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Reconsolidation and the regulation of plasticity: moving beyond memory

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Memory reconsolidation is a protein synthesis-dependent process that preserves, in some form, memories that have been destabilized through recall. Reconsolidation is a nearly universal phenomenon, occurring in a diverse array of species and learning tasks. The function of reconsolidation remains unclear but it has been proposed as a mechanism for updating or strengthening memories. Observations of an analog of reconsolidation *in vitro* and in sensory systems indicate that reconsolidation is unlikely to be a learning-specific phenomenon and may serve a broader function. We propose that reconsolidation arises from the activity-dependent induction of two coincident but opposing processes: the depotentiation and repotentiation of strengthened synapses. These processes suggest that reconsolidation reflects a fundamental mechanism that regulates and preserves synaptic strength.

Specific versus general view of reconsolidation

The ability to learn and store information in the form of memories is crucial for the survival of many organisms. Equally important is the ability to modify or update these memories to accurately reflect a changing environment. Over the past 15 years there has been a considerable amount of research into one process that is thought to enable the modification and updating of consolidated (see Glossary) memories: memory reconsolidation. The process of memory reconsolidation is triggered by the recall of a memory. Recall transiently destabilizes the reactivated memory and renders it labile, after which the memory restabilizes ('reconsolidates') to remain stored. Preventing the reconsolidation process, for example, by blocking protein synthesis, leads to disruption of the memory [1]. This cycle of memory destabilization and reconsolidation appears to provide a window of opportunity for the modification of learned associations [2,3].

Reconsolidation was brought to the fore of neuroscience research in 2000, when it was shown that inhibiting protein synthesis in the amygdala during the recall of a fear memory resulted in disruption of the memory [1]. The necessity of protein synthesis provided evidence for a cellular mechanism of reconsolidation that paralleled the well-studied process of memory consolidation [4], triggering an explosion of research into the mechanisms and parameters of memory reconsolidation. Since this revitalizing study, reconsolidation has been demonstrated to be a nearly universal phenomenon. Memory reconsolidation has been observed in more than 10 diverse species, from *C. elegans* to humans, and has been observed in several regions of the central nervous system (CNS) including the hippocampus, amygdala, and anterior cingulate cortex (reviewed in [3,5]). Despite this wealth of information, the overall function of reconsolidation remains unclear.

The scientific origin of reconsolidation has largely branded reconsolidation as a learning-specific phenomenon, and theories of the functional role of reconsolidation have centered on its putative role in the modification and updating of memories [2,3,6–8]. In this article we re-evaluate the functional role of reconsolidation in light of *in vitro* and *in vivo* evidence that this phenomenon may exist broadly throughout the CNS [9], and is thus unlikely to serve a learning-specific function. We argue that reconsolidation instead reflects a fundamental mechanism for the regulation of synaptic plasticity, and present evidence that the cellular processes mediating this regulation serve to constrain activity-dependent synaptic potentiation in the nervous system.

Functional significance of reconsolidation

Reconsolidation has been proposed to serve two general functions: the modification and/or strengthening of memories [2,7,8]. The modification of memories through reconsolidation may maintain memory relevance by allowing

Glossary

Consolidation: the stabilization of a memory trace after acquisition.
Depotentiation/repotentiation: a reduction/increase in the strength of a synapse that has been potentiated by some stimulus.
Fear conditioning: a learning paradigm in which a stimulus becomes associated with fear.
Heterosynaptic plasticity: changes in synaptic strength that can be induced through activity at other synapses or through other cellular processes.
Homeostatic plasticity: the adjustment of synaptic strength to regulate neuronal activity.
Homosynaptic plasticity: changes in synaptic strength that are input-specific and restricted to only the activated synapses.
Hyperalgesia: increased sensitivity to painful stimuli.
Long-term potentiation (LTP)/depression (LTD): an increase/decrease in synaptic strength that persists for hours or longer in response to an induction stimulus.
Synaptic plasticity: the ability to modify the strength of a synapse.

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the encoding of changes in the environment [10]. In humans, memories can be modified through the incorporation of new or conflicting information only after recall of the original memory [11,12]. Similar results were observed in animal studies, where memory recall rendered memory labile and vulnerable to modification [13–16].

One interesting prediction of the memory update function of reconsolidation is that the subsequent updating of memory should be most strongly triggered when recall occurs in a context that is slightly different than the original memory, necessitating an update of the stored memory to reflect the changes [17]. In this case, the induction of reconsolidation should be dependent on some element of novelty during recall. This was precisely the case in a study by Winters *et al.* [18], in which changing the texture of the flooring during a recall trial was necessary to enable reconsolidation of a well-trained object memory in rodents. Modifying the timing of a shock delivered during re-exposure to a fear-conditioning apparatus was also sufficient to induce reconsolidation of memories that were otherwise resistant to reconsolidation [19]. However, reconsolidation can occur even in the absence of explicitly novel information [1,15,20], indicating that the novelty is not an absolute requirement for reconsolidation.

