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Memory reconsolidation: an update

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Memory consolidation refers to the stabilization that a new memory has to undergo in order to persist. Recently, this dominant view of memory has been challenged by renewed interest in reconsolidation, where consolidated memories return to a transient unstable state following their retrieval, from which they must again stabilize in order to persist. In this review, we discuss how reconsolidation is supported by the same line of evidence as consolidation and recent findings of boundary conditions of reconsolidation. Furthermore, we discuss how recent controversies on the nature of amnesia following challenges to reconsolidation are using the same paradigm that failed to resolve the nature of amnesia after challenges to consolidation; we also discuss a new paradigm that can lead to more fruitful ways of studying amnesia in general.

Keywords: consolidation; reconsolidation; amnesia

Introduction

For well over 100 years, we have known that new memories go through qualitatively distinct phases over time.[1–3] Initially, new memories enter a labile or unstable state and are stabilized over time. An example of this transformation is when you attempt to remember a telephone number and are distracted close to the time when the number was acquired. Chances are that this distraction will impair retention of the telephone number. However, if the same distraction is experienced a few hours after acquisition of the telephone number, retention of the telephone number will likely be unimpaired. In both cases, the same number and distraction are used; the only difference being the time interval between acquisition of the number and the distractor. In this case the gradient of stabilization is minutes to hours, roughly consistent with the time course described by Muller and Pilzecker,[1] who were the first to ascribe the term consolidation to refer to the stabilization of a memory over time.

Consolidation is a term that has historically been used to refer to both a fast process that takes place over minutes to hours, and a slower one thought to take months or years. This has led to some confusion as they are thought to represent different phenomena. In an attempt to clarify this issue, we will follow the suggestion of Dudai and Morris,[4] and refer to the memory stabilization process that is on the order of hours as "synaptic consolidation" and the longer gradient on the order of years as "systems consolidation." The former process is considered a ubiquitous property of neurons, not just in memory systems, but neurons located anywhere in the brain. In contrast, the latter process is considered to apply only to memories that are initially hippocampus dependent. It is important to note that the neurobiological mechanisms that are thought to transform this memory into a hippocampus independent one over time engage synaptic consolidation mechanisms.[5,6] Therefore, reports of reconsolidation at the synaptic level have implications not just for theories of synaptic consolidation, but also for theories of system's consolidation.

This review will briefly describe some of the evidence on which synaptic consolidation theory is based. Consolidation theory posits that once a memory is consolidated, it remains consolidated. In contrast to this expectation, we will argue that memory retrieval can return a consolidated/fixed memory to an unstable state once again, from which the memory is then restabilized. In the last section, we discuss recent studies that have argued that memory

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impairments following challenges to reconsolidation reflect a retrieval deficit and how they repeat the logical pitfalls of the debate on the nature of amnesia that has remained unresolved for more than three decades, and suggest a paradigm that can start to resolve the issue.

Consolidation and reconsolidation are deduced from the same line of evidence

Three lines of evidence support the existence of a synaptic consolidation process. First, performance can be impaired if treatments such as electroconvulsive shock[7] or protein synthesis inhibitors[8] are given shortly after learning. Second, performance can be impaired if new competing learning occurs shortly after the initial learning.[9] Third, retention can be enhanced by administration of various compounds, such as strychnine.[10] Critically, all three manipulations are effective only when given shortly after new learning and not after a delay on the order of hours. Accumulating evidence of this nature led to several propositions of a consolidation theory of memory.[11–13] These theories propose an initial unstable short-term memory trace that lasts on the order of hours and a more permanent long-term memory trace that consolidates over that period. Although initial formulations of the theory assumed a serial process between the memory stages,[12,13] later ones did not.[11] Brain trauma such as electroconvulsive shock is effective in producing amnesia if administered shortly, but not a long time after training. Thus, if the memory is susceptible to enhancement or impairment, it is considered to be in a labile state, and if it is insensitive to administration of these amnesic treatments then the memory is, by definition, consolidated.[11,14] Furthermore, once consolidated, the memory is assumed to remain in a fixed state.

