Molecular mechanisms of memory reconsolidation

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Abstract | Memory reconsolidation has been argued to be a distinct process that serves to maintain, strengthen or modify memories. Specifically, the retrieval of a previously consolidated memory has been hypothesized to induce an additional activity-dependent labile period during which the memory can be modified. Understanding the molecular mechanisms of reconsolidation could provide crucial insights into the dynamic aspects of normal mnemonic function and psychiatric disorders that are characterized by exceptionally strong and salient emotional memories.

Consolidation
The process by which new memories are stored after a novel learning experience.

Retrieval
Return of a previously established memory into consciousness, resulting in lability of the memory.

Memory trace
Refers to the memory, stored as a result of the modification of synapses.

Lability
Instability of a previously consolidated memory, as identified by its susceptibility to manipulation.

Reconsolidation
The process by which previously consolidated memories are stabilized after retrieval.

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Memories for events, individuals, places, foods, motor behaviours and emotions are extremely important for the survival, well-being and adaptation of complex organisms. As humans, we are often of the opinion that memories shape our character and personality. It is not surprising, therefore, that memory has been the focus of much thinking and research in fields including philosophy, psychology, anthropology, molecular biology and neuroscience.

New memories are stabilized after an initial learning experience by a process called consolidation, and consolidation theory proposes that memories are stable once stored[1]. However, other data indicates that retrieval of a memory trace can induce an additional labile phase that requires an active process to stabilize memory after retrieval[2]. Recently, this process has been named reconsolidation, and is hypothesized to be an important component of long-term memory processing[3–7]. Despite its name, 'reconsolidation' is not a simple reiteration of consolidation; rather, it is thought that post-retrieval stabilization is a process distinct from consolidation, although overlap in both its function (storage) and underlying mechanisms (protein synthesis) does exist[4]. Crucially, the classification of reconsolidation as an independent process requires the demonstration of memory modification in a retrieval-dependent and time-limited fashion.

A cellular process that maintains memory after retrieval is theoretically plausible given ongoing neuroplasticity[8], which indicates that the concept of consolidation as a one-time process resulting in a rigid and persistent long-term memory through the strengthening and stabilization of synapses is insufficient. Instead, memory maintenance is likely to be a continuing, dynamic process. In the past five years, the study of reconsolidation has been extended to numerous species including crabs[9], chicks[10], honeybees[11], Medaka fish[12], *Lymnaea*[13], humans[14] and rodents[5,6,15]. Together, these data indicate an evolutionarily conserved role of post-retrieval lability for the induction of plasticity in old memories.

Reconsolidation theories are, however, controversial. Although some studies have shown a post-retrieval mechanism for the maintenance of memory to be a crucial process in long-term memory, other studies have either failed to disrupt memory after retrieval[16], questioning the conclusion that retrieval results in a new phase of stabilization, or have demonstrated only a transient disruption of memory[17–21] (TABLE 1), indicating that in some cases the post-retrieval disruption of memory might be an artefact of the experimental procedure, or due to transient retrieval deficits. The debate on the nature and longevity of post-reactivation modifications of memory continues unresolved; however, negative results might define conditions under which memories are not susceptible to a permanent disruption, thereby indicating determining factors for reconsolidation (BOX 1).

In this article, we discuss methods used for the study of reconsolidation and current hypotheses and controversies. We review recent evidence that has lead to an understanding of the molecular mechanisms of memory reconsolidation and discuss its possible functional role. Finally, we speculate on the theoretical implications of such a process for mnemonic function and psychiatric disorders.

How is reconsolidation studied?

Reconsolidation is a complex process, an understanding of which requires a knowledge of both the underlying molecular mechanisms and the psychological processes involved. To experimentally demonstrate reconsolidation,

Plasticity
Physical changes in neuronal connections or morphology as a result of external stimulation that results in long-lasting functional changes in excitability in a system of neurons. These physical changes at synapses underlie experience-dependent long-lasting changes in behaviour and memory.

Pavlovian conditioning
Procedure in which a stimulus (conditioned stimulus) — such as a tone — that elicits no response on its own, is paired with a biologically relevant stimulus (unconditioned stimulus) — such as footshock — during training. After consolidation, the conditioned stimulus elicits a conditioned response.

Reactivation
Cued retrieval of a memory under experimental conditions. In experiments on reconsolidation, reactivations are usually presentations of the previously conditioned stimulus or context. The length of the reactivation can be modified by changing the length of exposure to the conditioned stimulus or context.

or the role of a particular molecule in reconsolidation, a memory must first be consolidated, then reactivated (retrieved) contiguously with some form of manipulation. Finally, modification of the memory must be observed.

Reconsolidation is frequently studied using Pavlovian fear conditioning paradigms, and we shall use this as an example to describe the procedure and control groups required for studies of reconsolidation. Training is conducted in the absence of any mnemonic manipulations and consists of pairing a neutral stimulus (conditioned stimulus; CS), such as a tone, with a reinforcing stimulus (unconditioned stimulus; US), such as a footshock. Retrieval is induced in a reactivation session, which occurs at least 24 hours after training and consists of presentation of the CS (usually in the absence of the US). The manipulation (such as protein synthesis inhibition) is applied either prior to, or immediately after, the reactivation session. The reactivation session serves as both a retrieval cue and an initial test of memory strength and baseline for responding. Finally, at least 24 hours after the reactivation session the memory is tested by re-presenting the cues and measuring the conditioned responding (in this case, fear elicited by the CS) compared with animals in the non-manipulated control group (FIG. 1).

Table 1 | **Requirements for protein synthesis in memory reconsolidation**

Memory task	Injection site	Was reconsolidation disrupted?	References
Auditory fear conditioning	Basolateral amygdala	Yes	5,29,64,71,95
Contextual fear conditioning	Hippocampus	Yes	96
	Hippocampus	No	83
	Hippocampus	Recent memories only	81
	Anterior cingulate	No	81
	ICV	No	83
	Systemic	Transiently	20
	Systemic	Yes	9,12,24,97
Trace fear conditioning	Hippocampus	Yes	98
	Medial prefrontal cortex	No	99
Inactive avoidance	Systemic	Yes	10,30
	ICV	New memories	100
	Hippocampus	No	16,30,31
	Basolateral amygdala	No	16
	Entorhinal cortex	No	16
Conditioned taste aversion	Basolateral amygdala	No	101
	Central amygdala	No	101
	Systemic	Yes	12,102
Instrumental learning	Systemic	No	33
	Nucleus accumbens	No	32
Incentive learning	Amygdala	Yes	103
Morris water maze	Systemic	No	104
	Hippocampus	In limited conditions	23
	Hippocampus	Yes	25
Object recognition	Ventromedial prefrontal cortex	Yes	105
	Hippocampus CA1	Yes	106
Eyelid conditioning	Systemic	Yes	107
Conditioned place preference	Systemic	Yes (two injections)	35
	Basolateral amygdala	No	108
Gill withdrawal	Systemic	Yes	109
Paired training event	Systemic	Yes	110
Auditory discrimination	Auditory cortex	No	111

The table lists experiments that have utilized protein synthesis inhibitors (PSIs) to investigate reconsolidation processes. PSIs are administered after reactivation of a previously consolidated memory, and subjects are tested at least 24 hours later. ICV, intracerebroventricular.

Extinction
Refers either to the learning process by which a cue (or action) previously associated with a reinforcer becomes newly associated with no outcome, leading to a decrease in the previously established conditioned response or to the procedure by which a cue or action previously paired with a reinforcer is now paired with no reinforcer.

Spontaneous recovery
Retrieval of a previously extinguished memory, usually after a long period of time (weeks) after extinction, in the absence of experimental manipulation, retraining or changes in context.

Reinstatement
Retrieval of an extinguished memory after unpaired exposure to the unconditioned stimulus.

Demonstrating reconsolidation not only requires evidence of modification of a previously consolidated memory (FIG. 1a) but also evidence that, in the absence of retrieval, the memory remains unmodified by the experimental manipulation (FIG. 1b). It is also desirable to demonstrate the limits of the post-retrieval time window during which the memory remains labile (FIG. 1c), the specificity of the manipulation to previously trained stimuli or contexts (FIG. 1d,e), and to rule out alternative explanations of the effect, such as extinction (BOX 2; FIG. 1f). Ideally, experimental manipulations are applied after the reactivation session (for example, by drug infusion), although genetic manipulations (such as transgenic mice or viral vector-mediated gene expression) could require induction prior to reactivation due to a slower onset of peak activity, or the use of a constitutive genetic knockout.

In addition to these fundamental control groups, answering further questions might require modification of these protocols and the use of additional control groups. One pertinent example is the question of the longevity of post-retrieval memory disruptions. The longevity of mnemonic changes is often determined at an additional test session at some time after the reactivation session. The commonly used time-point is two weeks after the initial disruption. However, this is arbitrarily chosen and some studies have shown that retrieval of the original memory might occur only at later time points (for example, 21 days[20]). The longevity of the post-retrieval memory deficit has important ramifications for theories of reconsolidation: whereas long-term mnemonic disruptions indicate erasure of memory and a storage-like mechanism of reconsolidation (storage theory), short-term deficits indicate that the memory remains intact but transiently unavailable (retrieval theory). The role of this ongoing debate in current research on reconsolidation will be discussed below.

It is noteworthy that subtle changes in experimental procedure can dramatically alter the outcome of the experiment. Recently, the precise conditions under which reconsolidation can be manipulated have been conceptualized as boundary conditions of reconsolidation (BOX 1). The delineation of these boundary conditions[22–25], although currently at an early stage, is crucial to our understanding of the nature of memory reconsolidation.

Conceptualizations of reconsolidation

The initial conceptualization of reconsolidation occurred after an account of the disruption of fear memory by electroconvulsive shock (ECS) after retrieval was published[2]. Together with subsequent studies, this result introduced the concept of a retrieval-induced labile period during which memory could be modified[26,27]. Although this was not termed reconsolidation, these findings called into question the stability of long-term memory. However, disruptions of old memories by ECS or hypothermia after retrieval were often reversible by re-presentation of the amnestic agent itself[17,18], spontaneous recovery, or reinstatement by re-exposure to a non-contingent US[19], all leading to recovery of the original memory. An important debate about the nature of retrograde amnesia of old memories ensued: was the initial decrease in performance attributable to a loss of the memory itself (a storage deficit), or due to retrieval failure? This unresolved controversy remains an important issue in the current discussion on memory reconsolidation.

