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Review Article

Demystifying the Comprehensive Neurobiology of Memory Consolidation and its Affiliation with Psychopathologies

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I N F O

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A B S T R A C T

Memory is one of the crucial aspects of human existence that is essential for the survival of human beings, vital in order to pass on information from one generation to another, and obligatory in order to attain certain knowledge regarding specific threats and circumstances so that the same errors can be avoided in the future. Memory also serves as a significant component of mental well-being. Considering the recent advancement in medical sciences in the past few years, it has explored new promising methods for understanding and managing psychopathologies of various diseases by deeply understanding and exploring the principles that explain how consolidation and reconsolidation of memory take place inside the human brain, how fragile memory traces become robust with time and are desensitised to any intervention, etc. In this review, we will try to explain the mechanisms and processes involved in memory consolidation and the influence of various determinants on memory consolidation from a neurobiological perspective in a more pronounced and well-defined way in order to provide a better comprehension for addressing the various psychopathologies that are linked with different psychiatric diseases.

Keywords: Memory Augmentation, Memory Formation, Neurobiological Mechanisms, Posttraumatic Stress Disorder

Introduction

The ability of a living organism to recall and recollect learned and observed information for using it at a later time is deemed as memory. It is biologically one of the rudimentary aspects, which is essential for the survival of the living organism. Moreover, memories are the reason behind our identity; they are the reason for who we are as they define us in society. The decisions we make in our day-to-day life, our thoughts, our emotions, and our reactions to any interactions, are all the result of our memories.[1,2] Memories are found in different forms and are dependent on different neural systems. Based on the duration, memories can be classified into two types, short-term memory and long-term memory. Short-term memory, as the name itself suggests, is the ability of the brain to remember information for usually a short period of time, which lasts from a few seconds to minutes, whereas long-term memories are distinct from short-term memories as in the former, the information is stored for a long period of time, ranging from days to decades, even for an entire lifetime.

Short-term and long-term memories can also be individualised on the basis of underlying neurobiological mechanisms they incorporate. Short-term memories involve

existing networks and post-translational modifications, whereas long-term memories are the result of structural and functional changes in neural networks that require the expression of the *de novo*.[3,4]

Memories can also be differentiated as per their behavioural manifestation. Some memories are of the explicit type (also known as declarative memory) and some are of the implicit type (also known as procedural memory).[5] Implicit memory is the type of memory that can be consciously remembered and can be declared, hence it is also called declared memory, for example, the declaration of who is the president of a specific country, what's the colour of the sky, and other such things, mostly consists of recalling events, people, facts etc. On the other hand, procedural memories are those that store information regarding skills and procedures, for example, driving a motor vehicle, riding a horse or playing piano. The declarative memory particularly involves the medial temporal lobe region of the brain, specifically the hippocampus part, while the procedural memory critically employs the cerebellum. Despite this difference, the fact we all need to admit is that human memories are often complex and are the result of experiences ranging from multiple memory systems interacting and linking with each other.

The recent advancement in medical sciences has always created a keen interest among neuroscientists in the identification of mechanisms that are involved in the formation and storage of memories from a neurobiological perspective. In the past two decades, numerous studies have been carried out on memories that are temporal lobe-dependent. When deeply analysed from electrophysiological, anatomical and molecular perspectives, it has come to light that there have been various molecular modifications at all levels inside the brain including transcriptional, post-transcriptional and translational levels which play a major role in the formation of long-term memories. These changes include firstly the mechanisms of general long-term plasticity which takes place in many regions of the brain with all the cascade of events involving long-lasting changes and secondly selective mechanisms which only occur in specific areas of the brain and cell populations.[6,7]

One interesting feature regarding the formation of long-term memory is that when the memory is freshly encoded, it exists in a highly fragile state, which is susceptible to distortion and disruption, that can be either molecular, pharmacological or behavioural. As time passes, the memory becomes stronger and resistant to disruption. This process where the strengthening and stabilisation of memory takes place is called memory consolidation.[8] It was believed that once a memory becomes consolidated, it becomes fixed and resilient to any interference until recent studies (carried out in the past 15 years) concluded that memories that are consolidated again become labile when adequately reactivated by retrievals. During this, post-retrieval fragility period, which is similar to the initial acquisition of memory, is temporally limited and during this phase, the memory reverts to a stable state, which is known as reconsolidation. Both consolidation and reconsolidation are phases of the memory where it is at its most vulnerable condition to any interferences. It is this phase where strengthening or weakening of the memory trace can be achieved. The comprehension of these mechanisms (how various memories are involved in the aetiopathogenesis of psychiatric disorders like post-traumatic stress disorder (PTSD), anxiety etc.[9]) is extremely important for identifying the neural link between various psychopathologies.

Memory Consolidation

The process of memory consolidation starts with the gene expression-dependent phase, which ranges from a few hours to days. It is a type of molecular or cellular consolidation that indicates the initial and highly fragile state of memory storage. After this initial phase even though these memories are considered to be consolidated as per molecular interferences, they undergo a series of processes that involve high network rearrangement which is further achieved by a decline in the critical role of the hippocampus. Any kind of intervention to the hippocampus during this phase causes the memories to be lost. This process can last up to weeks in animals and years in humans and is known as system consolidation. The mechanisms of memory consolidation have been studied in trained rats via a pharmacological screening model known as an inhibitory avoidance task (IA). IA is a fear conditioning-based model where an animal encounters aversive behaviour when foot shock is given to it, hence the rats tried to avoid it during the later times. One of the fascinating things about this task is how quickly changes are made in the brain of the animal once encoding is accomplished and its progression over time even after a single trial of the experiment.[10–12]

We often forget the events and experiences that occur in our day-to-day lives, except for the important ones and the ones that have an emotional impact. The more the emotional impact, the more robust the memory becomes. The human brain invokes a varied set of emotions. They could be either positive such as good memories or negative such as trauma, pain etc. When negative memories cross a certain threshold, that's the point where psychopathological disorders occur. When deeply analysed, PTSD, depression and anxiety disorders are just chronic stress, painful and traumatic experiences which have crossed their threshold. A large number of studies ranging from behavioural to pharmacological studies have shown that the level of

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stress follows an inverted U relationship with memory retention. Elevated levels of stress are required for the formation of stronger and persistent long-lasting memories in the brain, but when this stress becomes too intense or is chronic, the impairment of memory initiates. As per the inverted U-shape curve, memory retention is modulated and mediated by the levels of the stress hormones noradrenaline and glucocorticoids, which are released in response to stress.[13,14]

Memory Reconsolidation

For a long time, the process of memory consolidation was perceived as an unambiguous process that causes the transformation of fragile memory traces into stable ones. However, studies carried out in the 1960s and from the past 15 years have demonstrated that memories that were perceived to be insensitive to disruption by certain types of interferences, become again transiently labile if they are adequately recalled. As the recalled memories must again be stabilised, this post-retrieval process is called memory reconsolidation. In the last decade, several questions and queries have been raised pertaining to memory reconsolidation; firstly, whether reconsolidation is a repetition of the consolidation process or a new process, as some studies suggest it employs distinct brain circuits and mechanisms, and secondly, does reconsolidation take place every time a memory is recalled or a trace is reactivated and do molecular mechanisms of long-term plasticity appear to be the common denominators, the answer to this question is still debatable and controversial.[15,16]

With IA, contextual fear conditioning and drug-induced memories in rodents as well as other types of fear memories in vertebrates like fish, the passage of time is a key regulating factor for the post-retrieval vulnerability of memory. In fact, on reactivation of memory, a young memory is more fragile and easily disrupted than an old one indicating that over time memory becomes increasingly stable, and in some cases, insensitive to post-reactivation interference. In our rat IA paradigm, systemic injection of protein synthesis inhibitors after reactivation produces a detrimentally graded amnaesia in 2-day and 1-week-old memories, but when the same treatment is performed on memories that are two and four weeks old, the amnestic effect is no longer observed. However, auditory fear conditioning, which is a signal association factor seems to remain sensitive to disruption following memory reactivation for at least 45 days suggesting that different types of memory have different sensitivity to post-reactivation interference. The third and an important question asked about memory reconsolidation is regarding its function and the reason why a memory becomes labile after retrieval or reactivation. Two main hypotheses have been proposed to explain the functional role of reconsolidation. The first suggests that reconsolidation strengthens the memories, in other words, the phase of temporary fragility mediates additional consolidation and therefore produces a stronger and longer-lasting memory. The second hypothesis posits that reconsolidation allows the association of new information into memories of past events, in order to integrate new learning with already established and reactivated memories.[17–19]

Role of Memory in Psychopathology

Based on the current knowledge of consolidation and reconsolidation, we suggest that an ideal therapeutical approach to psychopathology may be one that modulates only certain components of the memory trace, such as stress, fear and emotions in general, but spares the semantic representation. Although memories formed during the first few years of life are usually short-lived and become inaccessible after a relatively short time frame, considerable clinical evidence suggests that young children retain some forms of the internal representation of their trauma for months and even years and demonstrate trauma-specific behavioural reenactments, affective responses to traumatic triggers, as well as sensory and somatic symptoms. It is clear that better knowledge of the consolidation and reconsolidation mechanisms of fear memories is critical for a better understanding of how to approach fear- and trauma-induced pathologies. Interestingly, extinction after fear memory reactivation leads to a permanent loss of the fear expression, if the extinction is conducted within the reconsolidation's temporal window, for example, for persistent and intrusive memories like those associated with PTSD, it may be possible to target the mechanisms of consolidation and block or reduce the formation or persistence of a very intense memory.

The studies of the last 20 years show that the process of memory formation and storage is very dynamic and that the storage of information continuously changes through processes of consolidation, reconsolidation, and updation. Since traumatic memories are distressing and continuously retrieved in PTSD, studies have tried to block memory retrieval in patients with PTSD by daily administration of cortisol over a one-month period. If targeting memory reconsolidation does not prove to be sufficiently efficacious in ameliorating the symptoms of PTSD, an alternative approach would be to target reconsolidation to actually prevent the onset of trauma-induced pathologies. We reasoned that when a traumatic experience is recalled, a stress response is initiated, which, as shown in our studies described above, activates the cascade of gene expression mediating memory consolidation and strengthening. Furthermore, the mechanisms of consolidation and reconsolidation may offer an opportunity to restore the memory with a different emotional valence and intensity. Weakening the intensity of

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traumatic memories during the first few weeks or months of their consolidation phase may be effective in impeding the development of PTSD or other disorders, including substance abuse, anxiety, and depression.[20–22]

Conclusion

Various functional and temporal phases, including encoding, retrieval, storage, consolidation, and reconsolidation, are involved in the creation of long-term memories, which is a highly dynamic procedure. Over the past 20 years, there has been a significant advancement in our knowledge in understanding the mechanisms from a molecular and cellular perspective that take place in the brain in different stages, how they change with time, in which regions of the brain they occur, and how they are being modulated. This understanding, particularly with regard to memories connected to stress, fear, and trauma, has aided in the hunt for therapies that may lessen the psychopathologies including PTSD, phobias, addiction, and anxiety. The type of memory, its age and strength, its retrieval method, the temporal windows of interference, and its underlying mechanisms, are all significant factors.

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