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Addiction: a drug-induced disorder of memory reconsolidation

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Persistent maladaptive memories that maintain drug seeking and are resistant to extinction are a hallmark of addiction. As such, disruption of memory reconsolidation after retrieval has received attention for its therapeutic potential. Unrestrained reconsolidation may have the opposite effect, leading to reiterative and cumulative strengthening of memory over long periods of time. Here we review the molecular mechanisms underlying reconsolidation of appetitive and drug-rewarded memories, and discuss how these findings contribute to our understanding of the nature of this process. Finally, we suggest that drug-induced alterations to signal transduction might lead to dysregulation of reconsolidation, causing enhancements of drug-related memory after retrieval, and significantly contribute to the compulsive drug seeking that is a core component of addiction.

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Memory reconsolidation, the process by which memories are restabilized after retrieval, may have special relevance to addiction both for the treatment potential [1–4] and as a mechanism for maintaining and strengthening the cue–drug relationship over time. The study of reconsolidation was kick-started after a 30-year hiatus [5], by studies from Nader *et al.* [6], who described the disruption of Pavlovian fear memories by anisomycin administered after retrieval. This study demonstrated first, that consolidated memories could be 'erased' after retrieval, and second, that mechanistically, this so-called 'reconsolidation' process resembled the original consolidation in its requirement for protein synthesis.

Findings on reconsolidation come from a variety of memory tasks [7,8,9•,10,11] and species [11–14] and have several important implications. First, if memories can be disrupted after retrieval, then this may have potential for treatment of persistent or exaggerated memory in disorders such as post-traumatic stress disorders and addiction. Second, given the similarities between the initial storage of memory and an active reconsolidation process after retrieval, it is possible that reconsolidation may not only maintain, but also update or strengthen memories after retrieval. This latter possibility may be a means by which memories become exaggerated over time, even without additional training trials (or exposures to the reinforcer) and thus may contribute to the etiology of disorders such as PTSD and addiction.

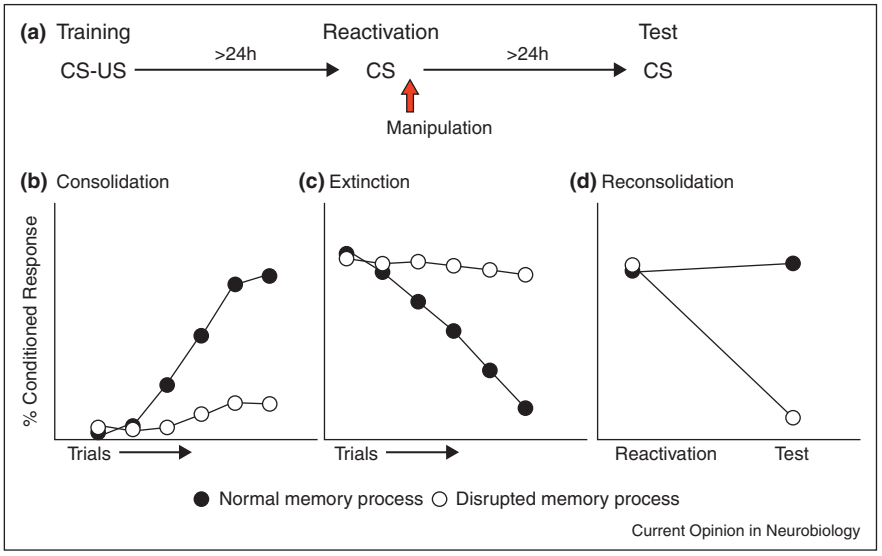
Studies of reconsolidation have begun to describe the signal transduction and transcription events required for postretrieval stabilization of memory. In this review, we will discuss these findings and how understanding the molecular networks required will inform our conceptualization of reconsolidation, its relationship with memory consolidation, and its potential role in both treatment and development of the compulsive drug seeking that is a core component of addiction.

How is reconsolidation studied?

The protocol for studying memory reconsolidation typically involves three phases: a training phase, a reactivation phase after which manipulations occur, and test (see Figure 1A). Memory reactivation is triggered by presentation of the conditioned stimulus (CS), without (and sometimes with) the occurrence of the unconditioned stimulus (US).

