Memory traces revisited

Lynn Nadel and Cantey Land

Recent findings on the possibility of disrupting a stable memory after retrieval challenge some of our widely accepted views on memory consolidation. This article comments on the implications of these and earlier findings to our understanding of consolidation, and explores their possible relationship to the idea that retrieval creates a new memory trace, increasing the resistance of older memories to disruption.

These are exciting times in memory research. What once seemed simple and settled now seems complex and open to new ideas. For 50 years or more, our ideas on memory have been as follows: an experience triggers a sequence of neural events ultimately leading to a stable memory trace, or engram. Although initially fragile, this memory trace is consolidated over time and becomes permanent. The medial temporal lobe (MTL), and the hippocampal formation in particular, is thought to be critical for the early, fragile stages of memory storage, but not to be the repository of consolidated engrams. Over time, memory is supposed to be lodged in circuits outside the MTL, and to be relatively immune to disruption. A report by Nader et al. and other recent findings call this widely accepted idea into question. In doing so, they hark back to earlier work that has been generally ignored.

Old challenges to consolidation theory

Early experimental tests of the consolidation hypothesis were largely supportive, but also revealed findings discrepant with some of its tenets. In a particularly innovative investigation, Misanin et al. sought to uncouple the age of a memory from its state of activity. They speculated that active memories, regardless of their age, might be susceptible to consolidation, whereas those that are not activated are not. In a test of this speculation, they trained rats on a conditioned emotional response (CER), in which an unconditioned stimulus (US; a footshock) was paired with a conditioned stimulus (CS; typically a tone or light). When such training was followed within 30 seconds by ECS, the memory for the pairing was disrupted, but if ECS was delayed until the next day, no disruption of the CER was observed; results such as this seem to support the consolidation hypothesis. However, if rats that had already learned a CER were exposed to ECS before the CS, the memory for the pairing was disrupted, but if ECS was delayed until the next day, no disruption of the CER was observed; results such as this seem to support the consolidation hypothesis. This was partly because of support from studies using discrete brain lesions, typically in the hippocampal formation, which were shown to cause retrograde amnesia. Although the time window for susceptibility to retrograde amnesia after such lesions was much longer than that of amnesia induced by ECS, hypothermia, hyperthermia or concussive treatments, the data were consistent with consolidation theory. In particular, they seemed to agree with the idea that consolidation could take a long time, but that it eventually led to a stable memory trace.

New challenges to consolidation theory

Nader et al. repeated the essential findings of Misanin et al. using more precise methods, undermining a key component of the standard story — the supposed stability of consolidated memory traces. Their study, much like those earlier, focused on the acquisition of fear conditioning. In the interim, however, a great deal had been discovered about how this kind of learning is subserved in the brain, which allowed Nader et al. to focus their manipulations in a much more targeted manner.

Cognitive and neural mechanisms underlying the consolidation of fear memories are now much better understood. The hippocampus, for example, is thought to be critical for the early consolidation of fear memories, with the amygdala playing a role in the late stages of consolidation.

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After the initial retrieval event (day 3), if the tone is presented before the injection of anisomycin. In the control group, fear conditioning persists if, however, they reactivated the memory about the CS–US association leading to the signal in the experimental context 30 days after initial training to expose the rats to the sequence of reactivation with a CS followed by anisomycin. As noted by the authors, nevertheless, the resultant vulnerability they observed suggests that such reconsolidation is indeed essential if memory is to survive. Memory for fear is disrupted in the test group presumably consolidated, memory trace renders it vulnerable once again, much as a new memory would be.

In a second experiment, Land et al. followed the procedure of Miller and Springer by presenting a non-contingent footshock (the reinforcer) to rats that received dorsal hippocampal lesions shortly after the original training. In the absence of this reminder, memory for the avoidance training seemed absent. Following the reminder, however, they observed a recovery of the fear memory for the signalled avoidance task.

Sara and colleagues have reported several results consistent with this general picture. For example, Przybyslawski and Sara showed that NMDA (N-methyl-D-aspartate)-receptor activation is essential for reconsolidation — the memory for a maze learning task is impaired if the receptors are blocked by injection of MK-801 within one hour of reactivation of the trace.

Stable memory traces revisited

This general pattern of findings has profound implications for how we think about the neural bases of memory and forces us to reconsider long-held views. Psychologists have often argued that memories are dynamic and subject to change, but neuroscientists have tended to shy away from these complexities. The research of Nader et al. and Sara has opened the door for investigation of the neural underpinnings of memory in all its dynamic complexity.