To define the cellular and molecular mechanisms of reconsolidation in a temporal and spatially specific manner, recent studies have used various post-retrieval manipulations previously used to delineate consolidation. These studies have made important contributions to the debate by providing evidence that the molecular mechanisms of reconsolidation and consolidation are similar, but not identical. This has been suggested to provide evidence in turn for a related role of reconsolidation and consolidation in the storage of memory. Reopening the reconsolidation debate is therefore an opportunity to re-examine the meaning of consolidation and the dynamic nature of long-term memory, although it should be noted that hypotheses of reconsolidation and consolidation theory might not be mutually exclusive.

Several modifications to traditional consolidation theory have been proposed to account for a reconsolidation-like process. First, as discussed above, reconsolidation has been hypothesized to be a storage mechanism, whereby retrieval of a long-term memory results in an additional labile period requiring reconsolidation, a process that is similar to, but distinct from, consolidation[3,5]. That reconsolidation is a storage mechanism challenges the traditional consolidation hypothesis, which proposes a single consolidation period immediately after learning that leads to permanent storage of new memories.

Box 1 | Boundary conditions: limits on reconsolidation

Conflicting findings on the existence of reconsolidation after retrieval have led to a discussion of the limiting factors. Several such boundary conditions have been described. The age of the memory (that is, time from training)[79–81], memory strength (or amount of training)[12,23] and the length of the reactivation trial[6,22,24,29,60] are important determinants of whether reconsolidation or extinction occur after a reactivation trial. New and strong memories are more susceptible to post-retrieval manipulations, and short reactivation sessions are more likely to result in reconsolidation. The availability of new information during reactivation might also be a boundary condition[23,61,82,83], initiating a 'new encoding state' that might be necessary for reconsolidation to occur.

The rules, however, are not always simple, and boundary conditions also interact: for example, long reactivation trials can induce reconsolidation in older memories[22], and well-trained (strong) auditory fear memories only become susceptible to protein synthesis inhibitor disruption of reconsolidation after 30 days or more[84]. In addition, very short reactivation sessions can result in incomplete disruption of reconsolidation and transient mnemonic deficits[25].

Identifying the molecular mechanisms that change as a result of age, memory strength and length of reactivation will allow for an objective determination of what underlies a boundary condition of memory reconsolidation. Some differences have already been noted. Resistance to lability after retrieval in strong auditory fear memories is correlated with NMDA (*N*-methyl-D-aspartate) receptor 2B expression[84]. In contextual fear, short reactivation sessions that trigger reconsolidation result in an increase in phosphorylated cyclic AMP response element-binding protein, whereas long reactivation sessions that initiate extinction do not[85].

Other boundary conditions (for example, type of memory) have also been noted[23,32,83], and more will probably be described. The behavioural and molecular delineation of the precise conditions under which reconsolidation occurs is required before debates on memory reconsolidation can be resolved.

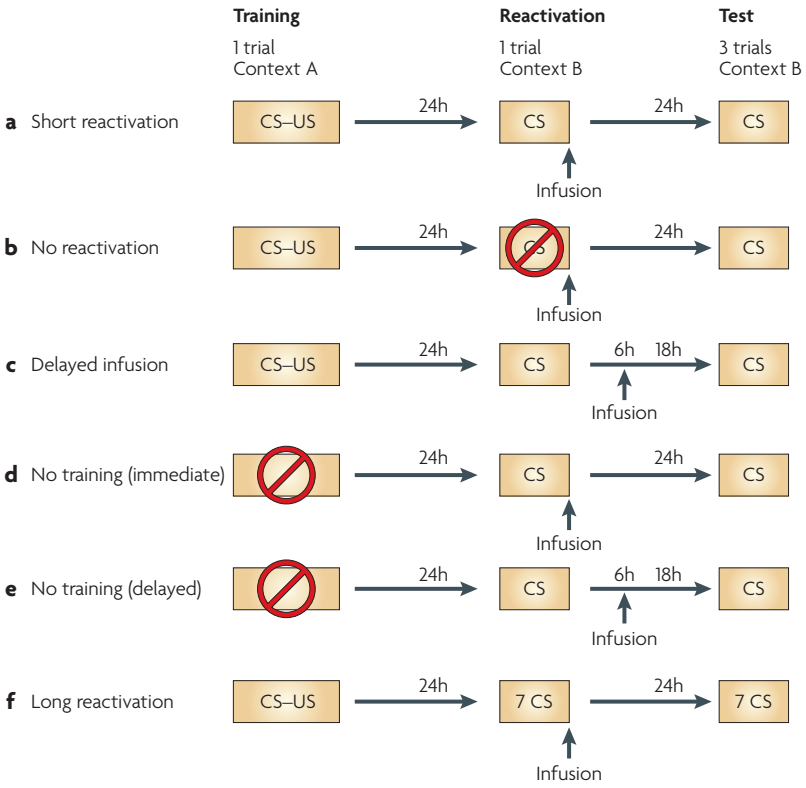

Figure 1 | **Experimental design for reconsolidation experiments.** The first column represents the training phase in which a novel conditioned stimulus (CS) is paired with an unconditioned stimulus (US). The second column represents the reactivation phase, at least 24 hours after conditioning. The third column represents behavioural tests, conducted at least 24 hours after reactivation. **a** | Protocol used to study the basic reconsolidation effect, showing what happens when a drug is infused after a short reactivation trial. **b**–**e** | Control protocols used to demonstrate a specific effect of a drug on a process initiated by retrieval and specific to the post-retrieval time point. **b** | A no-reactivation control, which ensures that the drug affects a process that is initiated by retrieval and not a long-lasting process in consolidation. **c** | A delayed infusion control, which demonstrates the time window after retrieval during which reconsolidation can be manipulated. **d**,**e** | This no-training control is especially important in studies showing an enhancement of memory after retrieval. It demonstrates that infusion of the drug does not increase freezing to the US either by forming an association with the CS or by increasing general cellular activity levels and responding. **f** | Long reactivation sessions can be used to examine extinction. Using comparable procedures to examine reconsolidation and extinction is important for determining the similarities and differences in molecular mechanisms for each, as well as beginning to study the processes involved in switching between these processes after memory retrieval.

The lingering consolidation hypothesis[28] attempts to reconcile conflicting data with regards to the permanence of disruptions by proposing that reconsolidation after retrieval acts as a late phase of memory consolidation, and continues to occur after retrieval until the memory is fully consolidated. The important implication of this theoretical stance is that memories will only become susceptible to disruption after retrieval for a limited period of time after the initial learning experience. However, the lingering consolidation hypothesis also conceptualizes reconsolidation as a storage process.

A third possibility is that consolidation and reconsolidation might involve both storage of the memory and the formation of 'retrieval links' that allow retrieval of the memory[28]. Formation of new, or maintenance of old, retrieval links both during consolidation and after reactivation of a previously established memory is required to maintain the ability to retrieve memories in the long term. The concept of retrieval links suggests that 'retrievability' and 'storage' are separable components of the consolidation and reconsolidation processes.

These three hypotheses all suggest that memories can be affected by events occurring after retrieval, and that these post-retrieval mechanisms involve some kind of storage process. In order to disambiguate the first two theories, it is necessary to show whether memories can be modified by post-retrieval manipulations at any time after learning, or whether such manipulations are only effective in a relatively short period after learning. So far, there is evidence for both hypotheses[22] (BOX 1); however, recent findings indicate that failure to induce lability in older memories is related to the strength of reactivation, and so the age of memory is not a limiting factor on reconsolidation[22]. The third hypothesis treads a line between the role of reconsolidation in storage of memory and in the later retrieval of memory. It provides a unique solution to the storage versus retrieval debate, suggesting a way in which the two mechanisms may be intertwined. However, it is unclear how the existence of retrieval links could be experimentally determined.

Of these modifications to consolidation theory, current evidence most strongly supports reconsolidation as a post-retrieval storage mechanism that is independent of consolidation. It is important to note that this does not require reconsolidation to be a precise recapitulation of consolidation. In this article, we would like to extend this hypothesis by proposing that reconsolidation is a reiterative process required for long-term strengthening and updating of useful (retrieved) memories.

The conceptualization of reconsolidation as a storage mechanism, together with technical advances allowing for spatially and temporally specific genetic and molecular manipulations during retrieval, has renewed the debate on reconsolidation. The cellular mechanisms that underlie consolidation have been the focus of recent research, and understanding the molecular cascades required for reconsolidation could provide insight into the function and mechanism of post-retrieval modifications of memory. Below, we review the key cell signalling cascades resulting in gene transcription, protein synthesis and cellular modifications involved in reconsolidation.

Molecular mechanisms of reconsolidation

Protein synthesis. *De novo* protein-synthesis is considered a hallmark of the consolidation process, required to render structural cellular changes permanent. Post-retrieval inhibition of protein synthesis has therefore been used to investigate the nature of memory reconsolidation. These studies have shown that the injection of protein synthesis inhibitors (PSIs) after retrieval of a previously consolidated memory can disrupt the original memory[5] (TABLE 1), and strengthen the assertion that retrieval of a previously consolidated memory induces

Box 2 | **Reconsolidation and extinction: a balancing act**

An additional complication of interpreting studies of reconsolidation is that extinction can occur under similar conditions after memory retrieval. Extinction occurs after repeated, non-reinforced presentations of the conditioned stimulus (CS), resulting in a decreased conditioned response. It is usually defined as new learning[86], and requires mechanisms of consolidation. Behaviourally, reconsolidation and extinction can be distinguished using short reactivation sessions or strong memories reconsolidation, and long reactivation sessions or weak memories for extinction[6,12,22,24,61,82,86]. Human fear memories are also sensitive to the type of reactivation trial, and seem to undergo extinction after long reactivation sessions but might be strengthened after short retrieval sessions[56].

