A single standard for memory: the case for reconsolidation

Karim Nader and Oliver Hardt

Abstract | Consolidated memories can re-enter states of transient instability following reactivation, from which they must again stabilize in order to persist, contradicting the previously dominant view that memory and its associated plasticity mechanisms progressively and irreversibly decline with time. We witness exciting times, as neuroscience begins embracing a position, long-held in cognitive psychology, that recognizes memory as a principally dynamic process. In light of remaining controversy, we here establish that the same operational definitions and types of evidence underpin the deduction of both reconsolidation and consolidation, thus validating the extrapolation that post-retrieval memory plasticity reflects processes akin to those that stabilized the memory following acquisition.

Fear conditioning
A Pavlovian conditioning paradigm in which an initially neutral stimulus (for example, a tone or the context in which the animals are conditioned) is paired with another stimulus that evokes pain or strong somatic discomfort (typically a footshock). After a single pairing the initially neutral stimulus will elicit a spectrum of fear-like or defensive responses.

Short-term memory
(STM). Transient memory for an experience that does not require synthesis of new proteins or RNA and that can be expressed immediately. Typically, STM duration ranges from immediately to a couple of hours after acquisition.

Psychology Department, McGill University, 1205 Doctor Penfield Avenue, Montreal, Quebec, H3A 1B1, Canada.
Correspondence to K.N.
e-mail:
karim.nader@mcgill.ca
doi:10.1038/nrn2590

Historically, learning and memory experiments used a variety of tasks in conjunction with global amnesic treatments[1]. The results from one task were generalized to others, as the prevailing notions assumed memory to be largely driven by the same principles regardless of the nature of the stimulus presented or the behaviour requested. Over time, the idea emerged of memory systems that can function mostly independently of each other, each controlling different kinds of knowledge and responses[2]. Consequently, well-established specific procedures are now used to study specific brain systems and thus specific types of learning and memory; for example, auditory fear conditioning is used for the amygdala[3–5], the water maze is used for the hippocampus[6] and eye-blink conditioning is used for the cerebellum[7].

Broadly speaking, the most prominent model of memory formation assumes that memory can make the transition over time from short-term memory (STM) to long-term memory (LTM) as a result of (synaptic) memory consolidation. Although consolidated memory can be forgotten, LTM is thought of as a state of (relative) permanence and thus stability. The finding that retrieval from LTM can again induce states of instability requiring additional stabilization (reconsolidation) fundamentally challenged this linear model.

Consolidation: the dominant model of memory

Consolidation is defined as a time-dependent stabilization process that leads eventually to the permanent storage of newly acquired memory[8–10] (FIG. 1a). In light of recent findings that, at the postsynaptic level, the molecular substrate of LTM requires continuous phosphorylation by protein kinase Mζ (PKMζ)[11], it should be noted that memory permanence requires continuous maintenance. The term consolidation is used for two processes: systems consolidation, in which it is asserted that a hippocampus-dependent memory becomes (over years in humans and over weeks in rodents) hippocampus-independent[12,13]; and 'cellular' or 'synaptic' consolidation, which is the time-dependent stabilization of changes in synaptic efficacy that occurs following acquisition and is thought to be a universal property of neurons[14,15]. Here, we focus exclusively on the latter process, using the term memory to refer to information retention in general, which is implemented on the cellular level as synaptic modifications and is therefore independent of the type of memory.

Evidence of a consolidation process. Empirical evidence for the existence of a consolidation process comes from various demonstrations of a post-acquisition time interval during which new memories are sensitive to challenges (FIG. 1a,b). First, performance on memory-recall tasks can be impaired by amnesic treatments, such as electroconvulsive shock[1] or protein synthesis inhibitors[16], or by new learning[17]. Second, retention can be enhanced by administration of certain compounds, such as strychnine[18]. Crucially, these manipulations are only effective when administered shortly after new learning. These results imply that memory exists in two states: a labile state, in which it is susceptible to enhancement or impairment; and a stable state, in which memory is insensitive to these treatments and therefore, by definition, consolidated[10,14]. The overwhelming evidence for this

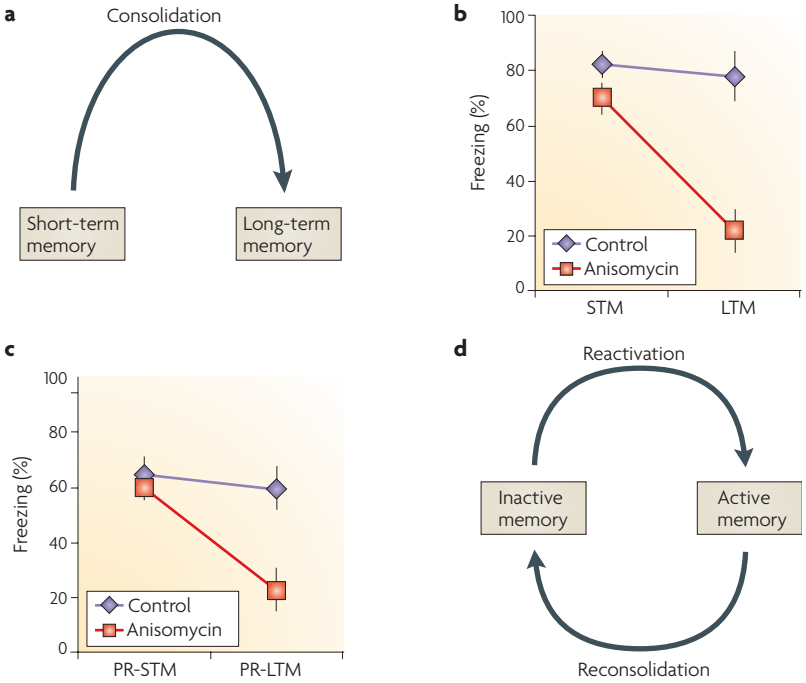

Figure 1 | **Principal properties of consolidation and reconsolidation accounted for by Lewis's memory model. a** | A textbook account of consolidation. Short-term memories consolidate over time into long-term memories, and once a memory is a long-term memory it remains fixed or permanent[9,10]. **b** | A typical demonstration of a consolidation blockade[34]. Applying anisomycin after fear conditioning results in intact short-term memory (STM) but impaired long-term memory (LTM), a pattern that defines a consolidation impairment[14,28]. **c** | A typical demonstration of a reconsolidation blockade of fear memory. Applying anisomycin during the reactivation period results in intact post-reactivation STM (PR-STM) and impaired post-reactivation LTM (PR-LTM), meeting the definitions for a consolidation blockade[14,28]. **d** | A model of memory that incorporates the findings of consolidation and reconsolidation data sets (proposed by Lewis[54]). New and reactivated memories are in an active state and stabilize over time into an inactive memory state. Remembering may return inactive memories to an active state.

interpretation prompted Spear and Mueller to state that "It does not take a great deal of courage or imagination to assert that 'consolidation' exists as a time-dependent associative process" (REF. 19).

Consolidation on the molecular and cellular level. It is assumed that synaptic consolidation — that is, the acquisition and stabilization of new memories — requires neurons to produce new RNA and proteins[15,16,20–24]. This can be studied by interfering with these processes, using appropriate agents infused directly into the brain structures thought critical for certain kinds of knowledge. For example, Guzowsky and McGaugh[25] tested the involvement of the dorsal hippocampus in consolidation of inhibitory avoidance memory by affecting the activation of the transcription factor cAMP-responsive element-binding protein (CREB), which has been proposed to be necessary for memory consolidation[26,27]. When CREB was inactivated by infusing antisense oligodeoxynucleotides into the dorsal hippocampus shortly after training, LTM but not STM was impaired. However, when this treatment was administered after a longer delay, LTM was intact. Taken together, these results establish that the amnesic treatment impaired memory consolidation, which takes time to complete and leads to stable memory that is immune to amnesic treatments. The fact that amnesic animals could be retrained in inhibitory avoidance supports the conclusion that the amnesic treatment did not lead to lesions, a possible alternative interpretation of the memory impairment[14,28]. It should be noted that in some hippocampus-dependent tasks lesions applied before training have no effect on subsequent learning. Thus, the ability of amnesic animals to relearn cannot be taken as conclusive evidence that the CREB inactivation did not impair hippocampus function by inducing permanent damage. CREB-mediated transcription in the hippocampus was thus concluded to be a key factor for the consolidation of LTM. In accordance with the established notion of multiple memory systems, which is part of the conceptual framework that underpins this research, these results imply that only consolidation of the hippocampus-mediated memory was blocked: other aspects of the training experience that depend on different brain areas were probably not affected.

As stated above, one of the basic tenets of the cellular consolidation model is that learning induces changes in synaptic efficacy. This suggests that the physiological 'unit' of cellular consolidation is the synapse. The two main candidate mechanisms that implement this modulation are long-term potentiation (LTP) and long-term depression (LTD)[29,30]. In parallel with the distinction of STM and LTM, LTP is also divided into an early transient phase (E-LTP) and a stabilized, RNA- and protein synthesis-dependent late phase (L-LTP)[20].

The vast majority of memory researchers would principally subscribe to this framework[31], although some of its aspects continue to attract various degrees of scrutiny — in terms of doubt expressed, the cellular model of memory[32] outranks the assumption that consolidation requires *de novo* protein synthesis[33]. There is little disagreement, however, about the existence of multiple learning and memory systems (see *Nature Reviews Neuroscience*'s Memory systems series). Our discussion of reconsolidation that follows is embedded into this established framework.