Consolidation theory became the central tenet around which neurobiology of memory has mushroomed as a field. The field has enjoyed numerous successes in creating models at different levels of analysis to describe the changes that occur when a memory is converted from labile trace to a fixed one. In addition to studies at the behavioral level, models of consolidation include long-term potentiation (LTP), a long-lasting enhancement in signal transmission between two neurons following high-frequency stimulation of a chemical synapse, typically in a hippocampal slice preparation. Such potentiation is considered to be analogous to cellular mechanisms of memory.[15,16] Similar to the distinction between short- and long-term memory, LTP can be divided into an early transient phase (E-LTP), and a more persistent late phase (L-LTP), which similar to long-term memory, requires protein-synthesis in order to stabilize. Finally, on a molecular level, specific transcription factors critical for consolidation into long-term memory such as cAMP-response element binding protein (CREB) have been identified.[17–19]

Because its inception, consolidation theory was challenged on two fronts. The first was the claim that amnesia for new information, induced by a variety of agents such as electroconvulsive shock, hypothermia and protein synthesis, was best described as an inability to retrieve a memory that still existed in the brain.[20–22] This issue will be addressed in more detail in a later section.

The second challenge came from a small number of studies demonstrating that a consolidated memory could return to an unstable state and then restabilize within minutes to hours following retrieval. As with consolidation, three lines of evidence were put forth to support the existence of a restabilization period. First, performance can be impaired if amnesic treatments such as electroconvulsive shock are given shortly after reactivation.[23,24] Second, performance can be impaired if new competing learning occurs in short temporal proximity to the reactivation.[25] Third, retention can be enhanced by administration of various compounds, such as strychnine after retrieval.[26] Critically, all three manipulations are effective only when given shortly after memory reactivation but not when given after a delay. These findings, acquired by different investigators, in different tasks and species, fundamentally challenged consolidation theory.[20,27–29]

The implications of these findings, originally referred to as cue-dependent amnesia, were that LTM was not the end of the road in terms of memory lability but simply a momentary pause until the memory was reactivated. A theory proposed by Lewis[20] accounting for these findings posited that memory was a dynamic process that entailed two memory states; an active state in which new and reactivated memories were labile and vulnerable to disruption, and an inactive state in which they stabilize over time. Lewis' model accounts for both the evidence supporting consolidation theory, as well as findings of

Table 1. Some of the paradigms in which reconsolidation has been reported

Experimental paradigm	Habituation: Rose and Rankin[42]
	Auditory fear conditioning: Nader *et al.*[31]
	Contextual fear conditioning: Debiec *et al.*[68]
	Instrumental Learning: Shangha *et al.*;[72] but see Hernandez and Kelley[122]
	Inhibitory Avoidance: Anokhin *et al.*;[101] Milekic and Alberini[62]
	Motor Sequence Learning: Walker *et al.*[36]
	Incentive Learning: Wang *et al.*[123]
	Object Recognition: Kelly *et al.*[124]
	Spatial Memory: Morris *et al.*;[63] Suzuki *et al.*[61]
	Memory for drug reward: Lee *et al.*;[69] Miller and Marshall;[40] Valjent *et al.*[41]
	Episodic memory: Hupbach *et al.*[44]
Treatment	Protein-synthesis inhibition: Nader *et al.*[31]
	RNA synthesis inhibition: Shangha *et al.*[72]
	Inhibition of kinase activity: Kelly *et al.*;[124] Duvarci *et al.*[125]
	Protein-knockout mice: Bozon *et al.*[70]
	Antisense: Lee *et al.*;[126] Taubenfeld *et al.*[127]
	Inducible knockout mice: Kida *et al.*[128]
	Receptor antagonists: Debiec and Ledoux;[129] Przybyslawski *et al.*;[130] Suzuki *et al.*[61]
	Interference by new learning: Walker *et al.*;[36] Hupbach *et al.*[44]
	Potentiated reconsolidation by increase in kinase activity: Tronson *et al.*[37]
Species	Nematodes: Rose and Rankin[42]
	Honeybees: Stollhoff *et al.*[66]
	Snails: Shangha *et al.*[72]
	Sea slugs: Child *et al.*[131]
	Fish: Eisenberg *et al.*[59]
	Crabs: Pedreira *et al.*[71]
	Chicks: Anokhin *et al.*[101]
	Mice: Kida *et al.*[128]
	Rats: Nader *et al.*[31]
	Humans: Hupbach *et al.*[44]

Note: This table lists some examples from various experimental paradigms, treatments, and species for studies reporting evidence for a reconsolidation process since the year 2000.