The ability to distinguish between reconsolidation and extinction by varying the length of a reactivation trial or the strength of a memory has indicated that a balance between reconsolidation and extinction processes occurs after a non-reinforced retrieval trial. The mechanisms underlying these processes could be the key to dissociating the processes of reconsolidation and extinction[85].

This theoretical balance leads to the question of whether only one occurs at a time, perhaps with the dominant process suppressing the weaker process, or whether both occur in parallel, with only the dominant process being behaviourally expressed. Recent evidence indicates that, at least in the basolateral amygdala, reconsolidation, but not extinction, is disrupted by infusions of protein synthesis inhibitors after short reactivation sessions, and after long-reactivation sessions in which extinction appears dominant[29]. Indeed, this study indicates that reconsolidation and extinction are separate processes that can coexist after non-reinforced presentations of an auditory fear CS.

The molecular dissection of these two processes should be an integral part of future reconsolidation research, for the development of reconsolidation theory, the roles of reconsolidation in ongoing maintenance of memory and for possible development of appropriate retrieval-based therapies for psychiatric disorders such as post-traumatic stress disorder.

a new labile period that requires an active process to stabilize and maintain the memory for future retrieval. PSIs have also been used to show a dissociation between reconsolidation and extinction, as PSIs infused into the amygdala disrupt the reconsolidation, but not extinction, of an auditory fear memory[29].

However, not all reports using PSIs have demonstrated disruption of reconsolidation. For example, inactive avoidance (IA) memories were not disrupted by hippocampal infusions of PSIs[16,30,31]. In addition, spontaneous recovery of a contextual fear memory 20 days after post-retrieval disruption by PSI has been demonstrated[20]. Similarly, appetitive, instrumental memories have not been shown to be susceptible to post-retrieval PSIs[32,33] (TABLE 1). These null results have fuelled the important debate on the nature and existence of reconsolidation and have initiated research on the boundary conditions of reconsolidation (BOX 1). However, it should be noted that, in some cases, technical issues such as infusion site or PSI dose might influence the results. For example, although hippocampal infusions of PSIs do not disrupt reconsolidation of an IA memory[16,30,31], systemic PSIs do[30,34], indicating that IA memories can undergo reconsolidation; in this case, reconsolidation is not identical to consolidation and does not require the hippocampus. Furthermore, it has been demonstrated that although a single PSI injection led to only transient inhibition of protein synthesis and transient performance deficits, increasing the time during which protein synthesis is inhibited after reactivation can lead to a more persistent disruption (that is, at least four weeks) of a conditioned place preference (CPP) memory[35].

A limitation for studies of protein synthesis and memory reconsolidation is that PSIs provide little information on the specific cellular mechanisms underlying plasticity after retrieval. For example, the fact that there must be more than 90% inhibition before an effect is observed with PSIs could reflect a non-specific effect of PSIs in mnemonic disruption[36]. The use of PSIs in studies of reconsolidation is also limited by the implicit assumption that a failure to disrupt memory after retrieval indicates the absence of a reconsolidation process. It is possible, however, that failure to disrupt reconsolidation by PSIs reflects the involvement of a protein synthesis-independent process. Despite these limitations, findings using PSIs in memory reconsolidation have indicated that various cell signalling and transcriptional events might be required for reconsolidation (TABLES 2,3).

Transcription factors. Several transcription factors have been implicated in memory reconsolidation (FIG. 2; TABLE 2). Targeted disruption of cyclic AMP-response element binding protein (CREB) in the hippocampus, amygdala and prefrontal cortex impairs reconsolidation of both auditory fear and contextual fear memories[15]. A role for CREB in reconsolidation has also been indicated by studies demonstrating increases in CREB activity (for example, by measuring phosphorylated CREB; pCREB) in the amygdala after exposure to a discrete CS[37]. CREB and the transcription factor ELK1 are also activated within the nucleus accumbens (NAC) core after retrieval of a place memory[38]. Another plasticity-related transcription factor, nuclear factor-κB (NF-κB), is also reported to be both required for reconsolidation and activated after retrieval[39]. The roles of CREB, ELK1 and NF-κB in reconsolidation are consistent with their previously demonstrated roles in the initial consolidation of memory[15,38,39], but differ from reported decreases in CREB activation after extinction[40] (BOX 1).

There are also notable differences in patterns of transcription factor activation between consolidation and reconsolidation. Within the hippocampus, a double dissociation has been reported between the transcription factor zinc finger 268 (ZIF268), which is selectively required for reconsolidation, and brain-derived neurotrophic factor (BDNF), which is selectively required for consolidation of contextual fear conditioning[41]. However, the dissociation between the role of ZIF268 in consolidation and reconsolidation does not extend to studies of all memory types. For example, ZIF268 is required for object recognition tasks after both initial training and memory retrieval[42]. Although these two studies demonstrate a role of ZIF268 in memory reconsolidation, the different requirements for ZIF268 in consolidation are probably due to a combination of several factors. First, the two training protocols used might require slightly different molecular pathways. Second, two different methods of eliminating ZIF268 were used: acute, focal knockdown of ZIF268 (REF. 41) can yield different results from constitutive knockout of the gene[42], due to developmental effects and functional compensation by similar proteins.

Inactive avoidance
(IA). A fear conditioning procedure in which an animal has to learn to inhibit a naturally occurring response (for example moving from a light area to a dark area) in order to avoid an aversive event (such as footshock).

Conditioned place preference
(CPP). Behavioural test in which an unconditioned stimulus is paired with one distinctive context, and a neutral event is paired with a different context. Preference is determined by allowing the animal to move between the two contexts, and measuring the amount of time spent in each context.

Double dissociation
Situation in which one experimental manipulation affects process A but not process B, and a second manipulation affects process B but not process A. Meeting both of these criteria for a double dissociation is considered strong evidence for two separable processes.

Table 2 | **Molecular mechanisms of reconsolidation, as described by gain- and loss-of-function studies**

Molecule	Task	Infusion	Required for reconsolidation?	Refs
Neurotransmitters, receptors and ion channels				
Glutamate	Radial spatial maze	Systemic	Yes	91
	Object recognition	vmPFC	Yes	105
	Contextual fear	Systemic	Yes	22
mGluR	Inactive avoidance	Systemic	Yes	112
AMPAR	Auditory fear	BLA	No	92
NMDAR	Auditory fear	BLA	Induces lability	92
	Auditory fear	BLA	Yes*	60
	Odour-reward	Systemic	Yes	93
	Avoidance	Systemic	Yes	9
Dopamine	Conditioned place preference	Systemic	Yes‡	59
D1	Inactive avoidance	Systemic	Yes	113
β-AR	Auditory fear	BLA	Yes	71
	Spatial radial arm maze	Systemic	Yes	87,88
	Conditioned place preference	Systemic	Yes	89
	Instrumental learning	Systemic	Yes	90
CB1	Contextual fear	Systemic	No	22
	Contextual fear	BLA	Yes	114
LVGCC	Contextual fear	Systemic	No	22
Acetylcholine	Inactive avoidance	ICV	Yes	115
	Contextual fear	BLA	No	114
Hormones				
Angiotensin II	Avoidance	Systemic	Yes	58
IEGs				
ZIF268	Contextual fear	Hippocampus	Yes	41
	Drug-associated memory	BLA	Yes	43–45
	Object recognition	KO mice	Yes	42
Growth factors				
BDNF	Contextual fear	Hippocampus	No	41
Signalling molecules				
PKA	Auditory fear	BLA	Yes*	6
	Conditioned taste aversion	Amygdala	Yes	49
	Reward learning	Systemic	New memories only	50
ERK	Auditory fear	BLA	Yes	46
	Conditioned place preference	NAC	Yes	38
	Conditioned place preference	Systemic	Yes	48
	Object recognition	ICV	Yes	47
ERK2	Auditory fear	Systemic	Yes	94
Transcription factors				
CREB	Contextual / auditory fear	Forebrain	Yes	15
NFκB	Avoidance	Systemic	Yes	39
C/EBPβ	Inactive avoidance	Hippocampus	No	30,34
	Inactive avoidance	BLA	Yes	34

The table shows studies using pharmacological or genetic inhibition and activation of molecular pathways after (or during) reactivation to determine the roles of specific signalling molecules and pathways in memory reconsolidation. *Indicates bidirectional modulation of memory: agonists enhance reconsolidation and inhibitors disrupt reconsolidation. ‡Indicates pathway can be activated, resulting in enhanced reconsolidation. β-AR, β-adrenergic receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; CB1, cannabinoid receptor type 1; C/EBPβ, CCAAT enhancer-binding protein-β; CREB, cyclic AMP response element-binding protein; D1, dopamine receptor type 1; ERK, extracellular signal-regulated kinase; ICV, intracerebroventricular, IEGs, immediate-early genes; KO, knockout; LVGCC, L-type voltage-gated calcium channel; mGluR, metabotropic glutamate receptor; NAC, nucleus accumbens; NF-κB, nuclear factor-κB; NMDAR, *N*-methyl-D-aspartate receptor; PKA, protein kinase A; vmPFC, vetromedial prefrontal cortex; ZIF268, zinc finger 268.

A role for ZIF268 in reconsolidation is not restricted to hippocampal-dependent memories. Indeed, it has also been shown to be crucial within the basolateral amygdala (BLA) for reconsolidation of auditory fear memory and drug-associated memories[43–45]. Whether there is a dissociation of the role of ZIF268 in reconsolidation and consolidation in these tasks has not yet been shown.

