Memory reconsolidation

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The formation, storage and use of memories is critical for normal adaptive functioning, including the execution of goal-directed behavior, thinking, problem solving and decision-making, and is at the center of a variety of cognitive, addictive, mood, anxiety, and developmental disorders. Memory also significantly contributes to the shaping of human personality and character, and to social interactions. Hence, understanding how memories are formed, stored, retrieved, modified, updated and used potentially impacts many areas in human life, including mental health.

The traditional view of memory storage assumes that each time we remember some past experience, the original memory trace is retrieved. This view has been challenged by data showing that when memories are retrieved they are susceptible to change, such that future retrievals call upon the changed information. This is called reconsolidation. That reconsolidation exists is not at issue, but what really reconsolidation is, how it occurs, and what it means are heavily investigated and debated topics.

The classical view and the change

For about a century, the process by which a persistent or long-term memory is formed, stored and retrieved was believed to be a singular, linear process. In brief, it was thought that a freshly acquired memory trace remains in a fragile state for a limited time during which it is sensitive to disruption by a variety of means. Over this time, the memory undergoes a series of changes in the brain that convert the labile entity into one that is stable and long lasting. This stabilization process by which a newly formed, labile memory is converted into a lasting and stable long-term memory is known as memory consolidation.

In its early fragile state the memory is sensitive to many different types of interference, including behavioral or cognitive interference, brain trauma, seizures, and pharmacological or molecular manipulations. The definition and features of memory consolidation emerged from the pattern of amnesia collectively caused by all these different types of interventions. Memory consolidation appeared to be a complex and quite prolonged process, during which different types of amnestic manipulation were shown to disrupt different mechanisms in the series of changes occurring throughout the consolidation process. The initial phase of consolidation is known to require a number of regulated steps of post-translational, translational and gene expression mechanisms, and blockade of any of these can impede the entire consolidation process.

A century of studies on memory consolidation proposed that, despite the fact that it is a long process that progresses through a sequence of changes, memory formation involves a single type of stabilization process, and once a memory reaches a consolidated level it becomes insensitive to disruption.

More recently, this classic view of the consolidation process has undergone revision. Drawing upon earlier observations, a large number of studies over the last 15 or so years have shown that consolidated memories, which should be insensitive to amnesic agents, again revert to a vulnerable state if they are retrieved (the trace is reactivated). These active (or reactivated) memories can then again undergo another consolidation process, which is in many ways similar to that of a new memory (Figure 1). This additional process has hence been named memory reconsolidation.

Reconsolidation has been found for a variety of different kinds of memories (explicit and implicit; aversive and appetitive) in many kinds of organisms (from invertebrates to humans). It is clear from the results of the large number of studies that have experimentally addressed the topic that consolidation is not a singular process of stabilization that occurs once for each memory. Memories, in other words, can reconsolidate after retrieval, and this may occur many times.

The picture that emerges is that long-term memories are stabilized and then de-stabilized and re-stabilized according to the reactivation schedule of their traces. Hence they appear to undergo many reconsolidation cycles in the course of their existence. Memory storage is thus a dynamic process and a consolidated memory is far from being 'fixed'. One important consequence of this dynamic process is that established memories, which have reached a level of stability, can be bidirectionally modulated and modified: they can be weakened, disrupted or enhanced, and be associated to parallel memory traces. These possibilities for trace strengthening or weakening, and also for qualitative modifications via retrieval and reconsolidation, have important behavioral and clinical implications. They offer opportunities for finding strategies that could change learning and memory to make it more efficient and adaptive, to prevent or rescue memory impairments, and to help treat diseases linked to abnormally consolidated memories. As we will see below, however, reconsolidation processes in different systems/networks have distinctive features, suggesting that potential treatments will need to be flexibly tailored to specific circumstances.

Reconsolidation has a variety of important theoretical and practical implications, and has stirred a great deal of debate. Many questions have been raised in numerous discussions. Why does memory reconsolidate? How general is this process? Is it simply a duplication of consolidation or does it involve unique mechanisms? Is reconsolidation a true, independent process, or is it a deceptive effect that actually involves the regulation of other memory processes, like retrieval, extinction, and new learning? Can reconsolidation offer an opportunity to weaken, even perhaps eliminate pathogenic memories? We will discuss some of these issues here.