Reconsolidation

The existence of a consolidation process in the lateral and basal amygdala (LBA) for auditory fear memory has been concluded from studies that vary the time interval between training and interference with neural processing in this region. When, for example, the protein synthesis inhibitor anisomycin is infused into the LBA shortly after training, STM is intact but LTM is impaired[34] (FIG. 1b); however, delaying the infusion for 6 h leaves LTM intact. Amnesic animals can be retrained, suggesting that anisomycin infusions do not permanently compromise the integrity of the LBA. As discussed in the previous section, this pattern of results conforms to the operational definition of consolidation, and thus supports the interpretation that the aspect of fear-conditioning memory that requires protein synthesis in the LBA occurs within at most 6 h after learning, and that the treatment blocks computations that the LBA mediates[14–16]. These results do not demonstrate absence of memory for the entire fear-conditioning

Long-term memory
(LTM). Relatively stable memory that develops over time and is assumed to be mediated by changes in synaptic efficacy. LTM depends on synthesis of new proteins and RNA. Typically it is tested one or more days after training, as it takes several hours to stabilize. Once stabilized it can last for the remainder of the animal's life.

Long-term potentiation
(LTP). Traditionally demonstrated in hippocampal slice preparations, LTP is a persistent (lasting hours to days) enhancement of synaptic efficacy. It is rapidly induced by short high-frequency (tetanic) stimulation of a synaptic pathway.

Long-term depression
(LTD). A persistent reduction of synaptic efficacy that can be induced by repeated low-frequency stimulation of a synaptic pathway. Maintenance of LTD might require *de novo* protein synthesis.

Post-reactivation short-term memory
(PR-STM). By analogy with STM, PR-STM refers to a transient state into which existing LTM enters after it has been reactivated. The initial studies on reconsolidation indicate that PR-STM does not require synthesis of new RNA or proteins.

Post-reactivation long-term memory
(PR-LTM). By analogy with LTM, PR-LTM refers to the period of stability that reactivated memory enters after completing reconsolidation.

episode, as other brain systems — for example, the hippocampus — also acquire and store information about the events that occurred during learning[34]. Given the operational definitions, it is important to note that the term 'consolidated' signifies that that memory is insensitive to amnesic treatments. Thus, the term does not imply that all molecular and cellular changes induced by learning are complete. In fact, the changes might never reach completion: they might continue to some extent during the entire lifetime of a memory.

Evidence for a reconsolidation process. The existence of a reconsolidation process in the LBA for consolidated — that is, long-term — auditory fear memory has been concluded from a study that in logic and design followed the study we just described[35]. One day after conditioning, at a time when, according to the results from the consolidation study, memory should be fully stabilized and immune to the amnesic agent, animals were reminded of the conditioning session by again exposing them to the conditioning tone. Anisomycin, at the same dose, concentration and rate as in the consolidation study, was then either immediately or later infused into the LBA. Such anisomycin-treated animals had intact post-reactivation STM (PR-STM) but impaired post-reactivation LTM (PR-LTM) (FIG. 1c), a pattern of results that is identical to what is found when blocking consolidation, as described above[25,34] (FIG. 1b). However, if the post-reactivation infusion was delayed by 6 h it had no effect, demonstrating that the reactivation-induced instability was transient. Importantly, animals that were not reminded of the conditioning session before anisomycin infusions had intact memory, showing that it was indeed reactivation that made this consolidated memory labile again.

Staying strictly within the commonly accepted consolidation framework, and applying only the definitions on which this framework is based, four conclusions can be drawn (for example, see REFS 35–42). First, because the memory was insensitive to anisomycin when it was not reactivated, it was consolidated 24 h after training — at least with regards to the amnesic treatment applied. Second, only reactivated memory was sensitive to disruption and therefore in a labile state. Third, because anisomycin-treated animals had intact STM but impaired LTM after reactivation, a consolidation-like process is probably triggered by reactivation. Fourth, because the amnesic treatment was ineffective 6 h after reactivation, this post-reactivation re-stabilization process is probably time-dependent, like consolidation.

Taken together, these four conclusions yield the interpretation that reactivation of a consolidated memory bestows upon it a labile state from which it has to stabilize (that is, reconsolidate) over time[35]. In parallel with the consolidation framework described above, the post-reactivation treatment blocked re-stabilization/reconsolidation of local plasticity in the LBA. As is the case with local impairments of post-acquisition processing, the results do not imply that the entire memory for the training episode, which is distributed over several brain areas, was impaired. In addition, as only the amygdala-mediated component of fear memory was tested, it cannot be determined whether reactivation returned memory components in other brain areas to labile states. Thus, the very operational definitions, and conceptualizations that led to the proposal of consolidation as a unidirectional time-dependent memory-stabilization process that unfolds after memory acquisition, now lead us to the conclusion that memories are not consolidated, or stabilized, just once: they can return to a labile state and need to be reconsolidated, or restabilized, when reactivated.

Whether post-reactivation amnesic treatments eliminate the neurobiological substrate of consolidated memory has yet to be fully determined. That PR-STM remains intact provides some support for the possibility that the physiological changes that represent memory at the network level — for example, increased number of synapses[43] — are still present and sufficiently operational to allow normal expression of behaviour 4 h after reactivation and anisomycin infusion. However, it is also possible that the treatment causes immediate disintegration of the neurobiological substrate, and that PR-STM is mediated by a process similar to the one that mediated STM (covalent modification of existing proteins[15]). Protein synthesis could create the molecular and cellular changes that will mediate LTM. Thus, the most straightforward interpretation of the data is that reactivation induced a state in which conditioned responding was still possible but in which the synapses seemed to require the synthesis of new proteins, and infusing anisomycin interfered with this process[35,37,44]. Without normal protein synthesis, the synaptic morphology and mechanisms that mediate memory would either become dysfunctional or would be actively removed between 4 and 24 h after memory reactivation. This inferred role for new proteins in memory 're-stabilization' is merely a recapitulation of the widely accepted postulated role of protein synthesis in initial memory stabilization[45]. Some support for this explanation comes from an elegant recent experiment which showed that protein degradation by the ubiquitin–proteasome pathway is required in order for a consolidated memory to become labile again[46]. This might necessitate synthesis of new proteins during the reconsolidation phase following memory reactivation.

Consolidation and reconsolidation are thus both deduced from evidence of a transient period of instability. In the case of consolidation, this phase is initiated after acquisition of new information; in the case of reconsolidation, it is initiated after reactivation of an existing, consolidated memory. As is the case for consolidation, only during the reconsolidation phase can memory be enhanced[47–50], impaired by amnesic treatments[51] or interfered with by new learning[52]. These treatments are ineffective when reconsolidation is complete, which is also the case for consolidation.

The term reconsolidation was introduced in 1973 by Spear[53] (for a short historical overview, see Supplementary information S1 (box)). As a consequence of the perceived inability of the consolidation hypothesis to account for reconsolidation, new memory models were developed that treated new and reactivated consolidated memories in similar ways[53,54] (FIG. 1d).

Evidence for reconsolidation across levels of analysis. Since reconsolidation was again demonstrated in 2000, it has been shown to occur across a variety of tasks, amnesic treatments and species (FIG. 2; TABLE 1). Given that evidence for reconsolidation has been obtained from a wide range of manipulations, it clearly represents a fundamental mnemonic process.

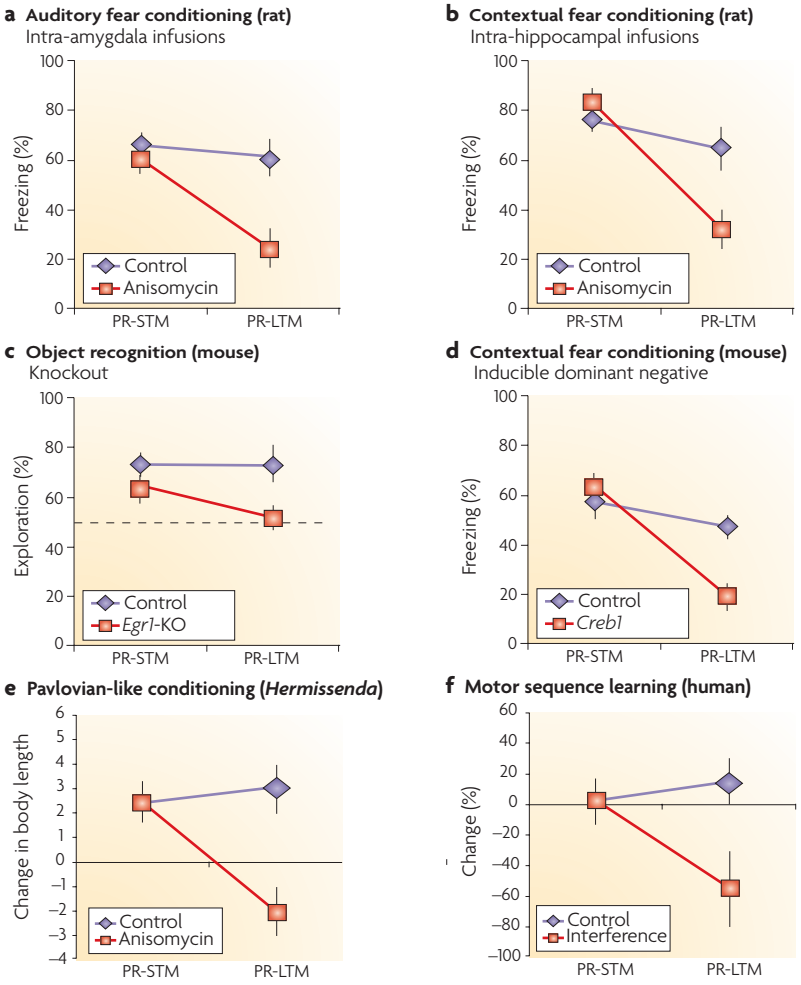

Figure 2 | **Representative data from studies reporting reconsolidation impairment.** Various data showing intact post-reactivation short-term memory (PR-STM) and impaired post-reactivation long-term memory (PR-LTM) after a combination of memory reactivation and amnesic treatment. **a** | Auditory fear conditioning in the rat: rats learn to fear a tone after it has been paired with a footshock. Presenting the tone reactivates the memory[35]. **b** | Contextual fear conditioning in the rat: rats learn to fear an environment in which they experienced footshocks. Placing them briefly into the environment reactivates the memory[37]. **c** | Object recognition in an *Egfr1*-knockout (KO) mouse: mice are exposed to two identical objects and their object memory is later tested by presenting one of these familiar objects together with a new one. As mice and rats preferentially explore novel objects, memory for the old object manifests itself by more time spent exploring the novel than the familiar object. Re-exposure to the familiar objects reactivates the memory[36]. **d** | Contextual fear conditioning in a transgenic (*Creb1* dominant-negative) mouse[38]. **e** | Pavlovian-like conditioning in *Hermissenda*, the marine snail. *Hermissenda* responds to light with phototaxis, thereby lengthening its foot, but it responds to sudden rotation by clinging to a surface, shortening its foot. Pairings of light and rotation lead to a new response to light, namely foot shortening instead of lengthening. Presentation of light reactivates the conditioned response[42]. **f** | Motor-sequence learning in the human: subjects learn to finger-tap a specific sequence. Later, a single repetition of this sequence reactivates the memory, and subjects then learn a new sequence. Testing memory for the old sequence reveals memory interference only when it was reactivated[41].

