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Review

Updating memories—The role of prediction errors in memory reconsolidation

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HIGHLIGHTS

- Prediction error signals originate from midbrain dopaminergic neurons.
- Prediction errors during retrieval may be prerequisite for memory destabilisation.
- This allows modification of a stable memory to maintain relevance.
- Reconsolidation is the restabilisation of an existing memory.

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ABSTRACT

Memories are not static imprints of past experience, but rather are dynamic entities which enable us to predict outcomes of future situations and inform appropriate behaviours. In order to maintain the relevance of existing memories to our daily lives, memories can be updated with new information via a process of reconsolidation.

In this review we describe recent experimental advances in the reconsolidation of both appetitive and aversive memory, and explore the neuronal mechanisms that underpin the conditions under which reconsolidation will occur. We propose that a prediction error signal, originating from dopaminergic midbrain neurons, is necessary for destabilisation and subsequent reconsolidation of a memory.

Contents

1. Introduction

An important role of our memories is to inform future behaviours based on previous experiences. Following initial learning, memories exist as labile, short-lived traces which are

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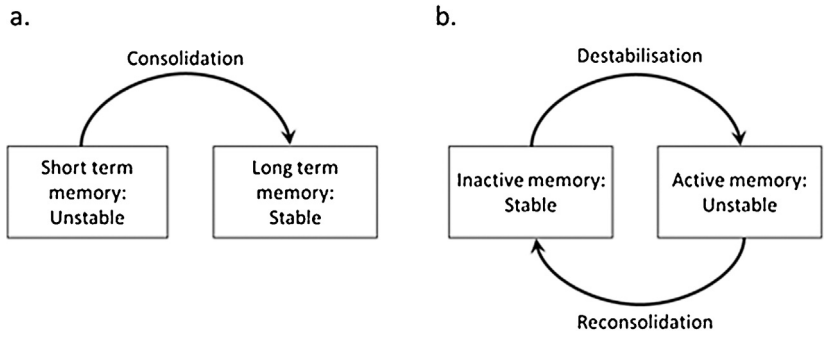

Fig. 1. Memory consolidation and reconsolidation. (A) Unstable sensory information is held in a short term memory store, while the acquired information is consolidated into a stable, long term memory. This gives rise to the apparent conversion of short-term memory into long-term memory via consolidation. (B) A stabilised, inactive memory can be destabilised and returned to an active, unstable form. In the active state the memory is malleable and can be modified. The updated memory is then restabilised through the process of reconsolidation; disrupting reconsolidation prevents the memory from restabilising, leading to an enduring amnesia.

susceptible to disruption. In order to persist in the longer term, newly acquired memories are consolidated into stable engrams, requiring protein synthesis and synaptic plasticity [76]. We often assume that our long term memories are constant in content. However, once acquired, our memories can be updated in both content and strength. The updating of long-term memories is essential to maintain their relevance in day-to-day life, allowing new information to be integrated into existing knowledge and avoiding interference between conflicting information. It is proposed that the use of memories can reinstate plasticity to allow maintenance of their relevance to daily life.

The mechanism by which memories are updated has been linked to the process of memory reconsolidation [60]. Memory retrieval is often triggered by a similar experience that can modify future recollections. A notable example of this is Bartlett's "War of the Ghosts" study, in which participants were asked to recall a folk story repeatedly over several days [6]. Interestingly, later recollections of the story were increasingly biased by prior recall. In the case of animal models, retrieval of a memory is measured by expression of a particular behaviour; for example, freezing following fear conditioning. In certain circumstances, the retrieval of a memory can lead to its destabilisation, requiring a restabilisation process that is known as reconsolidation [1,90]. In this review we focus on the parameters required to destabilise a consolidated, long-term memory in order to permit updating via reconsolidation.

2. Reconsolidation—Restabilising long term memories

Following initial acquisition, memories exist in an unstable state, vulnerable to disruption by amnestic agents, also known as the active state [71]. Their vulnerability is only short-lasting however, and through consolidation transition to an inactive form, becoming stable traces resistant to amnestic intervention. This phenomenon gives rise to a brief "consolidation window", in which memories can be manipulated or disrupted. During the consolidation window, protein synthesis and cellular mechanisms, including long term potentiation, stabilise the newly acquired memory. It is assumed that immediately following acquisition, information is held in short-term memory (STM), or working memory. As the memory is consolidated, we observe a transition from STM to long-term memory (LTM) as detailed in Fig. 1A.

Given the involvement of lasting cellular changes during consolidation, it became broadly believed that, once established, memories were permanent and unchanging. However, early experiments showed that expression of an already consolidated fear memory could be disrupted by electroconvulsive shock (ECS), provided ECS was administered following a brief reminder session [87,113]. ECS given outside the consolidation window, in the absence of a reminder, did not hinder later expression of the fear memory. It was proposed that the presentation of the conditioned stimulus (CS) caused the stable, consolidated memory to destabilise and return to its active form, once again vulnerable to amnesic intervention; the researchers termed this effect "cue-dependent amnesia" [71]. ECS treatment was also ineffective at disrupting memory when given 24 h after a reminder session. This implied that a restabilisation process returned the memory to its stable, inactive form. This restabilisation process was later termed "reconsolidation" [89,98]. The presence of a cue-induced period of memory instability provides a short "reconsolidation window", during which memory content and strength can be manipulated. Given the dynamic nature of memory, it was suggested that it was more useful to consider memories as being active or inactive, rather than unstable or stable [71] (Fig. 1B).

While both consolidation and reconsolidation depend upon protein synthesis, the reconsolidation window is typically shorter than that of consolidation [46,54]; reconsolidation also appears to be more easily disrupted than consolidation [75]. Notably, these findings have not been replicated in the 21st Century study of reconsolidation, with the exception of a single study of systems consolidation in the hippocampus [25]. The turn of the millennium saw a shift in the study of reconsolidation towards cellular mechanisms. Importantly, in brain regions including the hippocampus, insular cortex and central amygdala, consolidation and reconsolidation are dissociable on the basis of their cellular and molecular substrates [65,66,133], therefore providing evidence that reconsolidation is not simply a recapitulation of consolidation, but a distinct neural process.

Reconsolidation of memories has been observed in many species including invertebrates such as nematodes [111], honeybees [120,121], sea slugs [12,15,70], and crabs [13,96] and vertebrates including mice [56], rats [91] and humans [49,50]. Thus, reconsolidation appears to be a conserved mechanism of memory maintenance across the animal kingdom. Reconsolidation has also been demonstrated in a wide variety of appetitive (reviewed recently by [101]) and aversive settings [68,80,87], in addition to spatial [61,88] and episodic memories [42,49].

The existence of a reconsolidation process is typically demonstrated through its disruption. Disrupting the reconsolidation process is generally achieved through the application of pharmacological amnestic agents, such as *N*-methyl-D-aspartate receptor (NMDAR) antagonists [7,68], beta-adrenergic antagonists including propranolol [24,58,98], or protein synthesis inhibitors such as anisomycin [25,79,128] which leads to an enduring amnesia.

Disruption of the reconsolidation process leads to the loss or weakening of an existing memory. However, this requires the administration of a memory-disrupting agent within the