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Review Paper

Strengthening a consolidated memory: The key role of the reconsolidation process

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In memoriam to our science mentor Héctor Maldonado. A true scientist who inspired us with his endless creativity.

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ABSTRACT

The reconsolidation hypothesis posits that the presentation of a specific cue, previously associated with a life event, makes the stored memory pass from a stable to a reactivated state. In this state, memory is again labile and susceptible to different agents, which may either damage or improve the original memory. Such susceptibility decreases over time and leads to a re-stabilization phase known as reconsolidation process. This process has been assigned two biological roles: memory updating, which suggests that destabilization of the original memory allows the integration of new information into the background of the original memory; and memory strengthening, which postulates that the labilization-reconsolidation process strengthens the original memory. The aim of this review is to analyze the strengthening as an improvement obtained only by triggering such process without any other treatment. In our lab, we have demonstrated that when triggering the labilization-reconsolidation process at least once the original memory becomes strengthened and increases its persistence. We have also shown that repeated labilization-reconsolidation processes strengthened the original memory by enlarging its precision, and said reinforced memories were more resistant to interference. Finally, we have shown that the strengthening function is not operative in older memories. We present and discuss both our findings and those of others, trying to reveal the central role of reconsolidation in the modification of stored information.

Contents

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1. Introduction

The study of memory is one of the most challenging and exciting areas of basic and applied neuroscience research. During the twentieth century, the consolidation theory dominated the neurobiological field. Its starting point was the seminal research of Müller and Pilzecker (1900), Müller and Pilzecker (1970), who demonstrated that after an initial phase of fragility, the acquired information is stored in a stable memory which is resistant to disruption by amnesic agents (McGaugh, 2000). Consolidation is a conserved evolutionary process, which has been proved to be present in diverse species, ranging from nematodes to humans, and involving RNA and protein synthesis (McGaugh, 2000; Kandel, 2001). Two levels of description and analysis are commonly used to describe the consolidation process, that is, at the cellular/synaptic and at the brain systems level. Synaptic consolidation refers to process described above, which implies the activation of intracellular signaling cascades, modulation of gene expression, and synthesis of gene products that alter synaptic efficacy in the neural circuit that encodes the memory. Systems consolidation refers to the post-encoding reorganization of long-term memory over distributed brain circuits. The process may last days to years, depending on the memory system and paradigm (Dudai, 2012).

A considerable number of reports show that patients with damage in their medial temporal lobe (MTL) displayed temporally graded retrograde amnesia on declarative memory tasks. A central model that tries to explain this phenomenon is the standard consolidation theory (McClelland et al., 1995; Squire and Alvarez, 1995). This model hypothesize that the hippocampus is only a temporary repository for memory and that the neocortex stores the memory thereafter. However, some evidence that seems to be untenable under this model. More specifically, the effect of MTL lesions affects severely autobiographical episodes and the retrograde temporal gradient for this type of memory is very shallow for memories acquired several decades earlier. Based on these observations and analogous observations in animal models, Nadel and Moscovitch (1997) proposed the multiple-trace theory (MTT). MTT posits that the hippocampus rapidly and obligatorily encodes all episodic information which is encoded in distributed ensembles of HPC neurons, being an index for neurocortical neurons that attend the information, joining them into a coherent representation. The resulting hippocampal-neocortical ensemble constitutes the memory trace for the episode (Dudai, 2012).

In the last years, this theory suffered the impact of the reconsolidation hypothesis. By searching the term *reconsolidation* in *PubMed/Medline,* we were able to identify more than 400 studies published in the last decade, stating its relevance in the field. These studies have shown that by presenting a subject with a specific cue, previously associated with a life event (i.e. training session, episodic memories; Nader et al., 2000; Schiller and Phelps, 2011), the stored memory passes from a stable to a reactivated state. This reactivation implies that the memory is again labile and susceptible to different agents, which, depending on their nature, may either damage or improve the original memory. These studies have also shown that such susceptibility decreases over time and leads to a re-stabilization phase known as reconsolidation process. As well as for consolidation, the reconsolidation process seems to also be a conserved evolutionary process. It has been demonstrated in different paradigms and animals models (Nader and Hardt, 2009; Schiller and Phelps, 2011). These findings suggest that reconsolidation is a general property of memory and is common to different memory systems (Nader and Hardt, 2009; Dudai, 2012).

Many of these studies also seem to show that a memory is reactivated and reconsolidated every time it is retrieved (Nader et al., 2000; Sara, 2000). This fact could represent a real risk because the memory's susceptibility during this process could expose and modify the stored information, which is vital for animals' adaptation to an ever-changing environment. More recently, some researchers have defined some of the constraints present in the process: the strength of the original memory, the age of the memory, the duration of the reminder presentation, the cues included in the reminder structure, and the prediction error during reactivation (Hardt et al., 2010; Dudai, 2012).

Over the last fifteen years, most of the research on reconsolidation has been focused on the cellular and molecular mechanisms and the different neurotransmitters implicated, but little on the biological role of this process. Initially, two nonexclusive functions were proposed for this process (Alberini, 2005): memory updating, which suggests that destabilization of the original memory after the reminder allows the integration of new information into the background of the original memory (Lewis, 1979; Alberini, 2007), and memory strengthening, which postulates that the labilization-reconsolidation process strengthens the original memory (Sara, 2000). This indicates that memory restructuring may include changes not only in content (memory updating), but also in strength (memory strengthening).

Our laboratory began the characterization of the reconsolidation process by using an invertebrate model, the grapsid crab *Neohelice granulata*. In our research, we differentiated the retrieval from the reactivation process and considered that retrieval only evoked the consolidated memory. We found that, during reactivation, the memory is evoked and suffers a change from a stable to a labile state. Under these definitions, we demonstrated that the duration of the reminder and the discrepancy between current and past events (called *mismatch*) are features that constrain the labilization-reconsolidation process (Pedreira and Maldonado, 2003; Pedreira et al., 2004).

In humans involving different types of paradigms the process has been described in procedural, aversive, associative and declarative or episodic memories (see Schiller and Phelps, 2011). The declarative memory, i.e. the conscious recollection of facts and events, is considered as a hallmark of our species (Dudai, 2002). The research on this kind of memory aimed to explore the different processes associated with it. Different reports revealed the presence of the reconsolidation process ranging from autobiographical memories (Schwabe and Wolf, 2009), learn a list of objects (Hupbach et al., 2007, 2009) or verbal stimuli comprised by nouns (Strange et al., 2010). The study of the reconsolidation process using declarative memory paradigms not only supports the universality of some mechanisms, but also opens innovative research lines to find new treatments for traumatic memories (Kindt et al., 2009; Schiller and Phelps, 2011). In this context, our research in humans has aimed to show the existence of a reconsolidation process for declarative memories (Forcato et al., 2007), by characterizing boundary conditions (Forcato et al., 2009) and studying the biological role of this process (Forcato et al., 2010, 2011, 2013).

The aim of this review is to analyze the strengthening function of the reconsolidation process understood as a memory improvement obtained only by triggering such process without any other treatment. We thus present and discuss both our findings and those of others, trying to evidence the central role of reconsolidation in the modification of the stored information and in the fate of a consolidated memory usually doomed to be forgotten.

2. Memory strengthening by the reconsolidation process in animal models

Different researchers have analyzed memory enhancement during the reconsolidation process in animal models by using different