cue-dependent amnesia which consolidation theory could not explain. However, for reasons that remain unclear, the dozens of studies that demonstrated reconsolidation across species, tasks and amnesic agents had little impact in the status of consolidation theory in the field of memory research.[30]

Research on the reconsolidation effect was revitalized by its demonstration in auditory fear conditioning in the rat,[31] a well-defined behavioral paradigm in which the underlying neural circuitry had previously been extensively mapped out.[32] Targeting directly the basolateral nucleus of the amygdala (BLA), known to critically mediate auditory fear conditioning and its consolidation,[32–35] and using the commonly used protein synthesis inhibitor anisomycin, Nader and colleagues[31] showed that reminders could bring well-consolidated fear memories back to an unstable state, in which they could be disrupted by infusing the protein-synthesis inhibitor directly into the BLA. As in the original findings of reconsolidation, such impairments were not observed in the absence of reactivation.

Since this study, reconsolidation has been demonstrated in a range of species, tasks, and amnesic agents (see Table 1). The modern evidence for the existence of a reconsolidation period is once again found from the same three lines of evidence on which consolidation theory is based. First,

performance can be impaired if amnesic treatments such as targeted infusions of protein synthesis inhibitors are given shortly after reactivation.[31] Second, performance can be impaired if new competing learning occurs in short temporal proximity to reactivation.[36] Third, retention can be enhanced by administration of various compounds, such as activators of signaling pathways important for consolidation after reactivation of the memory.[37]

Recently, a number of studies have found cellular and molecular correlates of reconsolidation. For example, a cellular phenomenon akin to reconsolidation was shown for late L-LTP.[38] Initially, after stimulation of the input pathway, LTP requires protein synthesis for stabilization in order to persist into its late phase. As mentioned earlier, this property of LTP has been viewed as a model for memory consolidation.[39] Fonseca and colleagues[38] demonstrated that if the protein-synthesis inhibitor anisomycin was added two hours after the induction of LTP, it has no effect on the maintenance of L-LTP. If, however, the potentiated pathway was "reactivated" by high-frequency stimulation while exposed to protein-synthesis inhibition, the potentiation remained for a short while but dissipated soon thereafter. This suggests that reactivation of stabilized L-LTP returns it to a labile state again, in which it requires protein synthesis in order to restabilize.

At the molecular level of analyses, a number of studies have demonstrated blockade of reconsolidation leads to a reversal of molecular correlates of long-term memory.[40–42] One elegant study used *C. elegans* and a nonassociative task (habituation of the tap withdrawal effect).[42] One molecular correlate of habituation in this system is a decrease in the number of postsynaptic AMPA receptors (these receptors mediate the vast majority of excitatory neurotransmission in the brain) in the mechanosensory neuron mediating tap withdrawal.[43] Reconsolidation in this model can be blocked by administering either heat-shock or a transient AMPA receptor antagonist after reactivation. These manipulations are ineffective in the absence of memory reactivation. When postsynaptic levels of AMPA receptors were analyzed, the amnesic animals had AMPA receptor levels comparable to naïve animals in the mechanosensory neuron. In the absence of the reminder, the amnesic treatments did not change the extent of AMPA receptor expression. This is striking evidence for the specificity of the reconsolidation impairments.

Importantly, reconsolidation has been demonstrated in humans where interference from new learning impaired previously acquired motor sequence memory,[36] and episodic memory.[44] Similarly, two recent studies, one using rats[45] and the other human subjects,[46] show how cue-shock associative fear memory can be disrupted by an extinction session where the predictive cue is presented alone immediately following a separate retrieval trial. Extinction training, where a conditioned stimulus is repeatedly presented without the unconditioned stimulus, is known to gradually reduce the conditioned response.[47] For example, if animals are presented with a tone that coterminated with footshock, they can learn that the tone predicts the shock and will then fear the tone.[48] If the tone is now presented without shock, animals will decrease the fear responses.[49] The reduction in responding induced by extinction procedures are not thought to be due to memory erasure of the previously acquired memory. Rather, extinction is thought to lead to the formation of a memory that will inhibit the expression of the previously acquired memory.[47] The evidence for this is that after extinction has inhibited performance, with the passage of time (spontaneous recovery),[47] changing the test context from the one in which extinction occurred (renewal),[49] or presenting the unconditioned stimulus (reinstatement, in this example footshock)[50] will elevate the level of responding.[51] Furthermore, extinction learning undergoes consolidation (which if disrupted, results in the return of the conditioned response), depends on distinct brain structures and molecular mechanisms.[52] Thus, there is a great deal of data demonstrating that extinction entails the learning of a new memory that inhibits, but does not erase a previous memory.

