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Review

Determinants to trigger memory reconsolidation: The role of retrieval and updating information

Carlos J. Rodriguez-Ortiz [a], Federico Bermúdez-Rattoni [b,*]

[a] Department of Medicine, University of California, Irvine, 2216 Gillespie Neuroscience Research Facility, 837 Health Sciences Rd., Irvine, CA 92697-4545, USA
[b] División de Neurociencias, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán, 04510 México City, Mexico

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ABSTRACT

Long-term memories can undergo destabilization/restabilization processes, collectively called reconsolidation. However, the parameters that trigger memory reconsolidation are poorly understood and are a matter of intense investigation. Particularly, memory retrieval is widely held as requisite to initiate reconsolidation. This assumption makes sense since only relevant cues will induce reconsolidation of a specific memory. However, recent studies show that pharmacological inhibition of retrieval does not avoid memory from undergoing reconsolidation, indicating that memory reconsolidation occurs through a process that can be dissociated from retrieval. We propose that retrieval is not a unitary process but has two dissociable components; one leading to the expression of memory and the other to reconsolidation, referred herein as executer and integrator respectively. The executer would lead to the behavioral expression of the memory. This component would be the one disrupted on the studies that show reconsolidation independence from retrieval. The integrator would deal with reconsolidation. This component of retrieval would lead to long-term memory destabilization when specific conditions are met. We think that an important number of reports are consistent with the hypothesis that reconsolidation is only initiated when updating information is acquired. We suggest that the integrator would initiate reconsolidation to integrate updating information into long-term memory.

Contents

* Corresponding author.
E-mail addresses: cdrodrig@uci.edu (C.J. Rodriguez-Ortiz), fbermude@ifc.unam.mx (F. Bermúdez-Rattoni).

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1. Introduction

The consolidation theory states that incoming information is stabilized into long-term memory through a protein synthesis-dependent process (McGaugh, 1966; McGaugh, 2000). Reliability among an important number of studies sustains that interfering treatments, from electroconvulsive shocks to intracerebral microinjections of protein synthesis inhibitors, affect consolidation in a time-dependent manner. These treatments disrupt memory when applied after training. Moreover, memory impairments correlate with the interval between training and treatment application. Consistently, long-term memory is not affected if the intrusive treatment is applied outside the vulnerability window. These observations led to the idea that consolidation strengthens memory over time and that this stabilization process occurs only once (McGaugh, 1966; McGaugh, 2000).

However, consolidated memories can undergo destabilization-restabilization processes conjointly referred to as reconsolidation. Typical experiments aimed to evaluate reconsolidation encompass three sessions. In the first session, animals are trained to create a long-term memory. On the second session, animals are exposed to a memory cue to initiate reconsolidation. For example, conditioned rats on a context-footshock association would be placed in the same context. Usually, an interfering agent is applied on this session, *e.g.* intracerebral injection of the translation inhibitor, anisomycin. Disruptive effects of the agent are unveiled by poor performance when memory is assessed on a third session, indicating that the consolidated memory was destabilized and that the restabilization process was disrupted, *i.e.*, reconsolidation is unveiled (Nader & Einarsson, 2010; Nader, Schafe, & Le Doux, 2000; Sara, 2000).

Like consolidation, reconsolidation vulnerability to intrusive treatments is time-dependent. Thus, application of amnesic treatments several hours after presentation of the cue is unable to disrupt memory. Furthermore, disruptive agents are ineffective if the cue is not presented. However, the specific characteristics of the cues that trigger reconsolidation have not been fully described and are subject of intense research (Dudai, 2012; Nader & Einarsson, 2010). In this regard, it is implicit and even granted that retrieval is an essential condition to initiate reconsolidation. This assumption makes sense when we consider that cue specificity is a hallmark feature of reconsolidation, that is, only relevant cues will induce reconsolidation of a specific memory. Returning to the example of context-footshock conditioning, the same context used in training would trigger reconsolidation but a different context would be an ineffective cue to initiate this process. Another important consideration is that the cue must be identified with stored information to initiate reconsolidation, consequently, stored memories must somehow be accessed and retrieval seems the logic cognitive process to accomplish such goal. However, recent reports show that pharmacological inhibition of retrieval does not affect memory reconsolidation, indicating that retrieval is a dispensable condition to trigger reconsolidation. On the first part of this review, we examine the current literature that has assessed reconsolidation independence from retrieval. Later, we discuss the evidence that suggests that reconsolidation is initiated every time updating information is acquired to make the argument that updating information, and not retrieval *per se*, is the crucial factor that triggers the reconsolidation process.