Reconsolidation may also enable the strengthening of memories. This would allow the enhancement of behavioral responses through recall without requiring re-exposure to the original learning situation [7,8]. The strengthening of memory after reconsolidation has been described in both animal models [13,21,22] and in humans [12]. However, the strengthening of memory after recall is not seen in every case. Indeed, animal studies exploring reconsolidation often do not find stronger behavioral responses after memory recall that would indicate the enhancement of memory. For example, the degree of freezing used as a measure of memory in fear-conditioning studies does not typically increase after the recall trial (e.g., [1,15], but see [13,22]). This lack of effect is unlikely to result from a ceiling effect in training because it is possible to pharmacologically manipulate reconsolidation to generate memory strengthening after recall [23–25]. One possible explanation for a lack of memory strengthening after reconsolidation is that the recall of a memory in the absence of a conditioning stimulus such as an electric shock promotes memory extinction, which reduces the behavioral expression of the previously learned association and opposes the effects of memory strengthening induced by reconsolidation. In a recent report, Fukushima *et al.* [21] explore this possible balance through the elegant use an inhibitory avoidance assay designed to trigger reconsolidation under conditions that do not promote extinction learning. In the absence of extinction learning, the retrieval of a fear memory was shown to promote memory enhancement through reconsolidation. Thus, memory recall may activate multiple processes with opposite effects on memory strength, and whose net balance determines the overall effect of recall on memory strength.

The strengthening and modification of memories are not necessarily mutually exclusive outcomes of reconsolidation, and it is plausible that both of these effects can arise from similar underlying mechanisms. Indeed, both memory strengthening and modification can be seen after recall in the same behavioral assay, depending on the conditions of recall [15]. Nonetheless, these interpretations of reconsolidation are still rooted in the idea of reconsolidation as a learning-specific phenomenon. This is reasonable given that the study of behavioral reconsolidation has essentially been entirely restricted to learning tasks [2,3,6]. However, recent *in vitro* and *in vivo* work provides evidence that reconsolidation is not restricted to learning tasks and may exist broadly throughout the nervous system, encouraging a re-evaluation of the functional role of reconsolidation.

Reconsolidation beyond memory

We have recently demonstrated that a reconsolidation-like phenomenon can also be observed in pain-processing circuits of the spinal cord [9]. In this study, mechanical hyperalgesia was induced by the injection of capsaicin into the hind paws of mice. Three hours after the initial plantar injection, capsaicin was reinjected into the hind paw to reactivate the sensitized pain pathways. Although the second capsaicin injection did not modify hyperalgesia on its own, normal mechanosensitivity was quickly restored when this second injection of capsaicin was paired with the spinal administration of the protein synthesis inhibitor, anisomycin, via intrathecal injection. These findings indicate that the reactivation of sensitized spinal pain pathways rendered the hyperalgesia labile and reversible in a manner equivalent to the disruption of fear memories through reconsolidation impairment.

The observation of a reconsolidation-like phenomenon in spinal cord pain-processing circuits is not inconceivable given the strong mechanistic parallels between learning and the development of some forms of hyperalgesia (reviewed in [26–28]). Indeed, persistent hyperalgesia has been called a 'memory trace of pain' or pain 'engram' because of these mechanistic similarities [29,30]. Nevertheless, the observation of reconsolidation in spinal pain-processing pathways encourages a re-examination of the function of reconsolidation on the basis of one key point: given that reconsolidation is not restricted to learning tasks, it is unlikely to be a unique property of learned associations. This shift in the interpretation of reconsolidation does not contradict the proposals of reconsolidation as a means of memory trace strengthening or updating. Rather, we propose that the broad existence of reconsolidation suggests that it may serve a more fundamental role in the regulation of plasticity than possibly predicted from an analysis of reconsolidation solely within learning paradigms.

Re-evaluating the functional role of reconsolidation

A close examination of the processes triggered by reactivation of a memory trace reveals the existence of two opposing processes that can be recruited to enable the labilization of memory: a destabilizing process and a protein synthesis-dependent reconsolidation process (Figure 1A). The activity-dependent destabilizing process can be revealed by the inhibition of protein synthesis after reactivation of the memory trace. This typically leads to the disruption of the learned association that is a hallmark of assays designed to study reconsolidation. The labile state of memory has