However, both Monfils and colleagues[45] and Schiller and colleagues[46] demonstrated that the immediate but not delayed extinction procedures after the induction of reconsolidation lead to reductions in responding that were insensitive to recovery or reinstatement in rodents and humans, respectively. In addition, Monfils and colleagues[45] demonstrated reduced phosphorylation of GluR1 glutamate receptors, a molecular marker of reconsolidation, in the amygdala following immediate but not delayed extinction after reactivation. Thus, retrieving the

memory in a separate session immediately prior to extinction resulted in a more enduring reduction of the fear memory, than by extinction alone. This suggests that the memory had been modified by either updating the retrieved memory through reconsolidation, or disruption of reconsolidation of the original memory trace by interference of the new learning.

Given the richness of the demonstrating postreactivation memory plasticity mentioned above, including the original findings, it is safe to say that the reconsolidation phenomenon is now well established,[53] although a number of different perspectives have been advanced on the nature of reconsolidation.[54–58]

Constraints on reconsolidation

Although reconsolidation seems to be a fundamental property, not all memories seem to undergo reconsolidation. This property of reconsolidation was noted by those who first studied the phenomenon. Reconsolidation was not considered a universal property of memory, but rather that its induction critically depended on specific parameters.[20,22,28] Situations of physiological, environmental, or psychological nature, in which memory that normally would reconsolidate no longer does, are here referred to as boundary conditions. Several boundary conditions have been proposed, such as extinction consolidation,[59–61] memory age,[61,62] predictability of the reactivation stimulus,[63,64] training intensity,[61] and whether a memory is directly or indirectly reactivated.[65] However, these results remain controversial, as other studies were unable to replicate them (for extinction,[66,67] old memories,[68,69] predictability of the reactivation stimulus,[41,70–72] or strength of training[68,69]).

One source likely contributing to the observed inconsistencies is that the typical logic used to conclude that a boundary condition exists is by testing the sensitivity of a memory to postreactivation administration of an amnesic agent under one set of experimental parameters. If the treatment does not induce memory impairments on a subsequent test, then it is concluded that the memory does not undergo reconsolidation under those conditions. For example, associative context-shock fear memory that is acquired with a training protocol of three shocks has been found to be insensitive to systemic injection of anisomycin if the reactivation session takes three or five minutes, whereas reactivation trial of ten minutes triggers reconsolidation.[61] If only the two shorter reactivations had been used, the absence of a behavioral impairment might have been taken as evidence that memories acquired with strong training do not undergo reconsolidation, implying a true boundary condition. A number of reports, however, have demonstrated that a memory may undergo reconsolidation only under specific reactivation conditions.[61,70,73] The implication of these findings is that it is extremely difficult to conclude based on behavioral studies that a memory never undergoes reconsolidation, *i.e.,* findings of no difference between the experimental and control group (a null result) cannot prove that the phenomenon in question does not exist at these parameters. Do the null results upon which the boundary conditions are based imply that a given memory never undergoes reconsolidation under those conditions, or is the memory still capable of undergoing reconsolidation with slight parametric adjustments?

This kind of parametric manipulation has not been performed for most boundary conditions. Therefore, it is unclear whether these boundary conditions represent situations in which it is harder to induce reconsolidation, or whether they represent situations in which memory does not undergo reconsolidation. Given that the parameter space of reactivation protocols is infinite, a purely behavioral approach may not be logically possible or practical. Because of the logical shortcoming of this approach, Wang and colleagues[74] recently suggested a complementary reductionist approach to this issue of identifying the molecular mechanisms engaged in boundary conditions on reconsolidation (*i.e.,* mechanism that inhibit reconsolidation from occurring). The authors argued that if molecular mechanisms could be identified, strong predictions could be made, based on behavioral findings, when these mechanisms would be expressed. Specifically, if strong memories, old memories, or extinction represent true boundary conditions, then the putative molecular mechanisms mediating boundary conditions should be fully expressed within a given memory system. Conversely, under conditions when a memory does undergo reconsolidation (*e.g.,* weak training, little extinction, or young memories), then the mechanism mediating boundary conditions should be less engaged. This strategy would