Evidence for reconsolidation does not come solely from the behavioural level of analysis. Recently, a cellular phenomenon akin to reconsolidation was shown for L-LTP[55]. In one study, the authors reported that if anisomycin is added 2 h after the induction of L-LTP it has no effect on the maintenance of L-LTP. This is consistent with the suggestion that plasticity is reduced over time, just like memory is stabilized over time[20]. If, however, test pulses reactivate the potentiated pathway when protein synthesis is inhibited, the potentiation remains intact shortly after reactivation but reduces over time. This suggests that stabilized L-LTP enters a labile state after reactivation, in which inhibiting protein synthesis can disrupt it. Other evidence includes reports that blocking reconsolidation reverses the increases in field potentials that are induced by fear conditioning in the lateral amygdala (LA) of intact and behaving animals[56]. Thus, there is a cellular correlate of the behaviourally demonstrated reconsolidation impairment.

At the molecular level, interfering with reconsolidation can, in a time-dependent manner, remove molecular correlates of memory induced by learning and subsequent consolidation. It has been shown that place-preference learning activates extracellular signal-regulated kinase (ERK; also known as mitogen-activated protein kinase 1) in the nucleus accumbens[57]. Blocking the activated ERK after reactivation results in intact PR-STM but impaired PR-LTM and, in these amnesic animals, also leads to the absence of downstream transcription factors that are activated by ERK in the nucleus accumbens (see also REF. 58). In long-term habituation in *Caenorhabditis elegans*, administering a heat shock or the non-NMDA (*N*-methyl-D-aspartate) glutamate receptor antagonist DMQX after reactivation of consolidated memory lowers AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor expression in the mechanosensory neuron to levels typical for naive animals[59]. Importantly, the amnesic effects in all of these studies were contingent on memory reactivation. These studies provide striking evidence for the existence of a post-reactivation transient period of memory plasticity — that is, memory reconsolidation — on behavioural, physiological and molecular levels of analysis.

Reconsolidation is not universal. Memory reconsolidation has been found across many levels of analysis; however, we know from the early studies using different experimental paradigms, such as auditory fear conditioning, maze learning or passive avoidance learning, that reconsolidation is not ubiquitous[60–62]. Although the original demonstration of reconsolidation was replicated[63] and extended to other paradigms[53,54,64], reconsolidation was not considered a universal property of memory. It was thought that its induction depended on specific parameters[53,54,64], a position that has been affirmed by a wave of contemporary studies[65–75]. For example, in one of the early replications[51], reconsolidation could not be induced by presenting the conditioning stimulus (CS) alone — the CS had to be presented in the training environment[63]. A similar effect was recently observed for human episodic memory[76]:

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

Experimental paradigm	Treatment	Animal	Refs
Habituation	Heat shock, and DNQX (antagonist of non-NMDA-type glutamate receptor)	Nematode	59
Auditory fear conditioning	Protein synthesis inhibition, inhibition of kinase activity, and reconsolidation potentiation by protein kinase A activation	Rat	35,99,137
Classical fear conditioning	Transient anaesthesia	Medaka (a fish)	65
'Pavlovian-like' conditioning	Protein synthesis inhibition, sensory block, mRNA synthesis inhibition and blocking bond formation of cell-adhesion molecules	*Hermissenda*	42
Contextual fear conditioning	Protein synthesis inhibition, inducible CREB-knockout and antisense oligodeoxynucleotides	Rat and mouse	37–39
Context-signal memory	NMDA receptor antagonist	Crab	74
Operant conditioning	RNA synthesis inhibition, and cooling	Snail	40
Appetitive conditioning	Protein synthesis inhibtion	Honeybee	69
Conditioned taste aversion	Protein synthesis inhibition	Rat pups	138
Inhibitory avoidance	Protein synthesis inhibition, glycoprotein synthesis inhibition and antisense oligodeoxynucleotides	Chicks and rats	67,87,139
Motor sequence learning	Interference by new learning	Humans	41
Incentive learning	Protein synthesis inhibition	Rat	140
Object recognition	*Zif268*-deficient mouse, and inhibition of kinase activity	Mouse, rat	36,141
Spatial memory	Protein synthesis inhibition	Mouse and rat	68,75
Memory for drug reward	Inhibition of the ERK kinase MEK, *Zif268*-deficient knock-in mice and *Zif268* antisense oligodeoxynucleotides	Rat and knock-in mouse	57,58,77
Episodic memory	Interference by new learning	Humans	72,76

This table lists example experimental paradigms and the treatments and species involved for studies that reported evidence of a reconsolidation process since 2000. CREB, cAMP-responsive element-binding protein; DNQX, 6,7-dinitroquinoxaline-2,3-dione; ERK,extracellular signal-regulated kinase; MEK, MAPK/ERK kinase; NMDA, *N*-methyl-D-aspartate.

reactivation-dependent interference effects in consolidated episodic memory were found only when human subjects were exposed to the interfering material in the same environment in which the original learning took place. Thus, activating memory outside the spatial learning context was not sufficient to induce reconsolidation.

So-called boundary conditions are physiological, environmental or psychological situations in which memory that normally would reconsolidate does not. Several boundary conditions have been proposed, such as extinction consolidation[65,66,68], memory age[67,68], predictability of the reactivation stimulus[74,75] and training intensity[68]. However, these results remain controversial, as other studies were unable to replicate them (for extinction see REFS 69,70; for old memories see REFS 37,77; for predictability of the reactivation stimulus see REFS 36,40,58,78; and for strength of training see REFS 37,77). Therefore, it remains to be seen whether additional parameters moderate boundary conditions.

There is currently no universally applicable reconsolidation protocol to reliably destabilize consolidated memory, which in turn complicates establishing boundary conditions. If under certain conditions reconsolidation effects are not detected, one cannot conclude with certainty that a boundary condition has been found. For example, in contextual fear conditioning, memories that were acquired with a strong training protocol of three shocks did not undergo reconsolidation if the reactivation session took 3 or 5 minutes, but reactivating memory for 10 minutes triggered reconsolidation[68]. If only the two shorter reactivations had been used, the absence of reconsolidation might have been taken as evidence that memories acquired with strong training do not undergo reconsolidation, implying a true boundary condition. This kind of parametric manipulation has not been performed for most proposed boundary conditions suggested by certain experimental results. It is thus unclear whether these conditions are true boundary conditions or merely situations in which it is harder than normal to induce reconsolidation.

Alternative interpretations

Reconsolidation, as discussed above, has been defined using the very standards that define consolidation. Therefore, questioning certain aspects of the reconsolidation hypothesis poses the same challenges for the consolidation hypothesis. The reconsolidation hypothesis in its current form has come under considerable scrutiny. We now discuss some of the alternative interpretations of the data that have been proposed in the literature.

Lesion or nonspecific effects. One theory posits that the amnesic treatment induces a lesion and thus impairs reactivated consolidated memory[79] (FIG. 3). This suggestion explains the deficits in PR-LTM and, if the treatment took several hours to destroy the local tissue and produce the lesion, it might explain the intact PR-STM. However, amnesic animals can be retrained, demonstrating that the targeted brain structures remain functional[80]. Moreover, without memory reactivation the amnesic

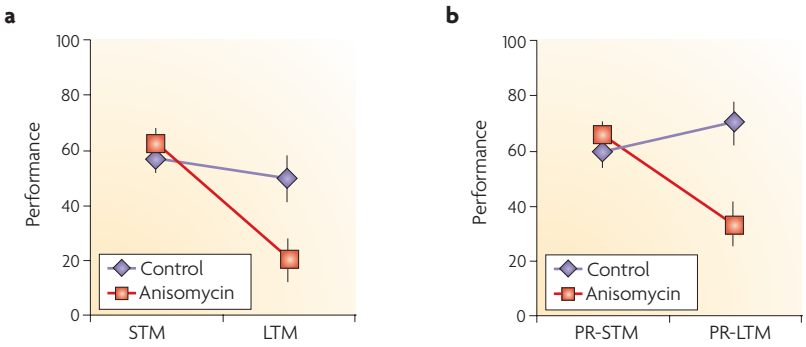

Figure 3 | **Is post-reactivation amnesia a nonspecific effect?** The results of two experiments are shown. The purple data points are from control animals and the red ones are from animals that received amnesic treatments, either after new learning[34] (**a**) or after reactivation[37] (**b**) of a consolidated memory. From the behavioural data alone it is impossible to distinguish the consolidation study from the reconsolidation study. Therefore, interpretations of behavioural data that selectively ascribe memory impairments following memory reactivation but not following memory acquisition to lesions[79] or to nonspecific transient retrieval impairments[82,134–136] are problematic. Irrespective of this shortcoming, these alternative interpretations cannot, for consolidation and reconsolidation alike, easily explain the intact short-term memory (STM) (although the amnesic treatment does supposedly induce a lesion). Transient retrieval impairment is unlikely given that animals can retrieve the memory during STM but not long-term memory (LTM), because that would mean that the retrieval impairment needs time to develop.