Why does memory reconsolidate?

What is the advantage of having established memories become labile and then restored? The general advantage of reconsolidation is that it provides the ability to respond in a flexible and adaptive manner to continuously changing environments. Evidence revealed that reconsolidation allows changes in memory strength, and although still a subject of debates, some authors propose that reconsolidation mediates updating of memory content.

If a learning experience reoccurs, memory may become labile, and over time, through mechanisms of reconsolidation, be re-stabilized and strengthened. The same occurs when instead of a second learning

event the memory is retrieved by a reminder of the learned experience. Retrieving, hence reconsolidating, memories may provide the advantage of strengthening adaptive memories, without requiring re-exposure to the original learning situation. This is likely to be useful in the case of rewarding as well as aversive, painful and/or dangerous events, especially when the memories are acquired after a single learning experience and cannot benefit from repetition. Clearly different conditions evoking reconsolidation, whether through repetitions of the learning experience (multiple training trials) or different types of retrieval, may result in distinct storage patterns. With multiple training trials the same experience is presented during the initial learning as well as the reactivating trials; hence the activation and recruitment of similar networks are likely to occur. In contrast, reconsolidations evoked by other types of experience, such as retrieval events that are different from the original learning experience, are likely to activate and recruit different networks. The reverse is also true: through reconsolidation, memory can also be weakened. For example, a threat stimulus that leads to heightened physiological arousal can result in a stronger memory but one that leads to less arousal can weaken the memory.

In addition to memory strengthening and weakening, retrievals can modify the trace content. Hence one function of reconsolidation is considered to be memory updating. While evidence exists that reconsolidation mediates the updating brought on by incremental learning following re-exposure to an experience similar to the original learning, the role of reconsolidation in adding distinct, novel information is debated. Some authors argue that reconsolidation mediates updating brought on by new experience co-presented with reactivated memories, whereas others propose that, although reactivation of the memory trace is essential and mediates this updating, novel experiences that differ from the original but that occur with reactivated memories may instead engage a new consolidation process; hence the updated memory actually constitutes a new memory that coexists in parallel with the old one.

As both consolidation and reconsolidation are sensitive to similar amnestic treatments, using these interferences does not distinguish whether there are parallel traces of consolidation as opposed to stabilization of an updated version of the original trace via reconsolidation. Methods of selective dissociation between new consolidation and reconsolidation will be needed to address this issue. A model that explains why the similarity between the events present at memory retrieval and the previously stored experience may lead to competition between new learning and memory updating (via reconsolidation) has been proposed recently for hippocampus-dependent memories: it suggests that low similarity between the old and the present experience would lead to new learning, but high similarity would lead to updating of the original memory. Whether this also occurs for other forms of memory is not known.

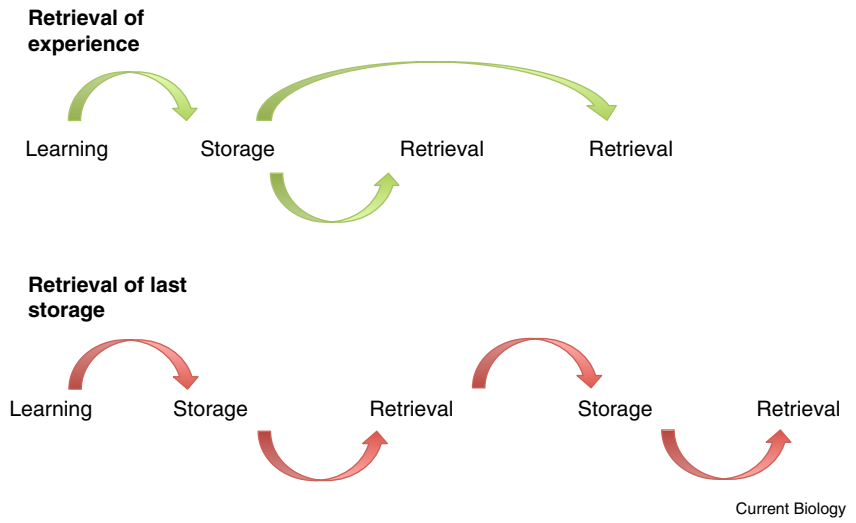

Figure 1. Two views of memory.
The conventional view was that memories are stored once and each time the memory is activated (remembered) a trace of the original experience is retrieved (top). According to the reconsolidation view, memories are susceptible to change each time they are retrieved. The next time the memory is activated the version stored during the last retrieval, rather than the version stored after the original experience, is called up.

Do all types of memory reconsolidate?

Memories in more than 10 species, spanning from the nematode worm *Caenorhabditis elegans* to humans, have been reported to undergo reconsolidation. The process also generalizes across memory paradigms and neural systems: reconsolidation occurs in aversive, appetitive, and neutral memories, in simple and complex tasks, in emotional, declarative, incidental, spatial, drug-paired, motor memories, and in hippocampal, amygdala and cortical-dependent memories. Although there are few examples of disagreement, in the majority of cases the disruption of memory reconsolidation produces a persistent decrease in memory retention, as shown by molecular and cellular readouts in animals, and also recently confirmed by imaging studies in humans.

Many different types of reactivation can evoke reconsolidation. Typically reconsolidation is studied using a non-reinforced stimulus as a reactivating experience, but, as mentioned above, reinforcing stimuli or a repetition of the whole training trial effectively returns the memory to a labile state, hence inducing reconsolidation. The type of reactivating event controls whether or not the memory becomes labile and reconsolidates, as well as the nature and features of that reconsolidation, including its accompanying network activation, neurotransmission, temporal progression and mechanisms. This also may account for differences found between consolidation and reconsolidation, which seem to mostly indicate distinctions in the temporal progression of the mechanisms or the activity network involved rather than profound mechanistic divergence. Whether the interfering agent

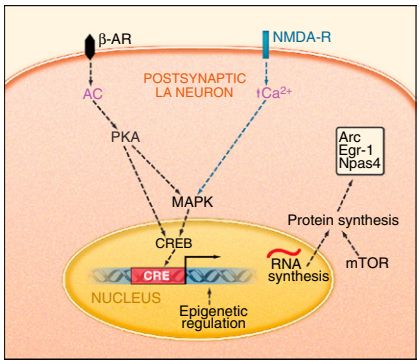

Figure 2. Working model of molecular mechanisms putatively involved in reconsolidation of Pavlovian threat (fear) conditioning.
Molecules and processes in blue are known to be involved in the initiation of reconsolidation. Molecules and processes in black are known to be involved in reconsolidation of fear conditioning. Purple labels denote molecules or elements whose role is not established for fear conditioning but are part of an established intracellular signaling pathway. AC, adenyl cyclase; AKAP, A-kinase anchoring protein; Arc, activity-regulated cytoskeletal-associated protein; β-AR, β-adrenergic receptor; BDNF, brain-derived neurotrophic factor; Ca^{2+}, calcium; CREB, cAMP response element (CRE) binding protein; Egr-1, early growth response protein 1; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NMDA-R, N-methyl-d-aspartate glutamate receptor; Npas4, neuronal PAS domain protein 4; RNA, ribonucleic acid. Reproduced from Johansen *et al.* (2011).

should be given before or after the reactivation is debated.

Does the passage of time affect reconsolidation?

In several cases, but not all, reconsolidation does not seem to occur or becomes much harder to be evoked as time passes. The passage of time is a critical determinant of memory formation and storage. It allows critical progressions and underlying sequences of mechanisms necessary for going from short-term to long-term memories, and is necessary for selecting what needs to become a long-lasting memory. With the passage of time the memory trace is likely reactivated many times by implicit or explicit events. Implicit activations of the trace likely occur during rest and sleep, and explicit activations occur upon the encounters of reminders. The effects of these trace reactivations with possible consequent reconsolidation, as well as other processes that remain to be identified, sequentially modify the storage of the memory, which progresses according to its history.

Perhaps the underlying sequential progression of changes is what leads to modifications in network representation of the more consolidated memories, as in the case of the remote representations of medial-temporal lobe-dependent memories. Memories that depend on the medial temporal lobe network, but also other simpler memories, show a temporal gradient of post-reactivation fragility, whereas more implicit types of memories maintain their post-reactivation vulnerability. Determining whether and how reconsolidation occurs in older memories and in which types of memories is important, not only for understanding memory processes but also for potential clinical applications. What appears to emerge is that the age of the memory together with strength of training and extent of reactivation interact to dictate whether or not reconsolidation occurs.

At present, the reason why some types of memories are differentially sensitive to reconsolidation interferences as they age is unclear, but a reasonable hypothesis is that different types of memories may utilize distinct storage mechanisms, hence have different abilities to reconsolidate. An amygdala-dependent memory, for example a memory of cued threat conditioning, may rely on storage mechanisms that, once reactivated, always become susceptible to disruption. In contrast, medial temporal lobe-dependent memories, which are known to undergo hippocampal-cortical trace redistribution over time, may utilize different storage mechanisms or a more distributed, hence stronger, storage system as memory ages. In this case reactivation of a remote memory may not trigger, or not sufficiently trigger, mechanisms that destabilize the memory. It is also possible that not all temporal lobe-dependent memories undergo a strong consolidation that renders them invulnerable to reconsolidation disruption as they age, and more studies on the reconsolidation of old and remote memories are needed.

One additional interesting boundary of reconsolidation and age of the memory relates to very strong training or overtraining. This, as also detailed below, is particularly relevant in severe stress and traumatic memories, where the learning is a very intense and uncontrollable emotional event. Some studies suggest that overtrained or strongly reinforced memories do not undergo reconsolidation if reactivated the first few days after training, but do become sensitive to reconsolidation interferences with time (weeks after training), confirming that the intensity of training in addition to the age of the memory regulate reconsolidation boundaries. One possible explanation for the differences in reconsolidation of strong vs. weak or milder training is the respective underlying network activations. Recent work, however, found that even strong new memories are susceptible to disruption if new information is added during retrieval.

What are the mechanisms of memory reconsolidation?

A number of mechanisms have been implicated in reconsolidation. Although it should be kept in mind that different types of memories or memory systems may recruit different mechanisms for their reconsolidation, here we will summarize the general understanding obtained thus far. Most of the molecular mechanisms found to be critical for memory reconsolidation are also engaged during consolidation. A few molecular processes, like those engaging the transcription factors C/EBP and Zif268 and the kinase ERK, have been found to be differentially recruited in reconsolidation. However, their distinctive implications in reconsolidation *versus* consolidation are probably due to differences in brain areas involved, temporal windows or dosage, rather than being unique selective molecules of each process. One interesting observation, however, suggests that there may be a selective mechanism for each process: the translation machinery required for new protein synthesis in the amygdala seems to differ during the consolidation and reconsolidation processes of auditory fear conditioning.

Upstream of the protein synthesis required for reconsolidation there may be an initial destabilization process, named deconsolidation, which, depending on the type of memory and brain region, may require protein degradation, cannabinoid receptors, histaminergic signaling and NR2B-containing NMDA receptors. Following deconsolidation, reconsolidation then engages L-type voltage-gated calcium channels (L-VGCCs) to promote synaptic plasticity as well as many

well-known plasticity mechanisms that lead to memory re-consolidation. These include activation of signal transduction pathways like those mediated by ERK, PKA and CamKII, which lead to the regulation of translation and transcription. Gene expression programs required in long-term synaptic plasticity and memory consolidation, like those mediated by the transcription factors CREB, C/EBP, and Zif268, are also required for memory reconsolidation, implying that, similar to that which takes place during the consolidation of a new memory, reconsolidation is accompanied by synaptic morphological changes. In agreement, mechanisms that are general regulators of gene expression, like epigenetic modification and neurotransmitter/hormonal regulation, control memory reconsolidation. Some amygdala mechanisms involved in the reconsolidation of amygdala-dependent memories are illustrated in Figure 2.

It is not possible to apply a rule of one size fits all when considering reconsolidation of different types of memories in different species at present, and different subregulations may surface with more detailed and extended investigations. Nevertheless, we can conclude that reconsolidation does seem to reopen a consolidation process. This conclusion greatly affects our view of how memories are maintained over time.

Can reconsolidation be used in the treatment of psychopathology?

One of the most exciting results emerging from the re-discovery of reconsolidation is that established memories can be disrupted when reconsolidation is induced and targeted with amnestic treatments. Because a great deal of animal and human experiments on reconsolidation have been done on aversive memories, it becomes apparent that memories of traumas could be potentially targeted for disruption by treatments that interfere with reconsolidation, with consequent amelioration of trauma-related pathologies. A pathology particularly suitable for such intervention is post-traumatic stress disorder (PTSD). PTSD is characterized by strong traumatic memories that are continuously retrieved in an intrusive manner, causing re-experiencing of the original trauma, avoidance and increased arousal and stress response. This has dramatic consequences in the daily functioning of affected individuals and leads to the development of associated pathologies like depression, aggression, substance abuse and high risk of suicide.

The available treatments are not very effective and novel intervention is needed. To date, two pharmacological treatments that target memory reconsolidation have been tested in PTSD populations. One is the β-adrenergic receptor antagonist propranolol and the other is the immunosuppressor/blocker of the mammalian target of rapamycin (mTOR) rapamycin. The suggestion that propranolol could be a useful treatment in PTSD stemmed from studies showing that this drug can disrupt the reconsolidation of cued threat conditioning in animal models and humans. Propranolol, however, does not seem to be effective in disrupting the reconsolidation of other, more complex aversive memories in animal models, or all human fear-related memories. One possibility is that propranolol preferentially affects the implicit emotional aspects of memory stored through circuits involving the amygdala (but perhaps other circuits as well) without significantly affecting the content or representation of complex memories stored via the medial temporal lobe circuits necessary for explicit memory. This difference may represent an advantage when the goal is to weaken the emotional significance without decreasing the cognitive representation. More studies are needed to understand the target mechanisms and the effects and/or boundary conditions of propranolol in clinical applications.

Rapamycin, also known as sirolimus, disrupts the reconsolidation of both hippocampal- and amygdala-dependent threat memories in animal models, suggesting that its effect may be more general than that of propranolol. This compound has been recently used in a pilot study targeting reconsolidation in male veterans and showed promising effects on veterans of more recent combats than for veterans from remote wars. This is in agreement with the findings that the effect on memory reconsolidation can be a function of the age of the memory.

Another approach for treating PTSD is extinction. Extinction (i.e. exposure) is a standard treatment for anxiety disorders. However, the effects of exposure are often temporary. This has led to the search for drugs that might enhance extinction learning and strengthen the effects of exposure, as well as for identification of the post-reactivation time windows during which the competing processes of extinction and reconsolidation favor long-term weakening of the original fear memory. Recent studies in rats and humans show that the effects of exposure treatment are much more persistent if after the first exposure trial a delay is inserted to allow reconsolidation processes to be initiated. If the delay is too long (if it is outside the reconsolidation window of approximately 4 hours), the treatment does not work. This approach has recently been used to significantly reduce craving in drug addicts. Addiction, like PTSD, is associated with very strong, persistent maladaptive memories that are resilient to extinction. Developing strategies that target the reconsolidation of these memories may open new frontiers in treating these disorders.

Importantly, most aversive memories studied thus far in the reconsolidation field are relatively mild and 'controllable', whereas the threat in traumatic experiences that lead to PTSD is so massive that it is hardly related to the stimuli used in reconsolidation studies — a mild electric body shock in rats or the memorization of emotional pictures by humans. The experience of a highly traumatic event or events is devastatingly threatening and terrifying, and this likely activates responses not recruited after a mild threat. Moreover, highly traumatic experiences evolve over time in a very different way, and rather than decreasing and becoming more controllable, they lead to 'uncontrollable' states of fear and panic, and to an inability to extinguish the feeling of fear and associated behavioral and physiological responses. Hence, it is imperative that studies aiming to inform the design of PTSD clinical trials also develop and use more representative models of traumatic memories.

Conclusions

The identification of memory reconsolidation has significantly changed our understanding of the way memory storage and retrieval are viewed. Reconsolidation research has offered an explanation for the

dynamic nature of memory storage, and is shedding light on how long-term memories are retained over time, and yet also allow behavioral flexibility and adaptation to changing environments. It may be possible to capitalize on flexibility in helping to ameliorate maladaptive memories and potentiate adaptive behaviors in psychopathology.

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Quick guide

Prospective memory

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What is prospective memory? To err is human: a fundamental part of human nature includes making mistakes (and we hope forgiveness is another ingredient of the human condition). In many cases, we 'remember to remember', but sometimes our mistakes are costly: a surgeon intends to remove an instrument before closing the body cavity, only to discover later that an instrument is missing. A pilot intends to adjust the position of wing flaps before takeoff, which can cause or prevent a successful takeoff. A patient intends to take her medication with dinner, and treatment outcomes depend on successful fulfillment of the intention. A bank manager intends to lock the vault, and forgetting has literal costs.

These examples highlight what is known as *prospective memory* — remembering to execute delayed intentions. As the examples above highlight, our intentions are typically interrupted by other pressing demands of everyday life (performing surgery, other preparations for takeoff, preparing dinner, assisting customers). Interruptions of our intentions provide a key ingredient that imposes a need for memory. Although we initially form the intention to act in the future, interruptions typically displace active processing of the intention. Instead, our intentions are temporarily put on hold — stored in memory — to be reactivated or retrieved at an appropriate point in the future. We err when we fail to retrieve these stored deferred-intentions. Prospective memory also includes other aspects of cognition, such as attention, executive control of cognitive function, episodic memory, and planning.

Additional everyday examples will help to underscore two approaches that are used in the burgeoning field of prospective memory research. After taking one's children to daycare in the morning, a parent needs to remember to pick up the kids at the scheduled time. When cooking, a chef needs to remember to remove the tray from the oven after 15 minutes. When I see my colleague next, I need to remember to share news about some interesting new data. When I pass the grocery store on the way home, I need to remember to buy milk. Two types of triggers may reactivate or retrieve a memory at an appropriate point in the future. In *time-based prospective* memory, time serves as the trigger; time may involve a specific time of day (as in daycare schedules) or an elapsing interval (as in cooking). In *event-based prospective* memory, the occurrence of an event serves as the trigger (the colleague or grocery store).

Both types of prospective memory have been investigated in the laboratory. A great deal of theoretical and applied interest focuses on understanding the causes of reactivation. According to one proposal, deferred intentions are automatically (effortlessly) activated when a target cue occurs. According to an alternative proposal, active (effortful) monitoring is needed to detect the occurrence of a target cue. Finally, according to the multiprocess view, both monitoring and spontaneous retrieval are utilized in prospective remembering.

Why is prospective memory important? In addition to everyday successes and failures to 'remember to remember', prospective memory is of great interest because it is implicated in cognitive decline. A major area of interest is cognitive decline associated with normal aging. Prospective memory declines in the elderly. Additional major areas of interest focus on cognitive decline associated with human diseases. For example, prospective memory impairments have been implicated in mild cognitive impairment, Alzheimer's disease, autism spectrum disorder, traumatic brain injury, Parkinson's disease, HIV infection, and substance abuse. Understanding prospective memory impairments in normal and clinical populations may be valuable for understanding biological mechanisms of prospective memory, especially when combined with human neuroimaging techniques. Prospective memory screening may also have great potential if it facilitates early detection of cognitive decline (for example, before the more dramatic memory failures associated with early onset of Alzheimer's disease). Another