significantly complement the behavioral studies described above in their search for true boundary conditions and help resolve some of the conflicting findings in the field. In their study, Wang and colleagues characterized the effects of strong training on the ability of auditory fear memory to undergo anisomycin-sensitive reconsolidation and identified one mechanism that can mediate boundary conditions on auditory fear memory in the BLA. They found that when 10 pairings were used for training, instead of 1, the memory did not undergo reconsolidation 2 or 7 days after training, even when multiple reactivation protocols were used, consistent with previous findings.[61] However, when 30 and 60 days passed from training to memory reactivation, the memory did undergo reconsolidation.[74] This 30-day time course was notable because of its similarity to the time course of systems consolidation of contextual fear memories in rats, during which the expression of contextual fear memory depends on the hippocampus, but not thereafter.[75] In turn, this suggested the possible involvement of the hippocampus in mediating the boundary condition. Indeed, when Wang and colleagues[74] lesioned the dorsal hippocampus, memories that were normally resistant to postreactivation infusions of anisomycin, became sensitive once more, suggesting that boundary conditions can be transient and be imposed by other memory systems.

Finally, Wang and colleagues[74] looked at molecular mechanism that might mediate boundary conditions. Recent findings suggest that NMDA receptor subunits must be activated in the BLA during reactivation in order for a consolidated auditory fear memory to return to a labile state from which it must reconsolidate.[76] Specifically, inhibition of NR2B subunits prior to memory reactivation had no effect on the expression of freezing during reactivation but made the fear memory insensitive to postreactivation infusions of anisomycin that would otherwise block reconsolidation. Based on these data, Wang and colleagues[74] postulated that strong training may inhibit the memory from undergoing reconsolidation by downregulation of the mechanisms that induce reconsolidation in the first place. Consistent with this hypothesis, the authors found a clear relationship between the expression of NR2B subunits and the ability of a strong auditory fear memory to undergo reconsolidation in the BLA. In summary, the study by Wang and colleagues suggests three new insights into boundary conditions. First, boundary conditions can be transient. Second, one memory system can inhibit reconsolidation in another memory system. Third, one rule by which boundary conditions are manifested is by downregulation of the mechanisms mediating the induction of reconsolidation.

Currently, most theories of reconsolidation are qualitative theories, in as much as they revolve around the relationship between reconsolidation and consolidation and do not make specific experimental predictions concerning when reconsolidation will and will not occur.[14,20,30,53,54,64] However, such a model addressing boundary issues has recently been proposed by Lee[58] which focuses on the role of surprise in learning and the induction of reconsolidation. Lee's model is based on Learning Theory as formulated by Rescorla and Wagner[77] that posits that learning is driven by prediction error of associations. The greater this difference or "error" is, the greater the learning for that contingency. When environmental contingencies are perfectly predicted then there is nothing left to learn. Lee[58] posits that when such a prediction error signal is sufficiently large, memory reconsolidation is triggered and memory updating ensues. Conversely, when reactivation contingencies are used that do not provide much new information then the model predicts that the memory will not undergo reconsolidation. Thus, Lee's memory updating hypothesis makes clear predictions, across training paradigms, which experimental parameters lead to memory updating through reconsolidation, and which do not, the latter being boundary conditions.

Possible functional role of reconsolidation

Demonstrations of the reconsolidation phenomenon suggest that memory reactivation may play a role in modulating memory strength, and in the updating memory content.[78] The traditional physiological view of memory processing regarded memory as becoming wired into the brain overtime and then remaining fixed.[11,79] This view, however, seems at odds with the cognitive tradition of memory, which considers memory as being a reconstructive dynamic process.[80] How then can memory be dynamic when it is wired into the brain? Part of the appeal of reconsolidation, is that it provides a plausible neurobiological mechanism for explaining

some of the dynamic properties of memory. Indeed based on the early studies on reconsolidation, it has been suggested that reconsolidation might be a mechanism underlying some false memories.[81] Recently, Hardt and colleagues[78] proposed a more formal and explicit formation of how reconsolidation may mediate the different types of memory distortions.