A second dissociation between transcription factor involvement in consolidation and reconsolidation has been shown with the CCAAT-enhancing binding protein-β (C/EBPβ). Within the hippocampus, C/EBPβ is required for consolidation, but not for reconsolidation of inactive avoidance (IA) learning[34]. In the amygdala, the opposite pattern has been observed, with C/EBPβ being required for reconsolidation but not consolidation of an IA memory[34]. The discrepancy between the hippocampus and amygdala in the consolidation and reconsolidation of IA memories indicates the possibility that inhibitory avoidance requires fundamentally different systems and patterns of activation for reconsolidation than other forms of fear conditioning. However, not all studies of IA memories have demonstrated this dissociation. Indeed, several studies have shown no evidence of reconsolidation using IA procedures with either hippocampal or BLA infusions of PSI[16]. This dissociation between the effects seen using PSIs and C/EBPβ in the BLA could be due to slight differences in procedure. However there is also the possibility that memory reconsolidation might be more sensitive to targeted molecular manipulations than to PSIs.

Kinases. Transcription factors are phosphorylated by upstream kinases. Two kinases, extracellular signal-regulated kinase (ERK) and protein kinase A (PKA), have been of particular interest due to their well-established roles in consolidation through transcription factors such as CREB, ELK1 and NF-κB (FIG. 2). ERK is required for reconsolidation of auditory fear memories[46], object recognition memories[47] and

Table 3 | **Signalling cascades, receptors and immediate early genes activated by memory retrieval**

Molecule	Task	Brain region activated	Exposure time	Activation by memory retrieval	Refs
ZIF268	Auditory fear	Amygdala	8 min	Yes	51
	Contextual fear	Hippocampus CA1	8 min	Yes	51
	Contextual fear	Anterior cingulate	8 min	Yes	52
	Contextual and auditory fear	Nucleus accumbens core	8 min	Yes	52
	Contextual fear	Nucleus accumbens shell	8 min	Yes	52
c-Fos	Conditioned place preference	Nucleus accumbens core	15 min	Yes	38
	Auditory fear	Amygdala	8 min	Yes	37
	Contextual fear	Hippocampus CA1	5 min	Yes	53
	Olfactory task	Habenula	2–5 min	Yes	54
	Olfactory task	Amygdala	2–5 min	No	54
	Olfactory task	Prefrontal cortex	2–5 min	No	54
JunB	Contextual fear	Hippocampus CA1	5 min	Yes	53
c-Jun, JunD	Contextual fear	Hippocampus CA1	5 min	No	53
SGK3	Contextual fear	Hippocampus	5 min	Yes	55
NGFI-B	Contextual fear	Hippocampus	5 min	No	55
GluR1	Conditioned place preference	Nucleus accumbens	18 min	Yes	48
	Conditioned place preference	Dorsal striatum	18 min	Yes	48
	Conditioned place preference	Prefrontal cortex	18 min	No	48
MAPK	Object recognition	Dentate gyrus	5 min	Yes	47
	Object recognition	Entorhinal cortex	5 min	Yes	47
	Conditioned place preference	Nucleus accumbens core	15 min	Yes	38
	Conditioned place preference	Nucleus accumbens	18 min	Yes	48
	Conditioned place preference	Dorsal striatum	18 min	Yes	48
	Conditioned place preference	Prefrontal cortex	18 min	Yes	48
ELK1	Conditioned place preference	Nucleus accumbens core	15 min	Yes	38
CREB	Conditioned place preference	Nucleus accumbens core	15 min	Yes	38
	Auditory fear	Amygdala	8 min	Yes	37
	Fear potentiated startle	Amygdala	30 presentations of 3.7s CS	Activity reduced	40

CREB, cyclic AMP response element-binding protein; CS, conditioned stimulus; GluR1, glutamate receptor type 1; MAPK, mitogen-activated protein kinase; NGFI-B, nerve growth factor-inducible gene B; SGK3, serum- and glucocorticoid-induced kinase 3; ZIF268, zinc finger 268.

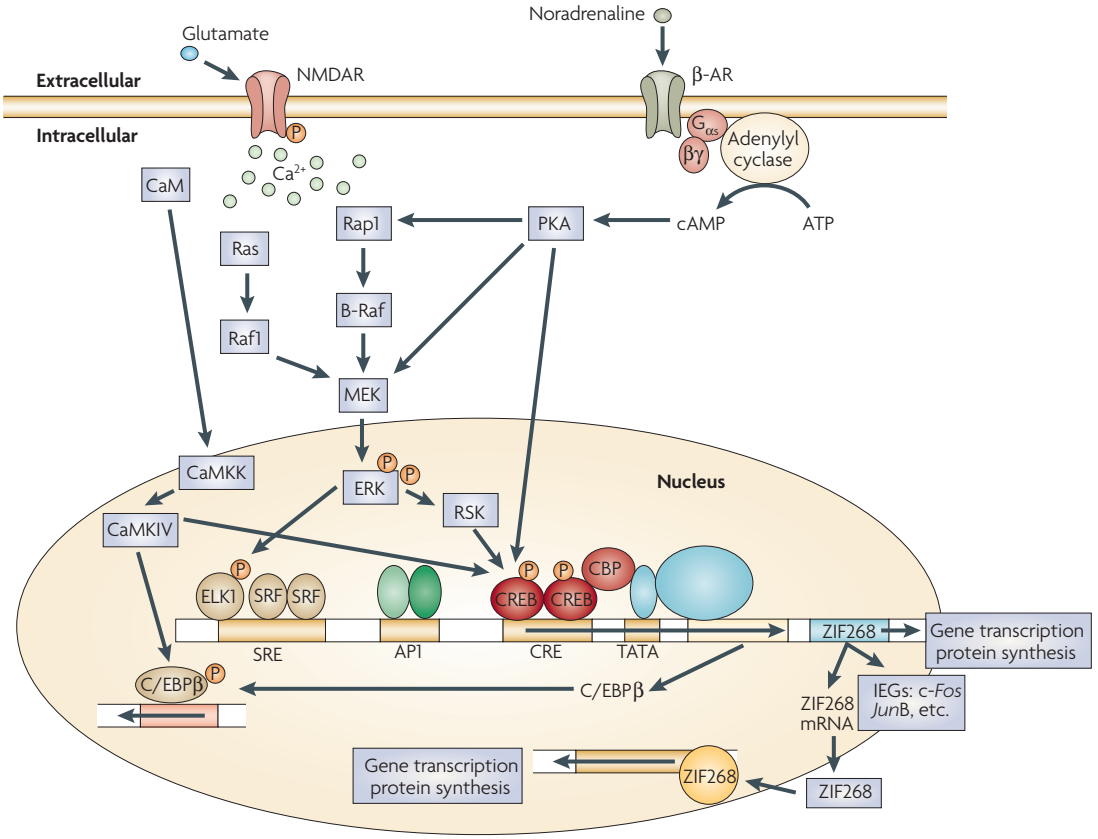

Figure 2 | **Key molecular mechanisms of memory reconsolidation.** Many individual molecules have been identified as being required for memory reconsolidation; however, few papers have put together schematic models for the pathways involved. This figure integrates findings from several studies. Of particular focus have been the molecular cascades previously demonstrated to be important in memory consolidation and those downstream of therapeutically relevant neurotransmitter targets including β-adrenergic receptors (β-AR)[70,71,87–90] and NMDARs[9,60,91–93] (*N*-methyl-D-aspartate receptors). Molecular signalling cascades downstream of these receptors have been implicated in reconsolidation. Small GTPases such as Ras, Raf and Rap activated by Ca^{2+} influx activate the extracellular signal-regulated kinase pathway (ERK)[38,46–48,94]. Protein kinase A (PKA)[6,49,50] is activated by cyclic AMP (cAMP) and acts directly, or indirectly through ERK and ribosomal protein S6 kinase (RSK), to activate transcription factors including cAMP response element-binding protein (CREB)[15,37,38], zinc finger 268 (ZIF268) (REFS 41–45,51,52) and ELK1 (REF. 38), which then initiate gene transcription. The immediate-early genes c-*Fos* and *JunB*[37,38,53–55] are activated during, and CCAAT-enhancing binding protein-β (C/EBPβ)[30,34] is required for, memory reconsolidation. Integrating all the available data aims to identify logical pathways to examine next. For example, a role for the calcium/calmodulin (CaM)–CaM-dependent protein kinase kinase (CaMKK)–CaMKIV cascade in memory reconsolidation might be inferred from NMDAR activity; however, the involvement of this pathway has not directly been examined. AP1, activator protein complex 1 (a complex of c-Fos and c-JUN); CBP, CREB binding protein; MEK, mitogen-activated protein kinase/ERK kinase; SRE, serine response element; SRF, serum response factor; TATA, box required for transcription. Figure modified, with permission, from *Nature Reviews Neuroscience* REF. 76 © (2001) Macmillan Publishers Ltd.

conditioned place preference[38,48].

PKA is also required for reconsolidation of auditory fear memories. Inhibition of PKA in the BLA by infusions of Rp-cAMPS, a PKA inhibitor, after memory retrieval disrupts auditory fear memories[6] (FIG. 3) or conditioned taste aversion memories[49]. Moreover, post-reactivation activation of PKA by injections of the PKA activator 6-BNZ-cAMP in the BLA enhances reconsolidation of an auditory fear memory[6]. Unlike its involvement in memory reconsolidation, amygdalar PKA does not seem to be involved in extinction of fear, indicating differential molecular or anatomical mechanisms in these two co-occurring processes[6]. However, PKA is not always involved in reconsolidation in every species; a recent study showed that retrieval of a memory shortly (6 hours) — but not 24 hours — after training triggers PKA-dependent reconsolidation[50]. At both times reconsolidation is PSI-dependent. This study extends previous models that have shown that older memories are more resistant to reconsolidation to suggest that, in addition, different processes are involved in reconsolidation of older than newer memories. Whether such differential involvement of PKA in memories at different times after training is true in mammalian models, or other types of memory, is as yet unknown.