treatment has no effect, suggesting that lesion induction would depend not on the treatment alone, as proposed, but also on memory reactivation. Furthermore, this interpretation also falls short of explaining how different amnesic treatments (new learning, kinase inhibitors and inducible dominant-negative *Creb1*-mutant mice) could induce lesions or nonspecific effects with the same outcome. Further doubt on this interpretation comes from demonstrations of memory enhancement following reactivation[47–50,81]. It should be noted that the same arguments apply to consolidation studies that show the typical STM–LTM dissociation following amnesia induction. Finally, this account cannot explain studies in which reactivated memory no longer reconsolidates, such as those that suggest possible boundary conditions, although it might be argued that lesion effects are moderated by certain parameters, such as the duration of the CS. Mechanisms to account for this differential effect or ways to demonstrate their existence have yet to be proposed. In summary, this account remains highly speculative, as it offers explanations only for some consolidation and reconsolidation findings and is at odds with others.

Retrieval deficit. Some reports show performance recovery after post-reactivation amnesia induction[82–87]. The PR-LTM performance deficit might thus represent not blocked memory re-storage, but rather a transient nonspecific impairment in the ability to retrieve otherwise intact memory[85,88,89], questioning the existence of reconsolidation.

It has yet to be resolved whether experimental amnesia, induced by blocking new learning or by impairing reactivated memories, represents an impairment of consolidation (that is, storage processes) or impaired retrieval of an otherwise sufficiently consolidated memory (for an overview see REFS 90–92). Both interpretations can explain the presence or absence of recovery from amnesia[90–92] and currently there is no behavioural paradigm that allows us to pit the two positions against each other for simple responses, such as fear conditioning (but for a complex response see REF. 93). Consequently, one cannot currently determine whether amnesia induced by post-learning or post-reactivation protein synthesis inhibition is due to impaired consolidation or retrieval.

It has been argued that some studies which showed recovery of performance from reactivation-induced amnesia but not from amnesia for new learning establish that the former represents a retrieval and the latter a storage impairment[79,85,89,94]. Given that both the early and current studies on reconsolidation have consistently shown that reconsolidation and consolidation have different time courses and dose–response functions, one would predict that there are different time courses for recovery from amnesia for new and reactivated memories. For example, it remains possible that if in these studies the consolidation group had been tested one day later there would have been memory recovery. But even if there had been no recovery, it would not unequivocally follow that memory was not stored, as there still could be recovery with a more appropriate or stronger reminder. These uncertainties are some of the inherent problems of an approach that tests the nature of amnesia using memory recovery as a criterion for the presence or absence of memory[90–92]; until a clear assessment method has been developed, conclusions derived from memory recovery after amnesia for both new and reactivated memories remain open to question.

Because the recovery-from-amnesia paradigm could not resolve the nature of amnesia, alternative approaches examined whether the molecular and cellular changes that occur during the post-training stabilization (consolidation) period are lost in amnesic animals[89]. In Aplysia, consolidation of long-term facilitation is accompanied by an increase in synapse number. In amnesic preparations the increase in synapse number is not observed[95], implying that amnesia represents a memory-storage impairment[89]. In the context of consolidation, if reversal of the molecular signatures of LTM is taken as evidence that amnesia is a storage impairment, then data demonstrating that post-reactivation amnesic treatments reverse cellular[56,96] and molecular[57–59] correlates of LTM should consequently be taken as evidence that post-reactivation memory impairments represent a failure in memory re-storage.

State-dependent learning. Another hypothesis proposes that drugs can produce discriminative internal states, namely that animals learn that the presence of both the drug and the reactivation stimulus predicts the unconditioned stimulus (US) during reactivation and subsequent drug treatment[97]. Thus, during the PR-LTM test, when only the CS is presented, not all cues that predict the US are available, decreasing response intensity. This interpretation can explain many of the reported impairments in PR-LTM but cannot explain how PR-STM is intact, as

the same cues are given during PR-STM and PR-LTM. It could be argued that the drugs are still active during the PR-STM test, such that the internal state is similar to the state following reactivation, and that they have degraded sufficiently by the time of the PR-LTM, leading to a different internal state. Although this could be the case for some pharmacological treatments, such as anisomycin administration, this account cannot easily explain why new learning after reactivation impairs PR-LTM but not PR-STM[41,98], and why in lesion studies, when the lesion is present for both PR-STM and PR-LTM, only PR-LTM is impaired[37]. This account also cannot explain why — as discussed above — some post-reactivation treatments can enhance memory[47–50,99]. Furthermore, this interpretation also predicts that the presence of partial cues during the PR-LTM test should lead to a reduced response but never to a response enhancement. In summary, state-dependent memory can explain only a subset of the reconsolidation findings and thus cannot serve as a general alternative.

Facilitated extinction. A non-reinforced presentation of the CS (that is, presentation of the CS without the US) typically reactivates memory in reconsolidation studies, constituting — by operational definition — an extinction trial[100]. Extinction is thought to lead to new learning that inhibits the conditioned reflex[100–102]. Thus, amnesic treatment following reactivation might facilitate extinction learning[83,103], resulting in the response reduction that is seen during the PR-LTM test. This interpretation seems unlikely for several reasons. First, there are two opposing facts that it cannot reconcile: injecting anisomycin, or any other drug with amnesic properties, into the LBA after new learning blocks consolidation, whereas this treatment when applied after reactivation facilitates consolidation of extinction learning. The idea that post-reactivation protein synthesis inhibition leads to enhanced consolidation of learning is more problematic to explain than the idea that this treatment impairs memory reconsolidation. Second, the properties of extinction include renewal (recovery of performance with a context change), reinstatement (recovery of performance after presentation of only a US) and the propensity for performance to spontaneously recover over time[101], and none of these phenomena were demonstrated after amnesia-inducing post-reactivation anisomycin administration[80]. Third, when memory was reactivated with a reinforced CS presentation, subsequent protein synthesis inhibition resulted in impaired PR-LTM. This should not have been the case if reconsolidation reflects facilitated extinction, as this form of memory reactivation represents a conditioning, not an extinction trial. There are many other demonstrations of reconsolidation initiated by conditioning procedures that constitute a learning trial[36,40,58,78], empirical data that the facilitation extinction hypothesis cannot explain. In addition, extinction and reconsolidation have different biochemical signatures[68,104].

New learning. There are currently two versions of the new-learning hypothesis. In the first it is assumed that amnesic treatment after memory reactivation leaves the original memory unaffected but impairs consolidation of information acquired during the reactivation session. There is therefore no need to postulate a reconsolidation process. However, this interpretation cannot fully explain the data: in typical reconsolidation studies, animals are first trained to associate the CS and the US. This memory is reactivated the next day by a non-reinforced CS presentation, which is followed by the amnesic treatment. According to the new-learning hypothesis, the original memory, namely that the CS predicts the US, should be available during the PR-LTM test and, as a consequence, performance should be intact. This is not observed. Furthermore, control animals that were not subjected to the amnesic treatment after reactivation should have intact memory for the original learning (predicting the US) as well as memory of the new learning (predicting the absence of the US). Thus, these control animals should perform worse on the PR-LTM test than the animals that received the amnesic treatment. However, the control animals show higher response levels. In summary, the first variant of the new-learning hypothesis is at odds with empirical results (FIG. 4c).

The second variant of the new-learning hypothesis, also called the internal-reinforcement hypothesis[105], assumes that presentation of the CS during reactivation extinguishes the original memory. As reactivation also leads to fear expression and therefore represents an aversive event, it is postulated that the animal also acquires an association between this recalled fear and the CS; thus, in essence, the animal receives some form of second-order conditioning, and the amnesic treatment disrupts memory for this new learning. As a consequence, performance during PR-LTM is impaired. However, this account cannot readily explain the impairment in PR-LTM that is seen after amnesia induction following reactivation by a CS–US presentation. Here, extinction of the original memory cannot occur as the CS is again reinforced by the US. The second variant of the new-learning hypothesis can therefore also only explain a subset of the data.

The straw men of the reconsolidation debate

Departing from a semantic assessment of the term itself, some issues questioning the reconsolidation hypothesis have been raised. These arguments assert that in order for the phenomenon to be called reconsolidation, it must be an exact recapitulation of consolidation[106,107]; furthermore, they assert that all memories must always undergo reconsolidation in order for the term to be meaningful[85].

Reconsolidation implies an exact recapitulation of consolidation. As the term reconsolidation is derived from consolidation, it is argued that the mechanisms that underpin reconsolidation need to be identical to those that mediate consolidation[106,107], despite the fact that early comparisons of consolidation and reconsolidation showed that they were not identical processes. For example, reconsolidation is completed faster than consolidation, and their dose–response curves are not identical[108,109]. These findings, which were replicated in recent studies[14,87,107], were incorporated from early on into theories of memory that acknowledged both phenomena[53,60,110–112].