A recent elegant paper by Lee[82] provide the first evidence for a functional role of reconsolidation in updating a previously acquired memory. Lee used the experimental design of Duvarci and Nader[83] in which animals were trained to associate a tone with a shock and then given the identical tone-shock pairing on the next day. On the third day the animals were then tested for their retention. Using this paradigm, Duvarci and Nader demonstrated that the second training induced reconsolidation of the memory for the first training. Using contextual fear conditioning associating a context with a footshock, Lee[82] asked whether an increase he observed in the conditioned fear response between the second day (before footshock presentation) and the third day was due to consolidation or reconsolidation mechanisms. By using previous findings of doubly dissociable mechanisms of consolidation and reconsolidation in contextual fear conditioning, he was able to use experimental manipulations that impair either reconsolidation (antisense against the immediate early gene, zif286) or consolidation (antisense to brain-derived neurotropic factor, BDNF). Lee reported that challenging consolidation-like mechanisms had no effect on the increase in performance induced the second training. However, challenging reconsolidation mechanisms blocked only the increase in memory strength induced by the second training, and the strength of the conditioned response remained the same on day two and three. This suggests that one functional role of reconsolidation might be to update and enhance existing memories. However, this does not rule out that reconsolidation is engaged every time new information is associated with previously acquired memory, as suggested by evidence that second-order conditioning engages consolidation processes, and not reconsolidation.[84] It will be very exciting to determine the kinds of new information that are learned by consolidation or reconsolidation mechanisms.

The unresolved nature of amnesia

The issue of whether experimental amnesia is a storage or retrieval deficit has been debated for decades without resolution, primarily because the paradigms that have been used to probe for whether amnesia is a storage or retrieval deficit are unable to differentiate between these two interpretations. We collectively refer to these paradigms as "recovery from amnesia" paradigms, which entail inducing experimental amnesia and then performing some manipulation involving a reminder to see if the impaired performance will recover. The treatments include, waiting for periods of time (spontaneous recovery),[85,86] performing repeated retention tests,[87] exposing animals to the unconditioned stimulus in a different context (reinstatement),[88] exposing the animals to the conditioned cue,[89] or exposing the animals to the conditioning context.[90] Successful recovery has been interpreted as an indication that the memory was present but inhibited, that the amnesia was a *retrieval* deficit. No recovery however, has been taken to indicate that the amnesia was reflecting a *storage* impairment. Thus, if the memory was absent then there should be no manipulation that would lead to recovery in performance.

The problem with the recovery from amnesia paradigm is that while the "retrieval view" can explain any finding in the recovery literature, it suffers from not being able to be disproven. If there was recovery from amnesia, then it was thought that the memory was always there and the deficit was one of retrieval. If there was no recovery from amnesia, it was entirely possible that the retrieval deficit was so great that the memory could not recover under the specific conditions in which it was tested.[21] Thus, even before animals were run in the recovery from amnesia paradigm, the retrieval position could account for whatever results followed (see Table 2).

On the other hand, the only prediction made by the storage impairment view of amnesia is that if the memory is not stored, then the performance will not recover. The strongest data supporting this view are cases where amnesia does not recover. In other words, there is a negative finding following the presentation of a reminder.[91] Using the absence of recovery (a null result) as scientific evidence that the memory was blocked from being stored and does not exist in the brain is a difficult hypothesis to prove empirically. This shortcoming

Table 2. The specific arguments invoked to explain the nature of amnesia before 1973 in the recovery from amnesia paradigms that led to a conceptual stalemate on the issue

Recovery from amnesia observed?	Storage impairment view	Retrieval impairment view
Yes	Inconsistent and can disprove this view	Consistent with overcoming retrieval impairment
No	Consistent with storage impairment	Consistent, as proper parameters to overcome the retrieval impairment have not been found

was clearly stated by Miller and Springer[21] in a review, "The experimental amnesia paradigm is such that, while the retrieval-failure explanation can be proven in principle, the consolidation-failure position is behaviorally untestable. That is. . . lack of recovery would not prove that recovery is impossible." (p. 472). Prior to 1973, any demonstration of recovery from amnesia was interpreted as evidence against the hypothesis that amnesia was as a storage impairment. Specifically, if the memory was absent, then reminders should not have increased performance. A number of studies demonstrated such recovery from amnesia, supporting the view that amnesia was indeed a retrieval impairment,[21,92,93] including spontaneous recovery.[8,85,86,94–98]