Immediate-early genes. Molecular events in reconsolidation have also been examined by imaging cellular activ-

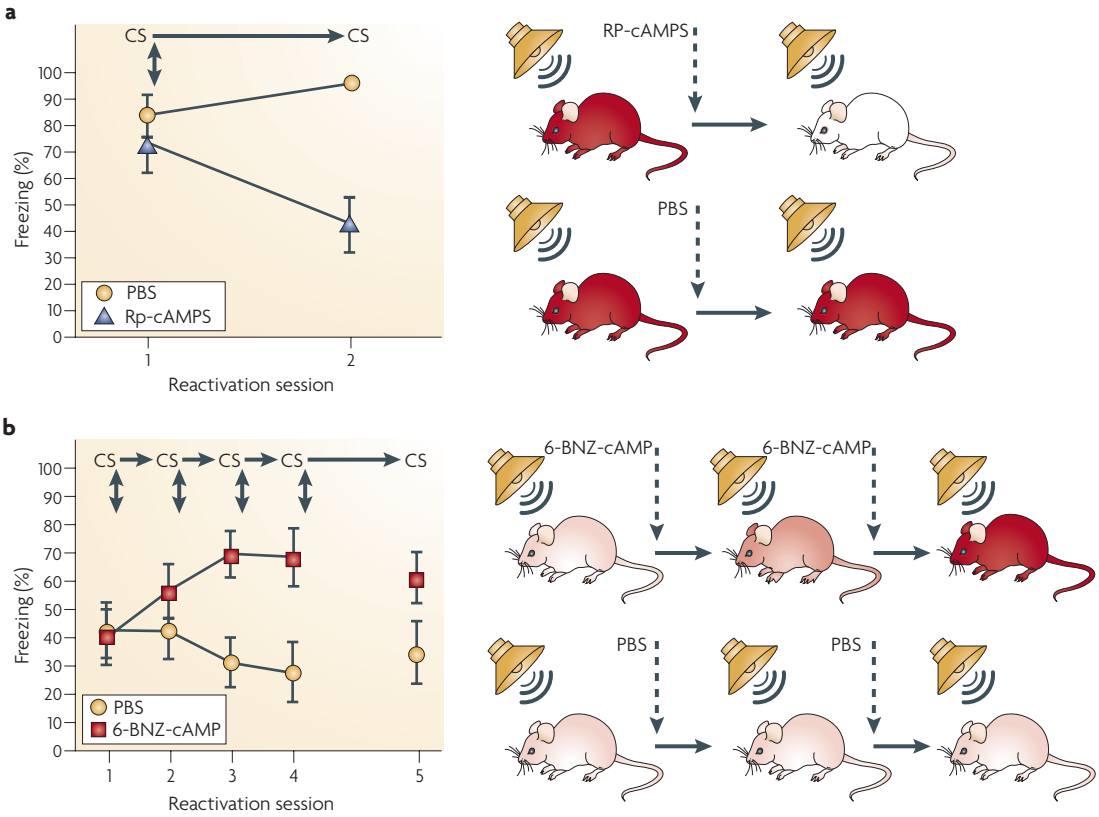

Figure 3 | **Bidirectional plasticity after memory retrieval modulated by PKA.** Inhibition of protein kinase A (PKA) after retrieval disrupts reconsolidation of auditory fear memory, whereas activation of PKA after retrieval enhances this process. All rats were conditioned with a single tone-shock pairing on day 1 (not shown). Intensity of the red colour of each rat indicates the intensity of fear responses — represented in the graphs as percentage of time that rats spent freezing: more red indicates greater fear. **a** | 24 hours after training, subjects were placed in a novel context for 5 minutes before presentation of the tone conditioned response (conditioned stimulus (CS); reactivation session 1). Immediately after the reactivation trial, the PKA inhibitor Rp-cAMPS or phosphate buffered saline (PBS) vehicle was infused through previously implanted cannulae in the basolateral amygdala (BLA). 24 hours later, subjects were placed into the reactivation context and presented with the tone CS (reactivation session 2). Inhibition of PKA after retrieval disrupted reconsolidation of an auditory fear memory. In the absence of memory retrieval, Rp-cAMPS did not disrupt memory (not shown). **b** | 24 hours after training, subjects were placed in a novel context for 5 minutes before presentation of the tone CS. Immediately after the reactivation trial, the PKA activator 6-BNZ-cyclic AMP (cAMP) or PBS vehicle was infused through previously implanted cannulae in the BLA. This procedure was repeated on four consecutive days (reactivation sessions 1–4). 72 hours later, animals were given a final test (reactivation session 5). Post-retrieval activation of PKA in the BLA enhanced reconsolidation of an auditory fear memory, and increased fear to the tone CS. In the absence of memory retrieval, activation of PKA did not affect reconsolidation (data not shown). Figure modified, with permission, from *Nature Neuroscience* REF. 6 © (2006) Macmillan Publishers Ltd.

ity after retrieval. Post-retrieval activity can be assayed using immunohistochemistry techniques to stain for proteins, such as immediate-early genes (IEGs) that are expressed in active cells. However, it is important to note that this activity might reflect several coincident psychological processes including reconsolidation, retrieval and extinction. Nevertheless, imaging IEGs after retrieval has provided important information on the brain regions activated after retrieval of a previously consolidated memory (TABLE 2). ZIF268 and c-Fos are activated in the amygdala and nucleus accumbens after retrieval of a cued fear memory, and ZIF268 in the hippocampus and prefrontal cortex is activated by retrieval of a contextual fear memory[51,52]. Within the CA1 region of the hippocampus, c-Fos and JunB, but not c-Jun or JunD, are activated after retrieval of contextual fear memory[53].

Cellular imaging as an index of activity has also shown an overlapping pattern of brain regions activated after retrieval and after an initial training trial (TABLE 3). The lateral habenula shows significant c-Fos expression after the retrieval of or training in an odour-reward task, but in the amygdala and prefrontal cortex this is seen only after training[54]. Other IEGs also show incomplete overlap between roles in reconsolidation and consolidation. Of two IEGs specific to learning associative memories (serum- and glucocorticoid-induced kinase 3 (SGK3) and nerve growth factor inducible gene B (NGFI-B)), only SGK3 is activated after retrieval of the memory, thereby being implicated in reconsolidation of

Second-order conditioning
Procedure in which a previously conditioned stimulus is used as the reinforcer for conditioning a second stimulus.

the memory[55]. Cellular imaging has had an extremely important role in identifying molecular mechanisms and brain loci that might differ between reconsolidation and consolidation, and in beginning to extend the list of molecular events potentially involved in reconsolidation to include those not required for consolidation. The identification of events occurring after retrieval could be extended to examine gene regulation and protein changes, using proteomic and gene array technologies. If applied to memory reconsolidation, these approaches could identify novel targets for further investigation.

Ultimately, understanding the molecular mechanisms of reconsolidation will aid the theoretical discussion of the role of reconsolidation in ongoing memory maintenance and its relation to other memory processes, including consolidation and extinction.

Functional roles of reconsolidation

Enhancing memory after retrieval. Reports indicating that memory reconsolidation might result in more persistent or stronger memories suggest a role for reconsolidation in the ongoing maintenance of long-term memories. Previous research has shown that re-exposure to conditioned cues or contexts can prevent the decrease in response due to forgetting[7,56,57], and reverse a decrease due to partial extinction[25]. More recently, manipulations including water deprivation and angiotensin II prior to memory reactivation have been shown to prolong memory maintenance at least 24 hours longer than in vehicle-treated groups[58]. Several reports also suggest that post-retrieval manipulations, including PKA activation[6], strychnine[57], amphetamine[59] (N.C.T. and J.R.T, unpublished observations) and D-cycloserine (DCS)[60], can actively strengthen memories.

Importantly, enhancements of reconsolidation[6,7,57,59,60] that maintain or strengthen memory after retrieval support the crucial role for specific mechanisms implicated by loss of function studies and support the hypothesis that reconsolidation is a storage process. Indeed, without assuming additional updating mechanisms, retrieval theory does not predict enhancements of memory strength after reactivation, and cannot easily account for both disruptions and enhancements of memory in a consistent manner. The ability to enhance memory after retrieval evokes an important philosophical question: can the original memory trace really become stronger without incorporating more information? With this in mind, enhancements of memory after retrieval highlight an additional possible conceptual role for reconsolidation: that reconsolidation is required for the incorporation of new information into a previously consolidated memory.

Updating old memories. After memory retrieval, several additional learning processes are likely to co-occur. For example, sensory and emotional information about the CS and contextual cues might be incorporated into the original memory trace. There is some evidence that memories can be updated after retrieval; however, whether such updating of memories is due to consolidation or reconsolidation processes remains controversial. An experimental study of reconsolidation indicated that protein synthesis-dependent reconsolidation occurs only in conjunction with the incorporation of new information[61]. A recent study[23] supports this idea, and also suggests that the availability of new information during reactivation triggers a 'new encoding state' that is required for memory reconsolidation. A role for reconsolidation in updating memories is consistent with the ability to strengthen memories after retrieval[6,7,58–60]. Updating memories might involve the incorporation of new information (such as context)[23,62], or simply reinforce the fact that the memory is still relevant, but the role of reconsolidation in this process is unclear.

One method for examining the role of reconsolidation in updating memories is to identify differential mechanisms of reconsolidation and consolidation. Tronel *et al.*[34] demonstrated that in an inhibitory avoidance procedure, modifications of the context initiated mechanisms of both reconsolidation and consolidation, but that only the original memory was impaired after inhibition of amygdalar C/EBPβ (that is, a reconsolidation-specific pathway), whereas only the new contextual information was impaired by disruption of hippocampal C/EBPβ (that is, a consolidation-specific pathway). They concluded that consolidation, but not reconsolidation, is required for updating old IA memories[34]. However, it is unclear whether a second-order memory (one indirectly associated with the US) is an updated old memory, or a new and independent association. Second-order conditioning is usually considered to be the acquisition of a new memory, where a previously trained CS serves as a reinforcer in the new associative memory. Supporting this assertion, it was recently shown that retrieval of second-order memories does not induce lability of the original trace, indicating that second-order associations are new memories, not modifications of the first-order association[63]. Therefore, it remains unclear whether the procedure used by Tronel *et al.*[34] resulted in 'updating' the original trace, or in the formation of a new, linked, second-order association.

Several important questions arise from a conceptual role of reconsolidation in updating memories. First, if reconsolidation processes act to add or modify the original memory, is this the same as new consolidation, or is it a reconsolidation process? Second, is updating required for reconsolidation to occur? It is important to note that these are the first studies investigating the role of reconsolidation in updating memory, so these theoretical questions may remain unresolved for some time to come.