In general, study of memory requires a change in behavior. For example, we attribute expression of a response to a previously reinforced cue to the formation and storage of a memory (Figure 1B). Similarly, a decrease in behavior after multiple exposures to previously conditioned cues is attributed to expression of extinction learning (Figure 1C). In contrast, reconsolidation, a mechanism that maintains memory after retrieval, should result in no behavioral change (Figure 1D). Without further evidence, however, it is difficult to attribute 'no change' in behavior as evidence for an active process. In order to determine whether an active reconsolidation process occurs after memory retrieval, procedures aimed at disrupting or enhancing memory are used. Here, if manipulation after retrieval causes changes in behavior, then we can conclude there is an active process occurring at this time. Manipulations can range from behavioral [7,15,16•] to pharmacological [6,17,18] to genetic [19,20], allowing for the dissection of roles of various proteins and gene

Figure 1



How reconsolidation is studied. **(a)** Schematic of typical reconsolidation paradigms. Animals are trained on a Pavlovian memory task with one or many trials. At least one day after the end of training, memory reactivation is induced by re-exposure to the CS, at which time manipulations are applied. At least 24 hours after reactivation, animals undergo a test of responding to the CS. In **(b)** acquisition/consolidation, and **(c)** extinction, we infer an active process by observing a change in behavior (filled circles). Disruption of this process leads to no change in behavior (open circles). In contrast, **(d)** reconsolidation causes no observable change in behavior (filled circles). Evidence for an active process stems from changes in behavior as a consequence of manipulations (e.g. disruption, open circles).

products in the stabilization of memory after retrieval. In addition to behavioral changes, imaging and quantitative methods are used to determine which signaling pathways are active after retrieval, providing further evidence for activation of a memory-storage related process.

Molecular mechanisms of reconsolidation

In the studies discussed here, reward-related Pavlovian tasks, including conditioned place preference and Pavlovian approached are used, with drug, food, or sucrose reinforcers. By detailing the similarities with other processes and specificity of activation in time, task, and brain region after retrieval, a picture of the mechanisms of reconsolidation in these paradigms has started to emerge. NMDA receptors play a crucial role in memory reconsolidation [18,21–28] as does CB1R [29,30], and changes in GABA activity [9•,31]. Intracellular signaling molecules, including both PKA [17,32•] and CREB [33] are also required for reconsolidation of reward related memories. In these procedures, retrieval of appetitive memory activates a number of signaling cascades, including the extracellular signal regulated kinase (ERK) [33,34], the immediate early gene Egr1 [22,35–39] and phosphorylation of the AMPA subunit GluR1 [34,40], CdK5 [41] and glycogen synthase 3 [42].

Given the promiscuous nature of many kinases, the outcome of their activity is determined by subcellular localization and other concurrent signaling events [43], it will be important to understand the pathways through which each molecule is acting. Indeed, the same kinase can exert very different effects depending on mechanism of activation, the subcellular compartment, and the availability and proximity of downstream effectors [44]. There is some evidence detailing the pathways of by which identified proteins exert their effects (Figure 2). For example, reconsolidation requires activation NMDA receptors and CaMKII, possibly via prevention of GluR1 phosphorylation [40]. The activation of ERK, PKA/CREB pathways are consistent with the receptors required for memory reconsolidation and the role of Egr1 [45]. PKA/CREB is downstream of several receptor types, including β-adrenergic receptors, which are also required for memory reconsolidation [24,46–51]. Similarly, ERK is triggered by NMDAR receptor activation. Furthermore, CDK5 modulates glutamatergic signaling [52] and may influence reconsolidation via NMDARs. The apparent similarities in molecular mechanisms underlying consolidation and reconsolidation suggest that the latter process plays a crucial role in the maintenance and long-term storage of memory. This suggests that enhancement of reconsolidation, like the enhancement of consolidation, may lead to strengthened memory [37,53,54,55••].

This basic protocol has also been used to study the enhancement of memory after retrieval of both fear and appetitive Pavlovian conditioning. In fear memories,