In 1973, however, interpretations of recovery from amnesia that were consistent with a storage impairment view of amnesia were proposed.[99] The proponents of this view argued that amnesia is never complete; that there is always some residual responding reflecting that a partial or residual memory trace existed. Gold and colleagues[99] performed a clever experiment suggesting that recovery from amnesia induced by reinstatement could be due to new learning strengthening a residual trace instead of overcoming a retrieval block. Specifically, if the footshock used for reinstatement was given to nonamnesic animals that were weakly trained in order to match the level of performance of the amnesic animals, then both groups showed the same increase in performance at a subsequent retention test. The reinstatement protocol was ineffective in untrained animals demonstrating the requirement for some initial baseline behavior. Given the behavioral change in animals that were never amnesic, the increase in behavior induced by the noncontingent footshock could not have been due to overcoming a retrieval impairment. Therefore, they argued that an apparent recovery from amnesia following a footshock was in fact due to new learning added onto a residual trace in the amnesic animals.[100] In terms of recovery from amnesia in humans, one could imagine an individual who suffers a blow to the head and forgets many of the details of the events that occurred in the last two weeks, including memories of a cousin's wedding. Importantly, amnesia is rarely complete. Therefore, there is some residual memory for the events that happened over the last two weeks. Concerned family members and friends may tell the patient some details from the wedding, giving him functionally the equivalent of a reminder treatment in the recovery from amnesia experiments. This information might then be incorporated as new learning into the existing residual memory of that event providing enough information for the patient to reconstruct an event roughly similar to the wedding. Such memory recovery might give the impression that the memory for the event was always there but simply inaccessible after the trauma. However, it might also be possible that the amnesia was a storage impairment and the improvement in recall reflected the inclusion of new information into the residual memory. Thus, after 1973, any finding from the recovery from amnesia paradigm could be interpreted as consistent with either view of amnesia, precluding any resolution of the issue by this paradigm (see Table 3). Even by 2006, more than thirty years later, the nature of amnesia remains disputed (see debate in *Learning & Memory*, Volume 13, No. 5 [http://learnmem.cshlp.org/content/13/5.toc]).

Recent demonstrations that consolidated memories can undergo another time-dependent memory stabilization process of reconsolidation renewed interest in the nature of experimental amnesia. However, reconsolidation did not bring any new behavioral techniques to bear on whether amnesia is due to a storage or a retrieval impairment. Several

Table 3. The specific arguments invoked to explain the nature of amnesia after 1973 in the recovery from amnesia paradigms[a]

Recovery from amnesia observed?	Storage impairment view	Retrieval impairment view
Yes	Consistent with storage impairment. The recovery reflects new learning added onto residual memory	Consistent with overcoming retrieval impairment
No	Consistent with storage impairment	Consistent, as proper parameters to overcome the retrieval impairment have not been found

[a]Notice all possible outcomes can be explained by all positions.

studies tested whether the postreactivation amnesia reported in reconsolidation studies were due to a retrieval or storage impairment.[101–106] Unfortunately, these studies used the same recovery from amnesia paradigms that, as discussed above, failed in the past to reveal the nature of amnesia and was abandoned in the mid 1970s. Currently, the majority of studies interprets recovery as categorical evidence for amnesia being a retrieval impairment and do not consider alternative interpretations consistent with storage impairment view of amnesia (the one exception is de Hoz *et al.*[107]). For example, one study reported spontaneous recovery in animals that were administered anisomycin after reactivation, but not in animals that were administered the drug after initial learning.[103] However, if one uses the interpretations forwarded after 1973, then the absence of recovery from amnesia induced by impairing new learning is consistent with both retrieval impairment and storage impairment views of amnesia. Similarly, recovery from amnesia induced by impairing postretrieval stabilization could suggest either retrieval or storage impairments. Thus, there is no empirical basis for studies demonstrating recovery after reconsolidation impairment to favor retrieval impairment interpretation of amnesia.

Recently, however, a new paradigm has been proposed to test the nature of amnesia.[108] The stated goals of the authors were to develop a paradigm that would make a positive, falsifiable prediction for the absence of a memory and allow for different predictions for the retrieval and storage impairment views of amnesia. The paradigm capitalizes on the fact that some tasks have different behavioral or neurobiological signatures engaged in the 1st and 2nd time the animals learn that task. Thus, logically, if amnesia for the memory of the 1st learning reflects a storage impairment, then the system targeted by the infusion will treat the 2nd learning, effectively as a 1st learning. Furthermore, any manipulations that specifically challenge mechanisms involved in 1st learning of a task would then be affective. If amnesia is a retrieval impairment, then memory for the 1st learning would engage neurobiological mechanisms normally engaged by 2nd learning. Part of the appeal of this logic is that it only requires that the task in question has different neurobiological signatures for the 1st and a 2nd instance of learning. Under such conditions, the logic can be applied to any type of amnesic treatment and any behavioral response. Furthermore, the method does not require knowledge of the specific neurobiological mechanisms mediating the amnesic effect, nor the neural mechanisms responsible for detecting a 2nd instance of learning.