Permanence versus transience. The permanence or transience of reconsolidation manipulations remains a fundamental question for theories of reconsolidation. A problem for the theory of reconsolidation as a post-retrieval storage process is whether these changes in memory or performance are permanent, which would support the notion of permanently altered memory, or temporary, which would be suggestive of an altered retrieval of a trace that remains intact and unchanged.

Many recent studies have found that the deficits of memory after post-retrieval manipulations can last for at

Long-term potentiation (LTP). The prolonged strengthening of synaptic communication, which is induced by patterned input and is thought to be involved in learning and memory formation.

Long-term depression (LTD) A persistent reduction of synaptic transmission in response to weak, poorly-correlated input.

least 14 days (30 days in some studies), and studies utilizing localized infusions often report long-lasting memory decrements[5,38,43,64]. This pattern of results indicates that localized disruption of molecular pathways and protein synthesis results in permanent memory loss, and supports the hypothesis of reconsolidation as a storage mechanism.

The use of performance — which relies on both the presence of an intact memory and its retrieval — as an index of memory means that an objective test that can answer the 'storage or retrieval' question does not yet exist. Although often framed as a question of permanence (storage deficits) versus transience (retrieval deficits), it is unclear that this division is appropriate. Retrieval could be permanently disrupted even though the memory is still stored. Conversely, if only a part of a memory, such as a subset of a hypothetical distributed network encoding the memory, is permanently destroyed by a disruption of a post-retrieval storage mechanism, the remainder of this network might be sufficient to allow retrieval of the memory at a later time, and memory disruption could therefore seem to be transient. The interrelation of storage and retrieval, and our inability to distinguish between the molecular mechanisms of each, make this issue one of the most challenging and interesting of the reconsolidation debate.

At this point, we lack the necessary experimental tools to conclusively distinguish between an inability to retrieve a memory because it is erased (storage hypotheses) or because later retrieval of the intact memory is impaired. One novel method for further examination of the synaptic properties of reconsolidation comes from electrophysiological models of plasticity, including long-term potentiation (LTP) and long-term depression (LTD). The use of cellular activity as a measure of plasticity circumvents the psychological processes involved in memory processes and might provide important additions to previous findings. A recent, elegant study[65] begins to do just this, demonstrating that re-stimulation during the maintenance phase can re-sensitize LTP to PSI. Development of electrophysiological models of reconsolidation[116] might lead to novel ways to theorize about post-retrieval plasticity, further investigation of the hypothesis that reconsolidation is a storage mechanism, and the suggestion of new directions for pharmacological, genetic and behavioural studies of post-retrieval manipulations of memory. Developing multiple approaches for reconsolidation research not only aids understanding the mechanisms of normal dynamic memory processes, but will also provide insights into the nature and development of pathological memories and psychiatric disorders.

Relevance to psychiatric disorders

One important direction for reconsolidation research is the unequivocal demonstration of memory reconsolidation after retrieval in humans. A recently consolidated motor sequence was shown to be disrupted by learning a sequence immediately after retrieval of the old memory[14]. This demonstration of retrograde interference after retrieval of an established memory in a motor learning task indicates a selective reconsolidation disruption in humans. Retrieval of a word list might also trigger memory reconsolidation[62]. By contrast, one previous study failed to find disruption of old, episodic memories after retrieval, using ECS as the amnestic agent[66]. As previously discussed, the discrepancy between such studies might be due to several procedural differences including the type (motor versus episodic) or age (recent versus old) of the memory, the type of reactivation trial (performance versus self-retrieval), or the manipulation under study (retrograde interference versus ECS). Interestingly, neither study examined emotional memory, which has been extensively studied in animal models. Additional studies are required before any strong conclusions can be drawn.

The storage hypothesis of reconsolidation makes several important predictions for psychiatric disorders. Pathological memories made labile by reactivation could be susceptible to disruptions (that is, treatment). If memories can enter into a labile state regardless of age, then interventions to disrupt memory could be effective at any time after onset of the disorder. Finally, enhancements of reconsolidation might be a component of normal mnemonic function that could also contribute to the aetiology of psychiatric disorders involving abnormally persistent memories.

If memory can be disrupted during a retrieval-induced labile period, there is the possibility that disruption of reconsolidation could be particularly efficacious in the treatment of strong, intrusive memories in disorders such as post-traumatic stress disorder (PTSD), phobias and drug addiction[38,43–45]. Indeed, given that it is often not possible to administer a consolidation-blocking agent at an initial trauma or triggering event, the possibility of later eliminating the traumatic memory by pharmacologically blocking reconsolidation is particularly clinically relevant[67,68]. The β-adrenergic receptor antagonist propranolol has previously been utilized in human patients with PTSD[69] after a traumatic experience, and might be a specific and effective disruptor of reconsolidation of fear memories in PTSD[70,71]. Other anxiolytic and amnestic agents might also be useful in eliminating fear memories after retrieval; for example, benzodiazepines have recently been shown to disrupt reconsolidation of contextual fear in rats[72]. Understanding the cellular and molecular mechanisms required, and the boundary conditions of reconsolidation (BOX 1), will be increasingly important for the development of drugs targeted for therapeutic disruption of a specific memory after retrieval.

The demonstration that memory can be enhanced after retrieval[6,7,57,59,60] also illustrates an important caveat for types of extinction therapy. The use of exposure to cues to retrieve and extinguish memories could, under some circumstances, actually result in strengthening of the memory[7]. This factor is especially important when an enhancing agent such as DCS is used to facilitate extinction[73]. Consistent with the ability of this drug to enhance acquisition of memories[74], DCS has been shown to enhance reconsolidation of fear memories under some conditions[60], potentially strengthening already maladap-

tive memories after retrieval.

Evidence for enhanced memory reconsolidation raises the possibility that dysfunctional reconsolidation processes might also be involved in the aetiology of disorders such as PTSD, depression and addiction. Here, continuing to update and strengthen maladaptive memories after retrieval, repeated over long periods of time, could lead to strong, intrusive memories. One potential mechanism for such aberrant reconsolidation mechanisms could be long-lasting drug-induced adaptations, including long-lasting upregulation of activity of cell signalling pathways such as cAMP, and downstream transcription factors such as CREB and ΔFosB[75–77]. Additionally, memory retrieval-related increases in cAMP might also be important in the development of PTSD. An increase in noradrenaline activation is integral to the hyper-arousal that surrounds retrieval of traumatic memories in patients with PTSD. Noradrenaline also acts through cAMP and downstream pathways including ERK and CREB, and activating these pathways might enhance reconsolidation of traumatic memories after retrieval. The reiterative and cumulative nature of reconsolidation could thereby lead to stronger, more extinction-resistant memories over a period of time.

The future of reconsolidation research

In discussing and reviewing current findings on the molecular mechanisms of reconsolidation, it is important to note a systematic bias. Not surprisingly, studies of reconsolidation have taken the manipulations that are known to affect consolidation as a starting point, and examined their effects on reconsolidation. This approach has had much success in identifying multiple points of convergence and divergence between these memory processes. Expanding the focus from targeted molecular approaches to include structural changes induced by memory reconsolidation will probably identify unique cellular and molecular mechanisms and crucial anatomical loci. These structural changes may include receptor trafficking and cytoskeletal rearrangement, which are involved in neural plasticity and memory storage. These events, however, are yet to be examined in reconsolidation. There are several possible questions to be answered: first, does reactivation induce plasticity-associated changes in cytoskeletal conformation or receptor trafficking? Second, are the persistent structural changes induced by consolidation reversed by disruptions of reconsolidation? Only one published study so far has pursued this line of reasoning, and showed that alterations in glutamate receptor levels after training are reversed by disruption of reconsolidation[78]. Expanding the search for molecular mechanisms of reconsolidation from cell signalling pathways to structural changes is a novel way to examine the functional role of reconsolidation in long-term memory.

The study of memory reconsolidation is also constrained by the lack of conceptual roles for post-retrieval memory lability under normal conditions. So far, only two roles have been proposed — that reconsolidation acts to maintain and strengthen retrieved memories, or that it acts to update them. These roles can also be interpreted in two different ways: a mechanism that is required to return memories into storage, or a mechanism that actively strengthens memories after retrieval. The former indicates that reconsolidation is a by-product of stimulation-induced lability, whereas the latter suggests that retrieval could be a biologically useful time point at which to strengthen, update or modify previously established memories. It should also be noted that the role of reconsolidation might differ between types of memory, as could the specific processes involved. Conceptually, reconsolidation might be more fruitfully studied within the context of dynamic maintenance of long-term memories and with a focus on how attentional mechanisms during retrieval shift the balance between reconsolidation and extinction. Disentangling possible roles for reconsolidation and specifying the links between molecular mechanisms and psychological processes should be a focus of psychiatric neuroscience.

1. McGaugh, J. L. Memory — a century of consolidation. *Science* **287**, 248–251 (2000).
2. Misanin, J. R., Miller, R. R. & Lewis, D. J. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science* **160**, 554–555 (1968).
The first demonstration of a post-retrieval memory disruption; this set the basis for the thinking about reconsolidation that continues today.
3. Nader, K. Memory traces unbound. *Trends Neurosci.* **26**, 65–72 (2003).
4. Dudai, Y. Reconsolidation: the advantage of being refocused. *Curr. Opin. Neurobiol.* **16**, 174–178 (2006).
An important reassessment of what reconsolidation might mean and how it should be examined.
5. Nader, K., Schafe, G. E. & LeDoux, J. E. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* **406**, 722–726 (2000).
Landmark study that re-introduced reconsolidation into the mainstream dialogue on memory. The authors demonstrated that intra-amygdala inhibition of protein synthesis after retrieval of a previously consolidated memory resulted in amnesia for the retrieved memory, but not for consolidated memories that were not retrieved.
6. 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).
7. Gordon, W. C. in *Information Processing in Animals: Memory Mechanisms* (eds Spear, N. E. & Miller, R. R.) 319–343 (Erlbaum, Hillsdale, New Jersey,1981).
8. Segal, M. Dendritic spines and long-term plasticity. *Nature Rev. Neurosci.* **6**, 277–284 (2005).
9. 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).
10. 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).
11. Dacher, M., Lagarrigue, A. & Gauthier, M. Antennal tactile learning in the honeybee: effect of nicotinic antagonists on memory dynamics. *Neuroscience* **130**, 37–50 (2005).
12. Eisenberg, M., Kobilo, T., Berman, D. E. & Dudai, Y. Stability of retrieved memory: inverse correlation with trace dominance. *Science* **301**, 1102–1104 (2003).
13. 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).
14. Walker, M. P., Brakefield, T., Hobson, J. A. & Stickgold, R. Dissociable stages of human memory consolidation and reconsolidation. *Nature* **425**, 616–620 (2003).
This important study demonstrates reconsolidation of memory in human individuals using a novel motor sequence learning task.
15. Kida, S. *et al.* CREB required for the stability of new and reactivated fear memories. *Nature Neurosci.* **5**, 348–355 (2001).
16. 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).
17. Thompson, C. I. & Grossman, L. B. Loss and recovery of long-term memories after ECS in rats: evidence for state-dependent recall. *J. Comp. Physiol. Psychol.* **78**, 248–254 (1972).

18. Mactutus, C. F., Riccio, D. C. & Ferek, J. M. Retrograde amnesia for old (reactivated) memory: some anomalous characteristics. *Science* **204**, 1319–1320 (1979).
19. Riccio, D. C. & Richardson, R. The status of experimentally induced amnesias: gone, but not forgotten. *Physiol. Psychol.* **12**, 59–72 (1984).
20. 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).
21. Prado-Alcala, R. A. *et al.* Amygdala or hippocampus inactivation after retrieval induces temporary memory deficit. *Neurobiol. Learn. Mem.* **86**, 144–149 (2006).
22. Suzuki, A. *et al.* Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J. Neurosci.* **24**, 4787–4795 (2004).
This important study began to disambiguate molecular mechanisms of reconsolidation from those of extinction.
23. 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).
An elegant study showing specific conditions under which reconsolidation of spatial memories does and does not occur, and an important contribution to the theoretical debate on reconsolidation.
24. Pedreira, M. E. & Maldonado, H. Protein synthesis subserves reconsolidation or extinction depending on reminder duration. *Neuron* **38**, 863–869 (2003).
The first study to demonstrate that reconsolidation can be dissociated from extinction using reactivation session length.
25. Rossato, J. I., Bevilaqua, L. R., Medina, J. H., Izquierdo, I. & Cammarota, M. Retrieval induces hippocampal-dependent reconsolidation of spatial memory. *Learn. Mem.* **13**, 431–440 (2006).
26. Judge, M. E. & Quartermain, D. Characteristics of retrograde amnesia following reactivation of memory in mice. *Physiol. Behav.* **28**, 585–590 (1982).
27. Riccio D. C., Hodges L. A. & Randall P. K. Retrograde amnesia produced by hypothermia in rats. *J. Comp. Physiol. Psychol.* **66**, 618–622 (1968).
28. Dudai, Y. & Eisenberg, M. Rites of passage of the engram: reconsolidation and the lingering consolidation hypothesis. *Neuron* **44**, 93–100 (2004).
29. 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).
30. 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).
31. 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).
32. Hernandez, P. J., Sadeghian, K. & Kelley, A. E. Early consolidation of instrumental learning requires protein synthesis in the nucleus accumbens. *Nature Neurosci.* **5**, 1327–1331 (2002).
33. Hernandez, P. J. & Kelley, A. E. Long-term memory for instrumental responses does not undergo protein synthesis-dependent reconsolidation upon retrieval. *Learn. Mem.* **11**, 748–754 (2004).
34. 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).
35. Milekic, M. H., Brown, S. D., Castellini, C. & Alberini, C. M., Persistent disruption of an established morphine conditioned place preference. *J. Neurosci.* **26**, 3010–3020 (2006).
36. Routtenberg, A. & Rekart, J. L. Post-translational protein modification as the substrate for long-lasting memory. *Trends Neurosci.* **28**, 12–19 (2005).
37. Hall, J., Thomas, K. L. & Everitt, B. J. Fear memory retrieval induces CREB phosphorylation and Fos expression within the amygdala. *Eur. J. Neurosci.* **13**, 1453–1458 (2001).
38. Miller, C. A. & Marshall, J. F. Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. *Neuron* **47**, 873–884 (2005).
39. Merlo, E., Freudenthal, R., Maldonado, H. & Romano, A. Activation of the transcription factor NF-kappaB by retrieval is required for long-term memory reconsolidation. *Learn. Mem.* **12**, 23–29 (2005).
40. Lin, C. H., Yeh, S. H., Lu, H. Y. & Gean, P. W., The similarities and diversities of signal pathways leading to consolidation of conditioning and consolidation of extinction of fear memory. *J. Neurosci.* **23**, 8310–8317 (2003).
41. Lee, J. L., Everitt, B. J. & Thomas, K. L. Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science* **304**, 839–843 (2004).
This landmark study demonstrated a double dissociation between mechanisms of consolidation (BDNF) and reconsolidation (ZIF268) within the hippocampus.
42. 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).
43. 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).
Novel demonstration of reconsolidation of an appetitive, Pavlovian, drug-associated memory.
44. Lee, J. L., Milton, A. L. & Everitt, B. J. Cue-induced cocaine seeking and relapse are reduced by disruption of drug memory reconsolidation. *J. Neurosci.* **26**, 5881–5887 (2006).
45. Hellemans, K. G., Everitt, B. J. & Lee, J. L. Disrupting reconsolidation of conditioned withdrawal memories in the basolateral amygdala reduces suppression of heroin seeking in rats. *J. Neurosci.* **26**, 12694–12699 (2006).
46. 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).
47. 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).
48. Valjent, E., Corbille, A. G., Bertran-Gonzalez, J., Herve, D. & Girault, J. A. Inhibition of ERK pathway or protein synthesis during reexposure to drugs of abuse erases previously learned place preference. *Proc. Natl Acad. Sci. USA* **103**, 2932–2937 (2006).
49. Koh, M. T. & Bernstein, I. L. Inhibition of protein kinase A activity during conditioned taste aversion retrieval: interference with extinction or reconsolidation of a memory? *Neuroreport* **14**, 405–407 (2003).
50. Kemenes, G., Kemenes, I., Michel, M., Papp, A. & Muller, U. Phase-dependent molecular requirements for memory reconsolidation: differential roles for protein synthesis and protein kinase A activity. *J. Neurosci.* **26**, 6298–6302 (2006).
51. Hall, J., Thomas, K. L. & Everitt, B. J. Cellular imaging of *zif268* expression in the hippocampus and amygdala during contextual and cued fear memory retrieval: selective activation of hippocampal CA1 neurons during the recall of contextual memories. *J. Neurosci.* **21**, 2186–2193 (2001).
52. Thomas, K. L., Hall, J. & Everitt, B. J. Cellular imaging with *zif268* expression in the rat nucleus accumbens and frontal cortex further dissociates the neural pathways activated following the retrieval of contextual and cued fear memory. *Eur. J. Neurosci.* **16**, 1789–1796 (2002).
53. Strekalova, T. *et al.* Memory retrieval after contextual fear conditioning induces c-Fos and JunB expression in CA1 hippocampus. *Genes Brain Behav.* **2**, 3–10 (2003).
54. Tronel, S. & Sara S. J. Mapping of olfactory memory circuits: region-specific c-fos activation after odor-reward associative learning or after its retrieval. *Learn. Mem.* **9**, 105–111 (2002).
55. 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).
56. Rohrbaugh, M. & Riccio, D. C. Paradoxical enhancement of learned fear. *J. Abnorm. Psychol.* **75**, 210–216 (1970).
57. Gordon, W. C. & Spear N. E., The effects of strychnine on recently acquired and reactivated passive avoidance memories. *Physiol. Behav.* **10**, 1071–1075 (1973).
58. Frenkel, L., Maldonado, H. & Delorenz, A. Memory strengthening by a real-life episode during reconsolidation: an outcome of water deprivation via brain angiotensin II. *Eur. J. Neurosci.* **22**, 1757–1766 (2005).
59. Blaiss, C. A. & Janak, P. H. Post-training and post-reactivation administration of amphetamine enhances morphine conditioned place preference. *Behav. Brain. Res.* **171**, 329–337 (2006).
60. Lee, J. L. C., Milton, A. L. & Everitt, B. J. Reconsolidation and extinction of conditioned fear: inhibition and potentiation. *J. Neurosci.* **26**, 10051–10056 (2006).
61. Rodriguez-Ortiz, C. J., De la Cruz, V., Gutierrez, R. & Bermidez-Rattoni, F. Protein synthesis underlies post-retrieval memory consolidation to a restricted degree only when updated information is obtained. *Learn. Mem.* **12**, 533–537 (2005).
62. 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).
This important article demonstrates retrieval-initiated updating of memory in a traditional human memory task.
63. Debiec, J., Doyere, V., Nader, K. & Le Doux, J. E. Directly reactivated, but not indirectly reactivated, memories undergo reconsolidation in the amygdala. *Proc. Natl Acad. Sci. USA* **103**, 3428–3433 (2006).
An important demonstration of the specificity of reconsolidation of fear memories.
64. Duvarci, S. & Nader, K. Characterization of fear memory reconsolidation. *J. Neurosci.* **24**, 9269–9275 (2004).
65. Fonseca, R., Nagerl, U. V. & Bonhoeffer, T. Neuronal activity determines the protein synthesis dependence of long-term potentiation. *Nature Neurosci.* **9**, 478–480 (2006).
This seminal study is the first study to suggest a reconsolidation-like process in slice electrophysiology. Development of this model will contribute to the progress of research into mechanisms of memory reconsolidation.
66. Squire, L. R., Slater, P. C. & Chace, P. M. Reactivation of recent or remote memory before electroconvulsive therapy does not produce retrograde amnesia. *Behav. Biol.* **18**, 335–343 (1976).
67. McCleery, J. M. & Harvey, A. G. Integration of psychological and biological approaches to trauma memory: implications for pharmacological prevention of PTSD. *J. Trauma. Stress* **17**, 485–496 (2004).
68. Centonze, D., Siracusana, A., Calabresi, P. & Bernardi, G. Removing pathogenic memories: a neurobiology of psychotherapy. *Mol. Neurobiol.* **32**, 123–132 (2005).
69. Pitman, R. K. *et al.* Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biol. Psychiatry* **51**, 189–192 (2002).
70. Miller, M. M., Altemus, M., Debiec, J., LeDoux, J. E. & Phelps, E. A. Propranolol impairs reconsolidation of conditioned fear in humans. *Soc. Neurosci. Abstr.* 208.2 (2004).
71. Debiec, J. & LeDoux, J. E. Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. *Neuroscience* **129**, 267–272 (2004).
72. Bustos, S. G., Maldonado, H. & Molina, V. A. Midazolam disrupts fear memory reconsolidation. *Neuroscience* **139**, 831–842 (2006).
73. Walker, D. L., Ressler, K. J., Lu, K. T. & Davis, M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. *J. Neurosci.* **22**, 2343–2351 (2002).
74. Quartermain, D., Mower, J., Rafferty, M. F., Hertng, R. L. & Lanthorn, T. H. Acute but not chronic activation of the NMDA-coupled glycine receptor with D-cycloserine facilitates learning and retention. *Eur. J. Pharmacol.* **257**, 7–12 (1994).
75. McClung, C. A. & Nestler, E. J. Regulation of gene expression and cocaine reward by CREB and ΔFosB. *Nature Neurosci.* **6**, 1208–1215 (2003).
76. Nestler, E. J. Molecular basis of long-term plasticity underlying addiction. *Nature Rev. Neurosci.* **2**, 119–128 (2001).
77. Terwilliger, R. Z., Beitner-Johnson, D., Sevarino, K. A., Crain, S. M. & Nestler, E. J. A general role for adaptations in G-proteins and the cyclic AMP system in mediating the chronic actions of morphine and cocaine on neuronal function. *Brain Res.* **548**, 100–110 (1991).