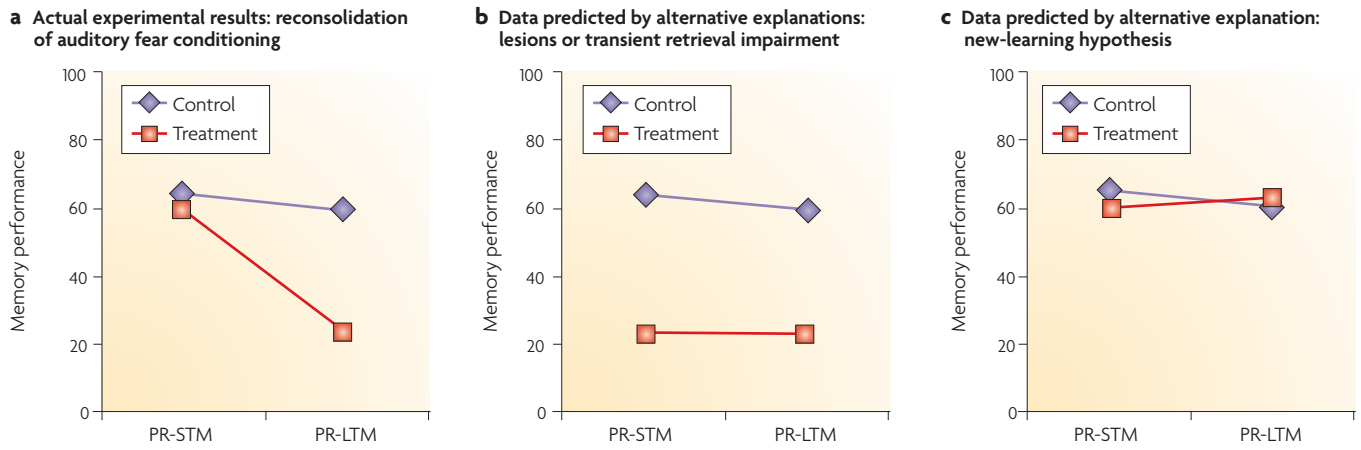

Figure 4 | **Predictions made by alternative interpretations of the reconsolidation impairment compared with actual reconsolidation data. a** | Reconsolidation data from an auditory fear-conditioning study. Rats first learned that a tone preceeded a footshock. The next day, when this memory was fully consolidated, the memory was reactivated by presentation of the tone alone, and anisomycin or vehicle was infused into the amygdala. Four hours later, post-reactivation short-term memory (PR-STM) was assessed by again exposing the animals to the tone. Twenty hours after the PR-STM test, post-reactivation long-term memory (PR-LTM) was measured the same way[35]. Data from control animals are shown in purple and from anisomycin-treated animals are shown in red (the same colours are used for graphs of hypothetical data predicted by the alternative interpretations). **b** | Predictions made by the assumption of a nonspecific impairment (that is, cognitive interference, lesions or neuronal dysfunction), as well as by the assumption of retrieval impairments. All these interpretations wrongly predict memory impairment for both PR-STM and PR-LTM for animals that received anisomycin. **c** | Predictions made by the new-learning interpretations of the reconsolidation deficit, which assume that anisomycin treatment after reactivation leads to memory impairment for the learning that the tone is no longer followed by a footshock. PR-LTM for the original memory, namely that the tone predicts the footshock, should be available and thus the tone should elicit a fear response.

An important but less-discussed aspect of this debate is that the protocols that are used to study reconsolidation are different from those that are used to study consolidation, which renders directly comparing results problematic[113]. Consolidation studies examine the neurobiological changes that occur after a CS and a US are presented together, whereas reconsolidation studies examine neurobiological changes that happen after presentation of a CS alone. For this reason, at the brain systems/circuits and molecular levels, consolidation and reconsolidation must be different, as only the former directly activates the pathways that relay US information to the amygdala. Therefore, the demonstration of differences between the brain regions or circuits that mediate consolidation and reconsolidation may be rather trivial[113]. For example, auditory fear conditioning leads to the activation of afferents that relay auditory (CS) and pain (US) information to the amygdala. Neurons that are thought to be the site of plasticity in the LBA are proposed to receive concurrent activation through these afferents[114]. As a consequence, a series of second-messenger systems are activated that are thought to lead to transcription and translation of proteins required for consolidation[5,115].

It remains unclear which of the reported differences between consolidation and reconsolidation actually reflect genuine differences between the two processes as opposed to differences in the protocols used to induce them. A study in which such differences were not attributable to differences in the protocols is the first to shed some light on this issue[39]. The authors report a double dissociation separating the mechanisms that mediate consolidation from those that mediate reconsolidation[39] (see also REF. 116).

Every memory must be able to undergo reconsolidation. Non-reinforced contextual memories do not undergo reconsolidation after they have been reactivated[117]. These findings have been interpreted as challenging the reconsolidation hypothesis, as the hypothesis assumedly posits that the phenomenon should be universal[85]. As it has long been acknowledged that reactivation does not always induce reconsolidation[60,108,118], such an understanding of reconsolidation seems unconventional. For example, Lewis demonstrated that electroconvulsive shock induces amnesia when predictive cues are presented to animals, consistent with a blockade in reconsolidation. However, if those cues were extinguished impairment was absent[60,118]. The absence of the reconsolidation effect under certain testing conditions thus does not challenge the existence of the phenomenon *per se*; rather, it improves our understanding of the phenomenon itself.

As with most biological processes, it seems unlikely that memory and learning phenomena are characterized by universality. For example, the absence of Pavlovian conditioning in some specific protocol does not question the validity of the concept itself; rather, it reveals certain parameters that must be satisfied in order for conditioning to be observed[119]. The same is true for consolidation: brains are exposed to huge amounts of information every day, but only a fraction is consolidated and remembered. The fact that some memories are acquired but not consolidated

illustrates that consolidation is not a universal property of all acquired new memories — again, reconsolidation and consolidation are similar in this respect.

Conclusion

Following the initial report that intra-amygdala infusion of anisomycin blocked reconsolidation of fear memory[35], there have been hundreds of publications describing reconsolidation across species, tasks and amnesic agents (see TABLE 1). Much of the controversy surrounding the reconsolidation phenomenon is rooted in the nature of amnesia. If recovery from amnesia induced by a treatment after reactivation is taken as evidence that the impairments reported in reconsolidation studies are retrieval impairments[79,85,88,89,94], we must conclude that amnesia for new learning is also a retrieval impairment because there are numerous examples of spontaneous recovery from amnesia for new learning[16,120–126]. Conversely, if arguments are made in the consolidation domain to reconcile the facts that there is recovery from amnesia and that amnesia is a storage impairment, then those same arguments might well apply to cases of recovery in the reconsolidation domain. Lastly, the fact that both consolidation and reconsolidation blockade lead to reversals of the cellular and molecular correlates of memory provides strong evidence that the nature of amnesia is the same in both cases — and the nature of experimentally induced amnesia has yet to be determined.

From a purely semantic perspective, the term reconsolidation has been qualified as a misnomer if the processes involved do not faithfully recapitulate those involved in consolidation[106,107]. However, since its introduction the term reconsolidation has never been used to signify anything more than a repeat instance of consolidation[53]. As mentioned above, in the current framework of memory, consolidation is defined as time-dependent stabilization of memory. Reactivation of a consolidated memory induces a time-dependent memory state that shares many properties with the state that follows initial learning. Therefore, reactivation of a consolidated memory initiates a consolidation-like process. Given the fact that the term consolidation refers to the stabilization of only new learning, it would be inappropriate to use it to refer to the memory state induced by reactivation of an already-acquired memory. We feel that it is reasonable to differentiate between these processes by using a similar name that adequately acknowledges the similarities and differences between the two memory processes (this is not an uncommon practice — consider the term 'relearning', which signifies a process different from initial learning[127]). We would also like to point out that the term reconsolidation itself does not necessarily imply an exact recapitulation of the original consolidation process.

To achieve an understanding of the post-reactivation state of plasticity, other questions seem more important: one of the most dynamic areas of research in reconsolidation is identifying the conditions that determine when a consolidated memory will and will not undergo reconsolidation[65–75,128,129]. Thus, the importance of the phenomenon is not diminished by the fact that reconsolidation does not always occur. Rather, this feature of the phenomenon allows a deeper understanding of memory. The fact that reactivation of a consolidated memory can return it to a labile state from which it must be re-stabilized in order to prevent memory loss is well established.

A domain of intense research aims to identify the molecular mechanisms involved in returning a consolidated memory to a labile state. An empirical framework to test this issue was recently published[130] and identified NMDA receptors in the amygdala[130], protein degradation[46] and CB1 cannabinoid receptors in the hippocampus[131] as crucial for rendering consolidated memory labile during or after reactivation.

The time seems ripe for a new model of memory that successfully integrates both consolidation and reconsolidation. In this context it should be noted that recent research demonstrated that consolidated memory crucially depends on constitutively active PKMζ[132], indicating that the apparent stability of consolidated LTM as observed in behavioural assessments requires ongoing maintenance of the morphological changes that form the neurobiological substrate of memory, and that at any time LTM can be abolished by disrupting these processes without a preceding memory reactivation[11,133]. Thus, the notion of stability that is currently inherent in the consolidation and reconsolidation hypothesis may be a PKMζ-mediated state. Future models of memory storage and maintenance will need to consider and integrate these and similar findings.

The current view of reconsolidation, characterized above, remains the most parsimonious interpretation of both consolidation and reconsolidation data, because it preserves the general framework that has been established for the former. It remains to be seen whether this model will stand the test of time. Given the range of evidence and the nature of the arguments stated above, we would apply Spear and Mueller's conclusion about consolidation to reconsolidation: it takes little courage and imagination to assert that reconsolidation exists as a time-dependent associative process that is initiated when a consolidated memory is reactivated.

