Is memory consolidation a multiple-circuit system?

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How is memory stored? This important question has been the focus of ample research in the neurosciences. Memory, from the neural point of view, is considered a process by which the brain maintains stable stimuli representations for a period and, depending on how long a particular representation lasts, becomes a short-term memory (STM) or a long-term memory (LTM) (1). At the beginning of the 20th century Muller and Pilzecker proposed that new memories are fragile and consolidated over time, a theory that gave rise to the consolidation hypothesis (2). Fifty years later it was reported that an electroconvulsive shock applied after training disrupted memory and that memory disruption correlated with the interval between training and electroconvulsive shock application. As the electroconvulsive shock was longer spaced in time from training, memory impairment was reduced (2). Since then, several other researchers have shown that interfering treatments—from electroconvulsive shock to intracerebral microinjections of protein synthesis inhibitors applied after acquisition—prevent LTM storage. Consistently, LTM is not affected if the intrusive treatment is applied outside the vulnerability time window.

Some of the recent advances in our knowledge of the functional and morphological changes related to experience have been focused in one region of the limbic system in vertebrates: the hippocampus. Direct evidence came from clinical cases like H.M., a patient in which surgical removal of the majority of the medial temporal lobe including the hippocampus led to profound memory consolidation deficits of declarative (explicit)* memory, such as episodic memory, but not of nondeclarative (implicit) memories, such as visual-motor skills (3, 4). Furthermore, these observations have been experimentally reproduced in animal lesion studies (5). In several papers it has been demonstrated that other structures in addition to the hippocampus, such as the nucleus accumbens or some cortical regions, are involved in episodic or recognition memory consolidation (6, 7). In PNAS, Ferretti et al. (8) show that the ventral striatum also has an important role in declarative memory consolidation. In their paper, they were able to show in two differentially motivated spatial memory tasks (object in context and water maze task) that reduction of a transcriptional factor such as CREB (cAMP-response element binding protein) and protein synthesis inhibition impaired spatial memory consolidation for both tasks.

Molecular and System Consolidation

The consolidation process implies important changes in brain function, and such changes can have different lengths of time. Donald Hebb proposed that memory is at first in a labile state maintained by a reverberating neural ensemble and that LTM arises from cellular changes in this ensemble allowing memory stabilization (1, 2, 9). This theory stressed the weight that cellular entities have in memory processing, focusing research on the cellular events underlying memory (2, 9, 10).

Areas outside the medial temporal lobe could be participating in the consolidation of declarative memories.

At the cellular level, STM undergoes activation of transduction cascades after neuronal stimulation. Thus, the STM remains as long as these cascades are active, but for LTM transduction signals are carried to the nucleus where transcription factors are activated, which in turn leads to RNA translation into protein synthesis (11). These proteins account for cellular plastic changes that are considered the cellular correlations of stable LTM traces, i.e., the cellular counterparts of consolidation. Hence, memory consolidation requires protein synthesis. It has been extensively reported that protein synthesis inhibition disrupts LTM without affecting STM; these cellular processes for memory consolidation have been called cellular consolidation. At the system level, i.e., where several brain structures are involved, a multiple memory systems hypothesis has been proposed (see refs. 12 and 13). This hypothesis implies that different kinds of memories are organized in independent brain systems. However, it is also possible that LTM stability could be supported by the proliferation of multiple memory circuits within the temporal lobe and other brain regions. Thus, constant neural communication between structures can be developed during memory consolidation if during this process an interaction between the hippocampus and cortical regions occurs.

It has been proposed that in the hippocampus the stimuli information remains for transitional periods, and for longer periods the information goes to the cortical regions (13). In this regard, simultaneous or sequential molecular changes related to memory consolidation could be occurring in different brain areas. A number of studies have shown that functional integrity of the amygdala and the cortex are important to consolidate and maintain an implicit aversive taste memory trace for the long term. To demonstrate a putative communication between the amygdala and the insular cortex involved in memory formation, the following experiments were done. First, behavioral enhancement of taste aversion memory was induced by high-frequency electrical or pharmacological stimulation of the amygdala, and then the observed memory facilitation was reversed by pharmacological manipulations in the cortex, suggesting strong interaction of both structures during memory consolidation (14, 15). Furthermore, it has been demonstrated that simultaneous electrical recordings of the amygdala and cortex during taste aversion encoding showed a significant enhancement of functional connectivity between the two structures (16). These results suggest that both the amygdala and the insular cortex are important for consolidation and for maintaining the aversive taste memory trace for the long term. Accordingly, protein synthesis blockers applied in either the amygdala or the insular cortex affect taste memory consolidation. Although it remains to be demonstrated whether similar interaction could be occurring among the hippocampus, ventral striatum, and cortical areas during spatial memory consolidation; the results of Ferretti et al. (8) suggest that different brain areas outside the medial temporal lobe could be participating in the consolidation of declarative memories.

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*Declarative or explicit memory is expressed through recollection of facts and events (times, space). Nondeclarative memory is expressed through performance of motor skills (habits).

Remodeling of Neuronal Circuits by Experience

The hypothesis that memory consolidation could produce functional and morphological modifications of neuronal circuits has led to a great deal of experimental studies. In this regard, it has been demonstrated that morphological rearrangements of dendrite spines and axonal redistribution in the hippocampus and cortex could occur after a variety of learning experiences (17). Accordingly, it has been demonstrated that axonal rearrangements in the mossy fibers of the hippocampus take place after several days of spatial water maze learning (11). However, these axonal rearrangements were not seen when animals were submitted to response implicit cue learning (11). In other words, the axonal rearrangement was seen only when animals consolidated explicit but not implicit spatial memory components. Interestingly, Ferretti et al. (8) further demonstrate that the ventral striatum is involved by means of a protein synthesis blocker and transcriptional factor antisense in the spatial memory explicit but not implicit response of memory consolidation. Therefore, these findings show that some areas that are not considered to be part of the medial temporal lobe could also be significantly involved in spatial memory consolidation. Another possible strategy for finding those brain circuits involved in memory consolidation could be to simultaneously analyze morphological changes in different brain structures during and after memory consolidation. Although technically challenging, this would be the most appropriate way to truly understand the brain circuits involved in memory consolidation. The use of noninvasive brain-imaging methodologies in human memory research has made great progress, such as the findings that areas outside the medial temporal lobe are also involved in spatial memory (see refs. 18 and 19). The combination of those techniques and brain experimental manipulation on lab animals will certainly shed light on our understanding of human memory and its integration processes.

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