78. Rose, J. K. & Rankin, C. H. Blocking memory reconsolidation reverses memory-associated changes in glutamate receptor expression. *J. Neurosci.* **26**, 1582–1587 (2006).
Important study showing that glutamate receptor removal from synapses coincides with behavioural measures of memory disruption after retrieval. The use of this novel dependent variable provides strong evidence for cellular changes that correlate with a reversal of learning-related changes, and therefore a role for reconsolidation in the maintenance of stored memories.
79. Eisenberg, M. & Dudai, Y. Reconsolidation of fresh, remote, and extinguished fear memory in Medaka: old fears don't die. *Eur. J. Neurosci.* **20**, 3397–3403 (2004).
80. Milekic, M. H. & Alberini, C. M. Temporally graded requirement for protein synthesis following memory reactivation. *Neuron* **36**, 521–525 (2002).
81. Frankland, P. W. *et al.* Stability of recent and remote contextual fear memory. *Learn. Mem.* **13**, 451–457 (2006).
82. 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).
83. Biedenkapp, J. C. & Rudy, J. W. Context memories and reactivation: constraints on the reconsolidation hypothesis. *Behav. Neurosci.* **118**, 956–964 (2004).
84. Wang, S., Marin, M. & Nader, K. Memory strength as a transient boundary condition on reconsolidation of auditory fear memories and its molecular correlates. *Soc. Neurosci. Abstr.* 650.2 (2005).
85. Mamiya, N., Suzuki, A. & Kida, S. Analyses of brain regions showing CREB activation in reconsolidation and extinction phases of contextual fear memory. *Soc. Neurosci. Abstr.* 208.2 (2006).
86. Bouton, M. E. Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. *Psychol. Bull.* **114**, 80–99 (1993).
87. Przybyslawski, J. Roullet, P. & Sara, S. J. Attenuation of emotional and nonemotional memories after their reactivation: role of β adrenergic receptors. *J. Neurosci.* **19**, 6623–6628 (1999).
88. Roullet, P. & Sara, S. Consolidation of memory after its reactivation: involvement of β noradrenergic receptors in the late phase. *Neural Plast.* **6**, 63–68 (1998).
89. Bernadi, R. E., Lattal, K. M. & Berger, S. P. Postretrieval propranolol disrupts a cocaine conditioned place preference. *Neuroreport* **17**, 1443–1447 (2006).
90. Diergaarde, L., Schoffelmeer, A. N. & De Vries, T. J. β-adrenoceptor mediated inhibition of long-term reward-related memory reconsolidation. *Behav. Brain. Res.* **170**, 333–336 (2006).
91. Przybyslawski, J., Roullet, P. & Sara, S. J. Reconsolidation of memory after its reactivation. *Behav. Brain. Res.* **84**, 241–246 (1997).
92. Mamou, C. B., Gamache, K. & Nader, K. NMDA receptors are critical for unleashing consolidated auditory fear memories. *Nat. Neurosci.* **9**, 1237–1239 (2006).
93. Torras-Garcia, M., Lelong, J., Tronel, S. & Sara, S. Reconsolidation after remembering an odor-reward association requires NMDA receptors. *Learn. Mem.* **12**, 18–22 (2005).
94. Cestari, V., Costanzi, M., Castellano, C. & Rossi-Arnaud, C. A role for ERK2 in reconsolidation of fear memories in mice. *Neurobiol. Learn. Mem.* **86**, 133–143 (2006).
95. Parsons, R. G., Gafford, G. M., Baruch, D. E., Riedner, B. A. & Helmstetter, F. J. Long-term stability of fear memory depends on the synthesis of protein but not mRNA in the amygdala. *Eur. J. Neurosci.* **23**, 1853–1859 (2006).
96. Debiec, J., LeDoux, J. E. & Nader, K. Cellular and systems reconsolidation in the hippocampus. *Neuron* **36**, 527–538 (2002).
97. Gainutdinova, T. H. *et al.* Reconsolidation of a context long-term memory in the terrestrial snail requires protein synthesis. *Learn. Mem.* **12**, 620–625 (2005).
98. Runyan, J. D. & Dash, P. K. Inhibition of hippocampal protein synthesis following recall disrupts expression of episodic-like memory in trace conditioning. *Hippocampus* **15**, 333–339 (2005).
99. Blum, S., Runyan, J. D. & Dash, P. K. Inhibition of prefrontal protein synthesis following recall does not disrupt memory for trace fear conditioning. *BMC Neurosci.* **7**, 67 (2006).
100. Litvin, O. O. & Anokhin, K. V., Mechanisms of memory reorganization during retrieval of acquired behavioral experience in chicks: the effects of protein synthesis inhibition in the brain. *Neurosci. Behav. Physiol.* **30**, 671–678 (2000).
101. Bahar, A., Dorfman, N. & Dudai, Y. Amygdalar circuits required for either consolidation or extinction of taste aversion memory are not required for reconsolidation. *Eur. J. Neurosci.* **19**, 1115–1118 (2004).
102. Gruest, N., Richer, P. & Hars, B. Memory consolidation and reconsolidation in the rat pup require protein synthesis. *J. Neurosci.* **24**, 10488–10492 (2004).
103. 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).
104. Lattal, K. M., Honarvar, S. & Abel, T. Effects of post-session injections of anisomycin on the extinction of a spatial preference and on the acquisition of a spatial reversal preference. *Behav. Brain. Res.* **153**, 327–339 (2004).
105. Akirav, I. & Maroun, M. Ventromedial prefrontal cortex is obligatory for consolidation and reconsolidation of object recognition memory. *Cereb. Cortex* **16**, 1739–1769 (2006).
106. Rossato, J. I *et al.* On the role of hippocampal protein synthesis in the consolidation and reconsolidation of object recognition memory. *Learn. Mem.* **14**, 36–46 (2007).
107. Inda, M. C., Delgado-Garcia, J. M. & Carrion, A. M. Acquisition, consolidation, reconsolidation, and extinction of eyelid conditioning responses require *de novo* protein synthesis. *J. Neurosci.* **25**, 2070–2080 (2005).
108. Yim, A. J., Moraes, C. R., Ferriera, T. L. & Oliveira, M. G. Protein synthesis inhibition in the basolateral amygdala following retrieval does not impair expression of morphine-associated conditioned place preference. *Behav. Brain. Res.* **171**, 162–169 (2006).
109. 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.* **3**, 8034–8040 (2003).
110. Child, F. M., Epstein, H. T., Kuzirian, A. M. & Alkon, D. L. Memory reconsolidation in *Hermissenda*. *Biol. Bull.* **205**, 218–219 (2003).
111. Kraus, M. *et al.* Memory consolidation for the discrimination of frequency-modulated tones in mongolian gerbils is sensitive to protein-synthesis inhibitors applied to the auditory cortex. *Learn. Mem.* **9**, 293–303 (2002).
112. Salinska, E. The role of group I metabotropic glutamate receptors in memory consolidation and reconsolidation in the passive avoidance task in 1-day-old chicks. *Neurochem. Int.* **48**, 447–452 (2006).
113. Sherry, J. M., Hale, M. W. & Crowe, S. F. The effects of the dopamine D1 receptor antagonist SCH23390 on memory reconsolidation following reminder-activated retrieval in day-old chicks. *Neurobiol. Learn. Mem.* **83**, 104–112 (2005).
114. Bucherelli, C., Baldi, E., Mariottini, C., Passani, M. B. & Blandina, P. Aversive memory reactivation engages in the amygdala only some neurotransmitters involved in consolidation. *Learn. Mem.* **13**, 426–430 (2006).
115. Boccia, M. M., Acosta, G. B., Blake, M. G. & Baratti, C. M. Memory consolidation and reconsolidation of an inhibitory avoidance response in mice: effects of i.c.v. injections of hemicholinium-3. *Neuroscience* **124**, 735–741 (2004).
116. 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.* (in the press).

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