1. Duncan, C. P. The retroactive effect of electroconvulsive shock. *J. Comp. Physiol. Psychol.* **42**, 32–44 (1949).
2. White, N. M. & McDonald, R. J. Multiple parallel memory systems in the brain of the rat. *Neurobiol. Learn. Mem.* **77**, 125–184 (2002).
3. Davis, M. Neurobiology of fear responses: the role of the amygdala. *J. Neuropsychiatry Clin. Neurosci.* **9**, 382–402 (1997).
4. LeDoux, J. E. Emotion circuits in the brain. *Annu. Rev. Neurosci.* **23**, 155–184 (2000).
5. Maren, S. Neurobiology of Pavlovian fear conditioning. *Annu. Rev. Neurosci.* **24**, 897–931 (2001).
6. Morris, R. G. Episodic-like memory in animals: psychological criteria, neural mechanisms and the value of episodic-like tasks to investigate animal models of neurodegenerative disease. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **356**, 1453–1465 (2001).
7. Thompson, R. F. & Krupa, D. J. Organization of memory traces in the mammalian brain. *Annu. Rev. Neurosci.* **17**, 519–549 (1994).
8. Ebbinghaus, M. *Über das Gedächtnis* (Buehler, Leipzig, 1885).
9. Glickman, S. Perseverative neural processes and consolidation of the memory trace. *Psychol. Bull.* **58**, 218–233 (1961).
10. McGaugh, J. L. Time-dependent processes in memory storage. *Science* **153**, 1351–1358 (1966).
11. Pastalkova, E. *et al.* Storage of spatial information by the maintenance mechanism of LTP. *Science* **313**, 1141–1144 (2006).
This paper identified PKMζ as the only molecule currently known to maintain LTM.
12. Scoville, W. B. & Milner, B. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Psychiatry* **20**, 11–21 (1957).
13. Squire, L. R. & Alvarez, P. Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr. Opin. Neurobiol.* **5**, 169–177 (1995).

14. Dudai, Y. The neurobiology of consolidations, or, how stable is the engram? *Annu. Rev. Psychol.* **55**, 51–86 (2004).
15. Kandel, E. R. The molecular biology of memory storage: a dialogue between genes and synapses. *Science* **294**, 1030–1038 (2001).
16. Flexner, L. B., Flexner, J. B. & Stellar, E. Memory and cerebral protein synthesis in mice as affected by graded amounts of puromycin. *Exp. Neurol.* **13**, 264–272 (1965).
17. Gordon, W. C. & Spear, N. E. Effect of reactivation of a previously acquired memory on the interaction between memories in the rat. *J. Exp. Psychol.* **99**, 349–355 (1973).
18. McGaugh, J. L. & Krivanek, J. A. Strychnine effects on discrimination learning in mice: effects of dose and time of administration. *Physiol. Behav.* **5**, 1437–1442 (1970).
19. Spear, N. & Mueller, C. in *Memory Consolidation: Psychobiology of Cognition* (eds Weingarten, H. & Parker, E.) 111–147 (Laurence Erlbaum Associates, London, 1984).
20. Goelet, P., Castellucci, V. F., Schacher, S. & Kandel, E. R. The long and short of long-term memory- a molecular framework. *Nature* **322**, 419–422 (1986).
21. McGaugh, J. L. Memory - a century of consolidation. *Science* **287**, 248–251 (2000).
22. Dudai, Y. & Morris, R. in *Brain, Perception, Memory: Advances in Cognitive Sciences* (ed. Bolhius, J.) 149–162 (Oxford Univ. Press, Oxford, 2000).
23. Davis, H. P. & Squire, L. R. Protein synthesis and memory. A review. *Psychol. Bull.* **96**, 518–559 (1984).
24. Klann, E. & Sweatt, J. D. Altered protein synthesis is a trigger for long-term memory formation. *Neurobiol. Learn. Mem.* **89**, 247–259 (2007).
25. Guzowski, J. F. & McGaugh, J. L. Antisense oligodeoxynucleotide-mediated disruption of hippocampal cAMP response element binding protein levels impairs consolidation of memory for water maze training. *Proc. Natl Acad. Sci. USA* **94**, 2693–2698 (1997).
26. Yin, J. C. P., Del Vecchio, M., Zhou, H. & Tully, T. CREB as a Memory Modulator: induced expression of a *dCREB2* activator isoform enhances long-term memory in *Drosophilia*. *Cell* **81**, 107–115 (1995).
27. Silva, A. J., Kogan, J. H., Frankland, P. W. & Kida, S. CREB and memory. *Annu. Rev. Neurosci.* **21**, 127–148 (1998).
28. McGaugh, J. L. The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci.* **27**, 1–28 (2004).
29. Martin, S. J., Grimwood, P. D. & Morris, R. G. Synaptic plasticity and memory: an evaluation of the hypothesis. *Annu. Rev. Neurosci.* **23**, 649–711 (2000).
30. Malenka, R. C. & Nicoll, R. A. Long-term potentiation--a decade of progress? *Science* **285**, 1870–1874 (1999).
31. Milner, B., Squire, L. R. & Kandel, E. R. Cognitive neuroscience and the study of memory. *Neuron* **20**, 445–468 (1998).
32. Shors, T. J. & Matzel, L. D. Long-term potentiation: what's learning got to do with it? *Behav. Brain Sci.* **20**, 597–614; discussion 614–655 (1997).
33. Routtenberg, A. & Rekart, J. L. Post-translational protein modification as the substrate for long-lasting memory. *Trends Neurosci.* **28**, 12–19 (2005).
34. Schafe, G. E. & LeDoux, J. E. Memory consolidation of auditory pavlovian fear conditioning requires protein synthesis and protein kinase A in the amygdala. *J. Neurosci.* **20**, RC96 (2000).
35. Nader, K., Schafe, G. E. & Le Doux, J. E. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* **406**, 722–726 (2000).
Sparking widespread renewed interest in reconsolidation, this seminal paper provided the first analytical demonstration of the phenomenon. It used localized infusions of anisomycin into the LBA, the site that putatively mediates memory consolidation for auditory fear conditioning.
36. Bozon, B., Davis, S. & Laroche, S. A requirement for the immediate early gene *zif268* in reconsolidation of recognition memory after retrieval. *Neuron* **40**, 695–701 (2003).
37. Debiec, J., LeDoux, J. E. & Nader, K. Cellular and systems reconsolidation in the hippocampus. *Neuron* **36**, 527–538 (2002).
38. Kida, S. *et al.* CREB required for the stability of new and reactivated fear memories. *Nature Neurosci.* **5**, 348–355 (2002).
39. Lee, J. L., Everitt, B. J. & Thomas, K. L. Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science* **304**, 839–843 (2004).
This paper showed that the mechanisms that mediate consolidation and reconsolidation can be doubly dissociated, suggesting that the differences between consolidation and reconsolidation cannot be explained by use of asymmetric protocols.
40. Sangha, S., Scheibenstock, A. & Lukowiak, K. Reconsolidation of a long-term memory in *Lymnaea* requires new protein and RNA synthesis and the soma of right pedal dorsal 1. *J. Neurosci.* **23**, 8034–8040 (2003).
41. Walker, M. P., Brakefield, T., Hobson, J. A. & Stickgold, R. Dissociable stages of human memory consolidation and reconsolidation. *Nature* **425**, 616–620 (2003).
This paper was the first to demonstrate reconsolidation in humans in a procedural memory task. It showed that learning of a new motor sequence after reactivation of an old one reduces memory accuracy for the reactivated old sequence on a later test, and that this effect is dependent on reactivation.
42. Child., F. M., Epstein, H. T., Kuzirian, A. M. & Alkon, D. L. Memory reconsolidation in *Hermissenda*. *Biol. Bull.* **205**, 218–219 (2003).
43. Bailey, C. H. & Chen, M. Morphological basis of long-term habituation and sensitization in *Aplysia*. *Science* **220**, 91–93 (1983).