How might this research unfold? One obvious avenue is an exploration of the processes involved in reconsolidation. Will original learning and reconsolidation share common mechanisms, or will there be unique elements to each of them? A second avenue concerns the dynamics of reconsolidation. Will it take as long as the initial consolidation phase, or might it be shorter? Nader et al. began to investigate this issue by testing the effect of imposing a 6-hour delay between the reactivation event and the injection of anisomycin. With this delay, inhibition of protein synthesis no longer had any effect on fear. So, in this situation, those aspects of reconsolidation requiring protein synthesis seem to require less than 6 hours.

Will exposing an already established memory to reconsolidation increase its resistance to future disruption? This latter idea is related to the suggestion that reactivating a memory creates a new memory trace, and that this multiplication of traces accounts for the increased resistance of older memories to disruption. At first glance, the reconsolidation results seem to conflict with the multiple

<table>
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<tr>
<th>Test group</th>
<th>Day 1</th>
<th>Training: tone + shock</th>
<th>Day 2</th>
<th>Test 1: tone only</th>
<th>Day 3</th>
<th>Test 2: tone only</th>
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<tbody>
<tr>
<td></td>
<td>Rat learns to fear tone</td>
<td></td>
<td>Rat freezes in response to tone</td>
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<td>Rat does not freeze</td>
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<tr>
<th>Control group</th>
<th>Day 1</th>
<th>Training: tone + shock</th>
<th>Day 2</th>
<th>Test 1: tone only</th>
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Figure 1: Manipulations used to show reconsolidation. Memory for fear is disrupted in the test group if the tone is presented before the injection of anisomycin. In the control group, fear conditioning persists after the initial retrieval event (day 3).
trace idea, because the former suggests the existence of memories of increased fragility, whereas the latter suggests memories of increased stability. Critically, these two ideas are addressing different time frames. Reconsolidation events apparently occur in the short term and lead to a newly stabilized memory trace within that short time. Multiple trace formation happens over the long term, and presumably involves repeated reconsolidation events.

The multiple trace idea itself was put forward as an alternative to the standard consolidation theory. Considering memory to be mutable, as in multiple trace theory, may set the stage for elucidating the mechanisms responsible for phenomena not readily predicted by consolidation theory, such as forgetting stimulus attributes21,22, where the fundamentals of a trace remain accessible but specific attributes do not. As initially formulated, consolidation theory considered memories as unitary entities, to be strengthened or forgotten as a whole. However, evidence from studies such as the ones we have discussed shows that the various aspects or attributes of a given memory may experience different fates with time. This statement has two broad implications. First, it means that when a memory is retrieved, some attributes will be more likely than others to be part of that memory. Second, it means that some attributes of a memory will be more efficient reminders than other attributes. This can occur at different times after the initial experience.

In particular, memory for context seems to undergo substantial change after learning, although this change is not simply a matter of diminished strength with time23. The fact that contextual attributes are subject to variations in retrievability over time is of particular importance when thinking about consolidation and the role of medial temporal lobe structures. The importance of the hippocampus for learning about context had been hypothesized for some time24 and has been amply demonstrated empirically in recent years25–27. This raises the possibility that the changing effect of hippocampal lesions with time after learning is a consequence of the shifting role of context cues in retrieving memory, rather than a consequence of a shift in the entire memory from hippocampus to other brain structures. Reconsolidation, as a function of reminding and reactivation, can then be viewed as a means by which specific attributes are selectively strengthened and memory as a whole made more retrievable. In the case of the amygdala, as in the study of Nader et al.2, it might be stimulus attributes instead.

“Reconsolidation, as a function of reminding and reactivation, can then be viewed as a means by which specific attributes are selectively strengthened and memory as a whole made more retrievable.”

This view may also explain time-dependent fluctuations in retention and time-dependent reorganization of memory attributes26,27. One virtue of a neuroscientific approach to the question of reconsolidation is that it might permit a careful analysis of the role of these different memory attributes and their neural underpinnings.

**Implications**

The practical implications of these results are exciting. In clinical practice, one way commonly used to overcome inappropriate fear and panic is to desensitize the individual by exposure to an element of the disturbing stimulus or situation. If these exposures render the original learning that caused the fear open to disruption, then one might imagine the use of desensitization in tandem with drug treatments to obliterate the now fragile reactivated memory.

The conceptual implications are also exciting. These results point to the dynamic nature of the neural representations underlying memory. Cognitive psychologists have long been aware of the mutability of memory, but have not been able to shed much light on the details. It is tempting to imagine that addressing questions of malleable memory in well-controlled animal models such as that used by Nader et al.2 will provide some of these long-sought-after details. To do so, however, the behaviour under study will have to approach the complexity of the types of memory that interest cognitive psychologists. Furthermore, such studies will have to take account of the different attributes of memory, such as the background context and the specific signalling stimuli. So far, most studies of memory using animal models have not done so.

The reconsolidation results also touch on other recent neuroscientific findings showing the extensive dynamism of neural circuits. The reshaping of circuits as a function of hormonal shifts28, the establishment of neurogenesis as a common event29 and the observation of seasonal changes in the volume of specific neural structures30,31, all signal an important shift in our understanding of the brain. Future advances in memory research in particular, and brain research in general, are likely to depend on our ability to understand how systems undergoing constant change can nonetheless give rise to apparently permanent entities such as perceptions, memories and thoughts.

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Strengthening the shaky trace through retrieval

Susan J. Sara

Retrieval of fear conditioning turns memory into a labile state sensitive to disruption. Here, I raise the issue that in addition to aversive, amygdala-dependent memories, other forms of memory are susceptible to the same effect, and I review evidence indicating that neuromodulation may have a significant influence on the reconsolidation process.

One of the dominant neurobiological paradigms for memory research finds its roots in the consolidation hypothesis formulated by Müller and Pilzecker at the end of the last century. Extensive literature from the 1970s supported this hypothesis by showing that memory was labile for a short period after acquisition and was subsequently resistant to amnesic treatments. Embedded in this literature, however, there were several papers showing that temporally graded retrograde amnesia could be obtained for a well-established memory when the trace was reactivated just before the amnesic treatment (for a review, see Ref. 3). The recent publication of Nader et al. should rekindle interest and promote re-evaluation of this substantial but largely ignored literature.

The earlier studies were not, for the most part, carried out with an explicit neurobiological framework, but results using treatments as diverse as protein synthesis inhibition, electroconvulsive shock (ECS) or hypothermia pointed out the lability of memory for a short time after retrieval. The experiments by Nader et al. go well beyond these studies by showing the need for new protein synthesis after retrieval within a specific neural circuit known to be involved in the initial formation of the conditioned fear memory. Their striking results raise several important questions that should influence future research in this area. For instance, do other forms of memory become labile after retrieval or is this effect exclusive to aversive tasks? Are the processes involved in reconsolidation similar to those involved in the initial consolidation? Does the transient lability imply that remembering actually compromises the stability of memories? We do not have precise answers for these questions but there is already some evidence that deserves consideration in this context.

Appetitive memories may turn labile

Most of the reactivation studies done so far have used some version of fear conditioning similar to that used by Nader and colleagues. However, there is significant evidence that memory for appetitive, food-rewarded tasks involving both procedural and declarative memory systems are similarly labile after retrieval. For instance, Donald Lewis and his co-workers showed that the memory of rats for a linear maze consisting of a series of consecutive left-right choices (Fig. 1) was susceptible to interference immediately after retrieval. If the memory was reactivated by a single run in the maze or just by exposing the animals to the start box and the click produced by the opening of the door, then ECS was effective in causing marked amnesia. Numerous control procedures ensured that the specific cues associated with the original learning, and not merely a reinstatement of an emotional or motivational state, were essential to the effect.

My own group has used a pharmacological approach to study reconsolidation of non-fearful memory for food-rewarded spatial discrimination. In these experiments, rats were trained to recover food pellets from three constant arms of an elevated eight-arm radial maze. Unlike the task used by Lewis and co-workers, this spatial discrimination task is dependent on the hippocampus and is considered to involve the participation of the declarative memory system. Blockade of NMDA (N-methyl-D-aspartate) receptors induced a robust and selective amnesia when the drug was administered within one hour after the rat performed an errorless retrieval trial. As in the experiments by Nader et al., trained animals receiving the drug treatment without the memory reactivation trial did not show amnesia.

A third appetitive task in which the lability of memory after retrieval has been demonstrated involves odour discrimination. In this case, food pellets are associated with one of three possible odours and the rat has to learn...