The 2nd learning effect was first demonstrated for spatial learning in the watermaze where pretraining intradorsal hippocampus infusions of the NMDA receptor antagonist AP5 only blocked the first instance of learning the task,[109] a finding later extended to contextual fear conditioning.[110] Hardt and colleagues[108] replicated the basic effect of intradorsal hippocampus infusions of AP5 blocking the acquisition of the 1st, but not 2nd contextual fear task. The authors then showed that AP5 infusions prior to first learning caused 2nd learning to be blocked by AP5, consistent with NMDA receptor being critical for consolidation of new information.[111]

Furthermore, Hardt and colleagues[108] demonstrated that when memory of a 1st learning exists, but is inhibited from being expressed after having been extinguished, 2nd learning is insensitive to AP5 infusions. Having established these effects, the authors used the sensitivity of the 1st learning to AP5

as an assay for the absence or presence of a memory for a previously acquired instance of the task. The *a priori* predictions were that if amnesia is a storage impairment, then the animals should respond in an analogous manner to 2nd learning as animals receiving AP5 prior to 1st learning. In other words, the 2nd learning should now effectively be treated as an instance of 1st learning, sensitive to AP5 infusions, a *positive* prediction for the absence of a memory. Conversely, if amnesia is a retrieval impairment, in a manner analogous to extinction, then during the 2nd learning, an existing memory should make the 2nd learning insensitive to AP5 infusions. The findings were that anisomycin caused the 2nd learning to be blocked by AP5, a mechanism that is normally engaged by 1st learning, suggesting a storage impairment.

As pointed out by Hardt and colleagues,[108] there is no reason why all cases of amnesia must be either storage or retrieval in nature. Unfortunately, amnesia has traditionally been seen as a global entity that is always either a retrieval[22,112–114] or a storage impairment[11,79,100,115–117] for all cases of amnesia, including all amnesic agents, species, paradigms. While these positions are parsimonious, they have not been very constructive or productive in creating theories of memory that could accommodate both views of memory processing. One of the most reasonable comments on this polarization of views on amnesia was stated by Donald Lewis[92]:

> The typical procedure for retrograde amnesia experiments has been to have an animal experience a simple learning task, wait varying time intervals, and administer an amnesic agent. Any resulting amnesia has commonly been attributed to the failure of the memory trace to fixate (see Refs. 11 and 79); to a failure in learning. But there is no necessary reason always to attribute a response decrement following learning as an amnesic agent to failure at the input end. There is a great deal going on subsequent to fixation as the learning-performance distinction has always made clear. And there is nothing in the design of amnesia experiments that demands that a response (output) failure be always attributable to a failure to fix the input (p. 470).

While this quote was originally directed at those who viewed amnesia as a consolidation impairment, it is equally applicable to those who view all amnesia as a retrieval impairment.

The importance of this new paradigm is that it provides a tool to test the nature of amnesia for memory representations in various memory systems and any amnesic treatment.[108] For example, it could be used to ask about the nature of forgetting at the cognitive level, the nature of amnesia in human amnesics, the nature of amnesia induced by targeting molecular mechanisms involved in learning and memory, some of which are clearly involved in retrieval,[118,119] PKA and MAPK.[120,121] It seems self evident that any approach other than the recovery from amnesia paradigm would be a reasonable first step to determine the nature of amnesia following challenges to reconsolidation.

Summary

In this review, we have described some of the studies that have been published following the initial report that infusions into the basolateral amygdala following the retrieval of a fear can lead to subsequent impairment of that memory.[31] These studies have challenged the main tenets of synaptic and systems consolidation theories, namely that following consolidation, a memory will remain in a fixed state. This return of a consolidated memory to a labile, unstable state seems to be a basic property of memory, and may serve to update memories of specific associations.[58] We have also argued that the recent controversy over the nature of amnesia following challenges of reconsolidation cannot be resolved unless without a new approach that can make different predictions for different views on the nature of amnesia.

Conflicts of interest

The authors declare no conflicts of interest.

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