44. Nader, K. Memory traces unbound. *Trends Neurosci.* **26**, 65–72 (2003).
45. Bailey, C. H. & Kandel, E. R. Structural changes accompanying memory storage. *Annu. Rev. Physiol.* **55**, 397–426 (1993).
46. Lee, S. H. *et al.* Synaptic protein degradation underlies destabilization of retrieved fear memory. *Science* **319**, 1253–1256 (2008).
This paper showed that proteins must be degraded in order to transform a reactivated memory from a fixed to a labile state, suggesting that after reactivation degraded proteins need to be replaced through protein synthesis or else the reactivated memory cannot be re-stabilized.
47. Gordon, W. C. Susceptibility of a reactivated memory to the effects of strychnine: a time-dependent phenomenon. *Physiol. Behav.* **18**, 95–99 (1977).
48. Rodriguez, W. A., Horne, C. A. & Padilla, J. L. Effects of glucose and fructose on recently reactivated and recently acquired memories. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **23**, 1285–1317 (1999).
49. Horne, C. A., Rodriguez, W. A., Wright, T. P. & Padilla, J. L. Time-dependent effects of fructose on the modulation of a reactivated memory. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **21**, 649–658 (1997).
50. Rodriguez, W. A., Rodriguez, S. B., Phillips, M. Y. & Martinez, J. L. Jr. Post-reactivation cocaine administration facilitates later acquisition of an avoidance response in rats. *Behav. Brain Res.* **59**, 125–129 (1993).
51. Misanin, J. R., Miller, R. R. & Lewis, D. J. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science* **160**, 203–204 (1968).
This seminal paper provided the first description of the reconsolidation phenomenon but, for historical reasons, reconsolidation remained outside the mainstream literature until 2000.
52. Gordon, W. C. Similarities of recently acquired and reactivated memories in interference. *Am. J. Psychol.* **90**, 231–242 (1977).
53. Spear, N. Retrieval of memory in animals. *Psychol. Rev.* **80**, 163–194 (1973).
54. Lewis, D. J. Psychobiology of active and inactive memory. *Psychol. Bull.* **86**, 1054–1083 (1979).
This conceptual paper was one of the earliest theoretical attempts to explain both the consolidation and the reconsolidation data sets.
55. Fonseca, R., Nagerl, U. V. & Bonhoeffer, T. Neuronal activity determines the protein synthesis dependence of long-term potentiation. *Nature Neurosci.* **9**, 478–480 (2006).
An elegant LTP study which found that administration of the protein synthesis inhibitor anisomycin after and only after reactivation of an already-potentiated pathway attenuated LTP, suggesting that reconsolidation effects are observed for LTP as well.
56. Doyere, V., Debiec, J., Monfils, M. H., Schafe, G. E. & LeDoux, J. E. Synapse-specific reconsolidation of distinct fear memories in the lateral amygdala. *Nature Neurosci.* **10**, 414–416 (2007).
This paper was the first to demonstrate that blocking reconsolidation reverses learning-induced changes in field potentials.
57. Miller, C. A. & Marshall, J. F. Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. *Neuron* **47**, 873–884 (2005).
58. Valjent, E. *et al.* Plasticity-associated gene *Krox24/Zif268* is required for long-lasting behavioral effects of cocaine. *J. Neurosci.* **26**, 4956–4960 (2006).
59. Rose, J. K. & Rankin, C. H. Blocking memory reconsolidation reverses memory-associated changes in glutamate receptor expression. *J. Neurosci.* **26**, 11582–11587 (2006).
This paper showed that blocking reconsolidation in nematodes reverses the molecular correlates of LTM to those of naive animals.
60. Lewis, D. J., Bregman, N. J. & Mahan, J. J. Jr. Cue-dependent amnesia in rats. *J. Comp. Physiol. Psychol.* **2**, 243–247 (1972).
61. Dawson, R. G. & McGaugh, J. L. Electroconvulsive shock effects on a reactivated memory trace: further examination. *Science* **166**, 525–527 (1969).
62. Gold, P. E. & King, R. A. Amnesia: tests of the effect of delayed footshock-electroconvulsive shock pairings. *Physiol. Behav.* **8**, 797–800 (1972).
63. De Vietti, T. & Holiday, J. H. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace: a replication. *Psychon. Sci.* **29**, 137–138 (1972).
64. Miller, R. R. & Springer, A. D. Amnesia, consolidation, and retrieval. *Psychol. Rev.* **80**, 69–79 (1973).
65. Eisenberg, M., Kobilo, T., Berman, D. E. & Dudai, Y. Stability of retrieved memory: inverse correlation with trace dominance. *Science* **301**, 1102–1104 (2003).
This elegant study showed in two different species that consolidation of extinction learning for a memory could inhibit reconsolidation for this memory.
66. Pederia, M. E. & Maldonado, H. Protein synthesis subserves reconsolidation or extinction depending on reminder duration. *Neuron* **38**, 863–869 (2003).
67. Milekic, M. H. & Alberini, C. M. Temporally graded requirement for protein synthesis following memory reactivation. *Neuron* **36**, 521–525 (2002).
68. Suzuki, A. *et al.* Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J. Neurosci.* **24**, 4787–4795 (2004).
69. Stollhoff, N., Menzel, R. & Eisenhardt, D. Spontaneous recovery from extinction depends on the reconsolidation of the acquisition memory in an appetitive learning paradigm in the honeybee (*Apis mellifera*). *J. Neurosci.* **25**, 4485–4492 (2005).
70. Duvarci, S., Mamou, C. B. & Nader, K. Extinction is not a sufficient condition to prevent fear memories from undergoing reconsolidation in the basolateral amygdala. *Eur. J. Neurosci.* **24**, 249–260 (2006).
71. Debiec, J., Doyere, V., Nader, K. & Ledoux, J. E. Directly reactivated, but not indirectly reactivated, memories undergo reconsolidation in the amygdala. *Proc. Natl Acad. Sci. USA* **103**, 3428–3433 (2006).
72. Hupbach, A., Gomez, R., Hardt, O. & Nadel, L. Reconsolidation of episodic memories: a subtle reminder triggers integration of new information. *Learn. Mem.* **14**, 47–53 (2007).
73. Forcato, C., Argibay, P. F., Pedreira, M. E. & Maldonado, H. Human reconsolidation does not always occur when a memory is retrieved: the relevance of the reminder structure. *Neurobiol. Learn. Mem.* **91**, 50–57 (2008).
74. Pedreira, M. E., Perez-Cuesta, L. M. & Maldonado, H. Mismatch between what is expected and what actually occurs triggers memory reconsolidation or extinction. *Learn. Mem.* **11**, 579–585 (2004).
75. Morris, R. G. *et al.* Memory reconsolidation: sensitivity of spatial memory to inhibition of protein synthesis in dorsal hippocampus during encoding and retrieval. *Neuron* **50**, 479–489 (2006).
76. Hupbach, A., Hardt, O., Gomez, R. & Nadel, L. The dynamics of memory: context-dependent updating. *Learn. Mem.* **15**, 574–579 (2008).
This paper demonstrated in humans that episodic memory reconsolidation depends on re-exposure to the spatial context in which the original learning occurred, suggesting that the spatial context is crucial for inducing reconsolidation in human episodic memory.
77. Lee, J. L., Di Ciano, P., Thomas, K. L. & Everitt, B. J. Disrupting reconsolidation of drug memories reduces cocaine-seeking behavior. *Neuron* **47**, 795–801 (2005).