2. Reconsolidation in the absence of retrieval

Ben-Mamou et al. in 2006 reported an interesting, but largely unnoticed observation in which rats were trained in a fear-conditioning paradigm, where an auditory tone was paired with a footshock. As a consequence, a long-lasting and strong freezing behavior was observed when the tone was presented on subsequent occasions. The next day, trained rats were exposed to the tone and the translation inhibitor anisomycin was injected in the basolateral amygdala (BLA) immediately after. When the rats were tested twenty-four hours later, they performed poorly compared to control animals when presented with the tone, revealing reconsolidation impairments. A second group of rats was trained on the tone-footshock conditioning as before. However, on the next day the AMPA receptor antagonist, CNQX, was injected in the BLA before the tone presentation. CNQX-treated animals showed no freezing on the injection session but the freezing behavior was back to control levels the next day, indicating that CNQX disrupted retrieval. Finally, one last group of rats was trained on the tone-footshock conditioning as above. This group was injected with CNQX before and anisomycin after the tone. These rats showed memory impairments on both the injection session and the following day, supporting that anisomycin disrupted reconsolidation despite retrieval inhibition by CNQX (Ben Mamou, Gamache, & Nader, 2006).

Several years after this finding, our group reported similar results on taste aversion memory (Rodriguez-Ortiz, Balderas, Garcia-DeLaTorre, & Bermudez-Rattoni, 2012). Taste aversion was achieved by pairing a taste with an intraperitoneal injection of the visceral malaise-inducing agent, lithium chloride. The taste-malaise association produces a long-term aversive memory evidenced by the reduced preference for that taste in a second presentation compared to baseline preference during training. In this case, reconsolidation was triggered by a second taste-aversion training, which produces memory strengthening. Rats infused with the AMPA receptor antagonist NBQX in the amygdala before the second training drank significantly more of the aversive taste than the control group on that trial. Nevertheless, both groups displayed similar taste aversion the next day, further supporting the notion that inhibition of AMPA receptors in the amygdala impairs retrieval of aversive memories. Previous research showed that conjoint anisomycin infusion into the amygdala and insula after the second taste-aversion training effectively disrupts reconsolidation of this memory (Garcia-DeLaTorre, Rodriguez-Ortiz, Arreguin-Martinez, Cruz-Castaneda, & Bermudez-Rattoni, 2009). Therefore, to assess reconsolidation dependence on retrieval, NBQX was applied in the amygdala and anisomycin in both the amygdala and insula of the same animals on the second training. These rats showed both retrieval and reconsolidation deficits, unveiled by larger consumption of the aversive taste on the injection session and next day, indicating, once more, that inhibition of retrieval did not affect anisomycin-mediated disruption of reconsolidation (Rodriguez-Ortiz et al., 2012).

To further describe glutamatergic participation on the retrieval and reconsolidation processes of taste aversion, another study was conducted in which rats were trained on the same protocol described above but injected with NBQX and the NMDA receptor antagonist APV in the BLA. Consistent with the previous report, the NBQX group showed impaired memory the day of injection but normal taste aversion twenty-four hours later. APV provoked the same effects as anisomycin, *i.e.*, consistent with reconsolidation blockade, rats presented memory deficits the next day after infusion. When NBQX and APV were applied to the same rats, taste aversion was impaired on the injection and the following session, reasserting that retrieval is a dispensable condition to undergo reconsolidation (Garcia-Delatorre, Perez-Sanchez, Guzman-Ramos, & Bermudez-Rattoni, 2014).

Our laboratory further studied reconsolidation and its independence from retrieval on a non-aversive memory model, object recognition (Balderas, Rodriguez-Ortiz, & Bermudez-Rattoni, 2013). The object recognition task relies on the natural tendency