nondeclarative) memory, for perceptual and motor skills [46,47]. Even though we acknowledge the presence of two major types of memory, little is known regarding how either type is created or saved.

The study of basic forms of learning has opened avenues for the investigation into the molecular foundation and the possible role of these basic building blocks of neural plasticity in learning and memory in more complex brains and more complicated types of memory. Studies of the synaptic connections between the sensory and motor neurons that control certain reflexes in organisms,such as Aplysia (sea slug), have revealed that a single stimulus can increase the intensity of these synaptic connections. Such a stimulus can lead to the activation of neurons that release serotonin [48-50], which in turn, increases the concentration of cyclic adenosine monophosphate (cAMP) in sensory neurons. The cAMP molecule itself causes sensory neurons to release more of the neurotransmitter glutamate into the synaptic junction, thereby, briefly increasing the association between sensory and motor neurons. Advanced methods have allowed the identification of the molecular mechanisms involved in short-term memory and the discovery of how short- and long- term memories are stored. Earlier reports showed that in certain organisms, mutations in single genes may interfere with short-term memory [51,52]. Subsequently, it was discovered that in several species of specific insects, the mutant gene is a component of the cAMP pathway, which is the same pathway that causes sensitization in Aplysia [53,54].

Much of what we understand about the molecular and cellular mechanisms of memory arise from simple animal systems with uncomplicated sensory elements in a well-defined circuit. The study of neural function in complicated memories is a significant challenge and new advances are expected to significantly build on our existing knowledge in this area. Many questions remain unanswered, such as how are complex forms of memory encoded? What are the specific types and nominal elements of these coding systems? Does memory processing require organized activation of numerous brain areas, or is it coordinated by small groups of cells representing specific elements? What is the signal-to-noise ratio (SNR) and how durable are these codes? How does plasticity change the synapses and neuronal circuits and how does it affect subsequent processing at multiple levels of an organization to provide or represent a memory?

Conclusion

To date, extensive progress has been made in uncovering the biological and cellular mechanisms of learning and memory. The modern tools of biology have revealed how neurons and cellular signaling pathways can be modified by learning. Changes in neuronal synapses as a result of electrochemical activities or the action of neurotransmitters can alter the processing of information that controls behavior. Both memory storage and synaptic plasticity have varying temporal stages. The change from short- to long-lasting synaptic function and behavioral memory requires new gene expression. The long-term memory uses numerous cellular mechanisms for preservation, such as synaptic recognition, changes in protein synthesis at the synapse, and perhaps protein kinase-based cascades. Throughout this review, we stress that memory is not a result of the creation of a sequence of events, but rather a result of several interactive processes such as encoding of information, short-term memory, association and preservation of long-term memory, stabilization of memory during retrieval, and integration of a specific memory into other memories. We can see these dynamics in multiple levels of brain organization at varying degrees, from simple to complex memory systems. These actions are initiated by molecular and cellular modifications at the level of neuronal synaptic junctions and are followed by further changes throughout multiple synaptic connections of many neurons embedded in larger neuronal networks. Their subsequent interactions among larger neuronal networks can be seen at the behavioral level. The study of short-term memory has revealed that its formation is as a result of plasticity and changes in the strength of certain critical neuronal synapses. Further studies have revealed that these temporary changes in synaptic strength resulting from changes in the activity of certain neurotransmitters secreted by presynaptic neurons. Consequently, we recognized psychological notions implying that behavioral changes can be explained in cellular

and molecular terms. Moreover, the study of sensory-to-motor neuron synapses has demonstrated that the storage of implicit memory does not depend on specialized neurons that store information; instead, its ability is built into the neural design of the reflex pathway itself and depends on synaptic plasticity. The study of simple forms of memory in simple systems has allowed investigation into the molecular structure and the potential role of these building blocks in learning and memory in more complex systems; however, much more work remains to be done.

Acknowledgments

This study was funded by West Coast Biomedius and contributions from several interested sponsors.

Consent for publication

The main author has reviewed and consented to publication of the paper.

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