78. Pedreira, M. E., Perez-Cuesta, L. M. & Maldonado, H. Reactivation and reconsolidation of long-term memory in the crab *Chasmagnathus*: protein synthesis requirement and mediation by NMDA-type glutamatergic receptors. *J. Neurosci.* **22**, 8305–8311 (2002).
79. Rudy, J. W., Biedenkapp, J. C., Moineau, J. & Bolding, K. Anisomycin and the reconsolidation hypothesis. *Learn. Mem.* **13**, 1–3 (2006).
80. Duvarci, S. & Nader, K. Characterization of fear memory reconsolidation. *J. Neurosci.* **24**, 9269–9275 (2004).
81. Gordon, W. C. & Spear, N. E. The effects of strychnine on recently acquired and reactivated passive avoidance memories. *Physiol. Behav.* **10**, 1071–1075 (1973).
82. Power, A. E., Berlau, D. J., McGaugh, J. L. & Steward, O. Anisomycin infused into the hippocampus fails to block "reconsolidation" but impairs extinction: the role of re-exposure duration. *Learn. Mem.* **13**, 27–34 (2006).
83. Fischer, A., Sananbenesi, F., Schrick, C., Spiess, J. & Radulovic, J. Distinct roles of hippocampal *de novo* protein synthesis and actin rearrangement in extinction of contextual fear. *J. Neurosci.* **24**, 1962–1966 (2004).
84. Vianna, M. R., Szapiro, G., McGaugh, J. L., Medina, J. H. & Izquierdo, I. Retrieval of memory for fear-motivated training initiates extinction requiring protein synthesis in the rat hippocampus. *Proc. Natl Acad. Sci. USA* **98**, 12251–12254 (2001).
85. McGaugh, J. L. Memory reconsolidation hypothesis revived but restrained: theoretical comment on Biedenkapp and Rudy (2004). *Behav. Neurosci.* **118**, 1140–1142 (2004).
86. Prado-Alcala, R. A. *et al.* Amygdala or hippocampus inactivation after retrieval induces temporary memory deficit. *Neurobiol. Learn. Mem.* **86**, 144–149 (2006).
87. Anokhin, K. V., Tiunova, A. A. & Rose, S. P. Reminder effects - reconsolidation or retrieval deficit? Pharmacological dissection with protein synthesis inhibitors following reminder for a passive-avoidance task in young chicks. *Eur. J. Neurosci.* **15**, 1759–1765 (2002).
88. Cahill, L., McGaugh, J. L. & Weinberger, N. M. The neurobiology of learning and memory: some reminders to remember. *Trends Neurosci.* **24**, 578–581 (2001).
89. Squire, L. R. Lost forever or temporarily misplaced? The long debate about the nature of memory impairment. *Learn. Mem.* **13**, 522–529 (2006).
90. Nader, K. & Wang, S. H. Fading in. *Learn. Mem.* **13**, 530–535 (2006).
91. Gold, P. & King, R. Storage failure versus retrieval failure. *Psychol. Rev.* **81**, 465–469 (1974).
92. Miller, R. & Springer, A. Implications of recovery from experimental amnesia. *Psychol. Rev.* **81**, 470–473 (1974).
93. de Hoz, L., Martin, S. J. & Morris, R. G. Forgetting, reminding, and remembering: the retrieval of lost spatial memory. *PLoS Biol.* **2**, 1233–1242 (2004).
94. Lattal, K. M. & Abel, T. Behavioral impairments caused by injections of the protein synthesis inhibitor anisomycin after contextual retrieval reverse with time. *Proc. Natl Acad. Sci. USA* **101**, 4667–4672 (2004).
95. Bailey, C. H., Bartsch, D. & Kandel, E. R. Toward a molecular definition of long-term memory storage. *Proc. Natl Acad. Sci. USA* **93**, 13445–13452 (1996).
96. Fonseca, R., Nagerl, U. V., Morris, R. G. & Bonhoeffer, T. Competing for memory: hippocampal LTP under regimes of reduced protein synthesis. *Neuron* **44**, 1011–1020 (2004).
97. Riccio, D. C., Millin, P. M. & Bogart, A. R. Reconsolidation: a brief history, a retrieval view, and some recent issues. *Learn. Mem.* **13**, 536–544 (2006).
98. Hupbach, A., Gomez, R., Hardt, O. & Nadel, L. Reconsolidation of episodic memories: a subtle reminder triggers integration of new information. *Learn. Mem.* **14**, 47–53 (2007).
99. Tronson, N. C., Wiseman, S. L., Olausson, P. & Taylor, J. R. Bidirectional behavioral plasticity of memory reconsolidation depends on amygdalar protein kinase A. *Nature Neurosci.* **9**, 167–169 (2006).
This paper provided the first demonstration that, like new memories, reactivated old memories could be enhanced by activating a kinase signalling pathway, showing that reactivation-induced plasticity allows memory modulation.
100. Pavlov, I. P. *Conditioned Reflexes* (Dover, New York, 1927).
101. Bouton, M. E. Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. *Psychol. Bull.* **114**, 80–99 (1993).
102. Rescorla, R. A. in *Contemporary Learning Theories* (eds Mowrer, R. R. & Klein, S. B.) 119–155 (Lawrence Erlbaum Associates, Mahwah, New Jersey, 2000).
103. Myers, K. M. & Davis, M. Systems-level reconsolidation: reengagement of the hippocampus with memory reactivation. *Neuron* **36**, 340–343 (2002).
104. Merlo, E. & Romano, A. Memory extinction entails the inhibition of the transcription factor NF-κB. *PLoS ONE* **3**, e3687 (2008).
105. Eisenhardt, D. & Menzel, R. Extinction learning, reconsolidation and the internal reinforcement hypothesis. *Neurobiol. Learn. Mem.* **87**, 167–173 (2007).
106. Dudai, Y. & Eisenberg, M. Rites of passage of the engram: reconsolidation and the lingering consolidation hypothesis. *Neuron* **44**, 93–100 (2004).
107. Alberini, C. M. Mechanisms of memory stabilization: are consolidation and reconsolidation similar or distinct processes? *Trends Neurosci.* **28**, 51–56 (2005).
108. Gordon, W. C. in *Information Processing in Animals: Memory Mechanisms* (eds Spear, N. E. & Kleim, J. A.) 319–339 (Erlbaum, Hillsdale, New Jersey, 1981).
109. Mactutus, C. F., Riccio, D. C. & Ferek, J. M. Retrograde amnesia for old (reactivated) memory: some anomalous characteristics. *Science* **204**, 1319–1320 (1979).
110. Riccio, D. C., Moody, E. W. & Millin, P. M. Reconsolidation reconsidered. *Integr. Physiol. Behav. Sci.* **37**, 245–253 (2002).
111. Miller, R. R. & Marlin, N. A. in *Memory Consolidation: Psychobiology of Cognition* (eds Weingartner, H. & Parker, E. S.) 85–109 (Lawrence Erlbaum Associates, Hillsdale, New Jersey, 1984).
112. Sara, S. J. Retrieval and reconsolidation: toward a neurobiology of remembering. *Learn. Mem.* **7**, 73–84 (2000).
113. Nader, K., Hardt, O. & Wang, S. H. Response to Alberini: right answer, wrong question. *Trends Neurosci.* **28**, 346–347 (2005).
114. Blair, H. T., Schafe, G. E., Bauer, E. P., Rodrigues, S. M. & LeDoux, J. E. Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. *Learn. Mem.* **8**, 229–242 (2001).
115. Schafe, G. E., Nader, K., Blair, H. T. & LeDoux, J. E. Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. *Trends Neurosci.* **24**, 540–546 (2001).
116. von Hertzen, L. S. & Giese, K. P. Memory reconsolidation engages only a subset of immediate-early genes induced during consolidation. *J. Neurosci.* **25**, 1935–1942 (2005).
117. Biedenkapp, J. C. & Rudy, J. W. Context memories and reactivation: constraints on the reconsolidation hypothesis. *Behav. Neurosci.* **118**, 956–964 (2004).
118. Lewis, D. J. & Bregman, N. J. Source of cues for cue-dependent amnesia in rats. *J. Comp. Physiol. Psychol.* **85**, 421–426 (1973).
119. Rescorla, R. A. Pavlovian conditioning and its proper control procedures. *Psychol. Rev.* **74**, 71–80 (1967).
120. Quartermain, D. & McEwen, B. S. Temporal characteristics of amnesia induced by protein synthesis inhibitor: determination by shock level. *Nature* **228**, 677–678 (1970).
121. Quartermain, D., McEwen, B. S. & Azmitia, E. C. Jr. Recovery of memory following amnesia in the rat and mouse. *J. Comp. Physiol. Psychol.* **79**, 360–370 (1972).
122. Serota, R. G. Acetoxycycloheximide and transient amnesia in the rat. *Proc. Natl Acad. Sci. USA* **68**, 1249–1250 (1971).
123. Squire, L. R. & Barondes, S. H. Variable decay of memory and its recovery in cycloheximide-treated mice. *Proc. Natl Acad. Sci. USA* **69**, 1416–1420 (1972).
124. Cooper, R. M. & Koppenaal, R. J. Suppression and recovery of a one-trial avoidance response after a single ECS. *Psychon. Sci.* **1**, 303–304 (1964).
125. Kohlenberg, R. & Trabasso, T. O. M. Recovery of a conditioned emotional response after one or two electroconvulsive shocks. *J. Comp. Physiol. Psychol.* **65**, 270–273 (1968).
126. Young, A. G. & Galluscio, E. H. Recovery from ECS-produced amnesia. *Psychon. Sci.* **22**, 149–151 (1971).
127. Berman, D. E. & Dudai, Y. Memory extinction, learning anew, and learning the new: dissociations in the molecular machinery of learning in cortex. *Science* **291**, 2417–2419 (2001).
128. Tronel, S., Milekic, M. H. & Alberini, C. M. Linking new information to a reactivated memory requires consolidation and not reconsolidation mechanisms. *PLoS Biol.* **3**, e293 (2005).
This paper is one of the first to study the functional role of reconsolidation. It showed that reconsolidation was not necessary for learning an additional association after an initial association had been acquired.
129. Lee, J. L. Memory reconsolidation mediates the strengthening of memories by additional learning. *Nature Neurosci.* **11**, 1264–1266 (2008).
This paper reported a functional difference between consolidation and reconsolidation, showing that strengthening an existing memory recruits reconsolidation but not consolidation mechanisms.
130. Ben Mamou, C., Gamache, K. & Nader, K. NMDA receptors are critical for unleashing consolidated auditory fear memories. *Nature Neurosci.* **9**, 1237–1239 (2006).
The first paper to propose a framework that permits testing of the mechanisms that mediate transformation of a memory from a fixed to a labile state. It also showed that the mechanism that mediates freezing can be doubly dissociated from the mechanisms involved in initiating reconsolidation.
131. Suzuki, A., Mukawa, T., Tsukagoshi, A., Frankland, P. W. & Kida, S. Activation of LVGCCs and CB1 receptors required for destabilization of reactivated contextual fear memories. *Learn. Mem.* **15**, 426–433 (2008).
132. Ling, D. S. *et al.* Protein kinase Mζ is necessary and sufficient for LTP maintenance. *Nature Neurosci.* **5**, 295–296 (2002).
133. Serrano, P. *et al.* PKMζ maintains spatial, instrumental, and classically conditioned long-term memories. *PLoS Biol.* **6**, e318 (2008).
134. Lattal, K. M. & Abel, T. Different requirements for protein synthesis in acquisition and extinction of spatial preferences and context-evoked fear. *J. Neurosci.* **21**, 5773–5780 (2001).
135. Cammarota, M., Bevilaqua, L. R., Medina, J. H. & Izquierdo, I. Retrieval does not induce reconsolidation of inhibitory avoidance memory. *Learn. Mem.* **11**, 572–578 (2004).
136. Torras-Garcia, M., Lelong, J., Tronel, S. & Sara, S. J. Reconsolidation after remembering an odor-reward association requires NMDA receptors. *Learn. Mem.* **12**, 18–22 (2005).
137. Duvarci, S., Nader, K. & Ledoux, J. E. Activation of extracellular signal-regulated kinase-mitogen-activated protein kinase cascade in the amygdala is required for memory reconsolidation of auditory fear conditioning. *Eur. J. Neurosci.* **21**, 283–289 (2005).
138. Gruest, N., Richer, P. & Hars, B. Memory consolidation and reconsolidation in the rat pup require protein synthesis. *J. Neurosci.* **24**, 10488–10492 (2004).
139. Taubenfeld, S. M., Milekic, M. H., Monti, B. & Alberini, C. M. The consolidation of new but not reactivated memory requires hippocampal C/EBPβ. *Nature Neurosci.* **4**, 813–818 (2001).
140. Wang, S. H., Ostlund, S. B., Nader, K. & Balleine, B. W. Consolidation and reconsolidation of incentive learning in the amygdala. *J. Neurosci.* **25**, 830–835 (2005).
141. Kelly, A., Laroche, S. & Davis, S. Activation of mitogen-activated protein kinase/extracellular signal-regulated kinase in hippocampal circuitry is required for consolidation and reconsolidation of recognition memory. *J. Neurosci.* **23**, 5354–5360 (2003).

Acknowledgements

K.N. was supported by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, the Canadian Foundation for Innovation and the Volkswagen, Alfred P. Sloan and EJLB Foundations; K.N. is a William Dawson chair and a E.W.R. Steacie Memorial Fellow; O.H. is supported by the Deutsche Forschungsgemeinschaft. We would like to thank the Fondation des Treilles for hosting us while we wrote this manuscript. We thank C. Rankin, P. Frankland, E. Balaban and J. LeDoux for their comments on this manuscript.

DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
CREB | ERK

FURTHER INFORMATION

Karim Nader's homepage: http://www.psych.mcgill.ca/faculty/nader.html
Oliver Hardt's homepage: http://web.mac.com/oliver.hardt
Nature Reviews Neuroscience's Memory systems series: http://www.nature.com/nrn/series/memorysystem/index.html

SUPPLEMENTARY INFORMATION

See online article: S1 (box)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF