Review TRENDS in Neurosciences Vol.28 No.1 January 2005

Mechanisms of memory stabilization: are consolidation and reconsolidation similar or distinct processes?

Cristina M. Alberini

Department of Physiology and Biophysics, Mount Sinai School of Medicine, New York, NY 10029, USA

Consolidation of new memories depends on a crucial phase of protein synthesis. It is widely held that, once consolidated, memories are stable and resilient to disruption. However, established memories become labile when recalled and require another phase of protein synthesis to be maintained. Therefore, it has been proposed that when a memory is reactivated it must undergo additional consolidation (reconsolidation) to persist. To determine whether reconsolidation recapitulates consolidation, in the past few years several groups have investigated whether the same molecules and pathways mediate the formation of a memory and its maintenance after reactivation. At first glance, the results appear conflicting: although both processes appear to engage the same molecules and mechanisms, brain areas involved in consolidation after initial training are not required for reconsolidation. In addition, the formation of a memory and its maintenance after reactivation seem to have distinctive temporal molecular requirements. This review concludes with a working model that could explain the apparent controversy of memory vulnerability after reactivation.

The processes of memory formation and elaboration are accompanied by transient yet crucial phases of protein synthesis. During memory 'consolidation', protein synthesis is required to transform newly learned information into stable modifications [1–3]. Several studies have shown that when a stabilized memory is recalled or reactivated, it again becomes sensitive to disruption and its maintenance requires protein synthesis [4–7] (reviewed in Refs [8,9]). Therefore, it has been proposed that reactivated memories must undergo another round of consolidation (i.e. 'reconsolidation') to be preserved [8,10,11]. However, the fact that a reactivated memory is labile and dependent on protein synthesis does not elucidate the nature of the underlying mechanisms. To show that the processes of consolidation and reconsolidation are identical would require (i) demonstration that the events occurring during initial consolidation are re-engaged following retrieval of fully consolidated memories and (ii) demonstration that these steps are then necessary to re-store them. This article reviews recent studies adding to the debate of whether reconsolidation, as implied by its definition, is truly a repetition of consolidation or in fact a distinct process.

Corresponding author: Cristina M. Alberini (cristina.alberini@mssm.edu).
Available online 11 November 2004

Mechanisms of memory consolidation

Memory consolidation has been studied for more than a century [3,9]. It has been defined on the basis of observations that a newly formed memory undergoes a transformation process, becoming stronger and more resilient over time until it is insensitive to disruption. Factors shown to interfere with consolidation include cerebral trauma, electroconvulsive shock, protein synthesis inhibitors and several drugs [3]. In several species and memory systems, many molecular, anatomical and system-level investigations have contributed to the characterization of this transformation process.

Insights into the anatomy of consolidation have been gained by testing the effects of functional inactivation or direct lesion of specific brain areas. These studies have shown that the consolidation of different types of memory (including spatial, contextual, fear-based and appetitive) require several distinct brain regions [12,13], thus suggesting the existence of distinct memory systems. Moreover, it has become clear that different brain regions are progressively engaged, indicating that the consolidation process is sustained by spatial and temporal changes [12,14–16] and occurs over an extended period. For example, consolidation of many types of memories depends on hippocampal processing during the first few weeks but subsequently becomes hippocampus-independent [17]. Furthermore, analyses of both human amnesic patients with anatomically defined cerebral injuries and animal models with ablations of specific brain regions indicate that graded retrograde amnesia, defined as a greater memory deficit for information acquired recently versus remotely, can occur for very old events (several years old in humans) [18].

Studies based on the use of inhibitors showed that memory consolidation requires RNA and protein synthesis. This discovery led to an intensive effort to identify the genes, proteins and molecular pathways involved. Over the past 15 years, signaling pathways involving Ca^{2+}, cAMP, mitogen-activated protein (MAP) kinases and tyrosine kinases have been shown to be required for the consolidation of various kinds of memories, and numerous genes have been identified as essential for

 0166-2236/$ - see front matter doi:10.1016/j.tins.2004.11.001

memory formation. Overall, these studies suggested that a cascade of molecular and cellular events initiated by an experience results in a durable form of synaptic modification [19,20]. They also indicated, in apparent contrast to what had been suggested by the anatomical investigations, that the molecular changes underlying consolidation are required only for a short time (i.e. hours or days). However, it must be stressed that most studies of the molecular requirements for memory consolidation have made observations at only a single or very few and early time points. Thus, the temporal evolution of this process still remains largely unknown. Furthermore, it is likely that the early and essential molecular events underlying memory consolidation are just the initial steps of a cascade of molecular and cellular modifications that evolve over an extended period, perhaps in different brain areas.

Molecular requirements of reconsolidation

The reconsolidation hypothesis, first suggested in the 1960s [10] and recently re-proposed following the work of Nader *et al.* [7], implies that every time a memory is reactivated it must undergo again a process of consolidation to be maintained. This idea contrasts with the classical view that a memory consolidates only once and, over time, becomes stronger and more stable.

To unravel this controversy, a great deal of effort has recently focused on determining whether reconsolidation, as implied by its definition, is a repetition of consolidation. Thus, several groups have investigated the molecular requirements of both consolidation and reconsolidation. In some studies, researchers examined the effects of protein synthesis inhibitors after memory reactivation; in others, they focused on specific molecular requirements by inactivating individual molecular pathways or disrupting expression of single genes. Some studies examined systemic requirements, whereas others focused on specific brain regions.

In numerous studies, protein synthesis was blocked systemically or in the whole brain [e.g. via intracerebroventricular (ICV) injections] after memory reactivation; all confirmed that this treatment blocks memory retention at later times (Table 1). These results imply that, in several different species and types of learning paradigms, some general features underlie both consolidation and reconsolidation. However, because these studies used global, non-specific inactivation, they did not provide any information on specific brain areas or molecular mechanisms involved.

Because some of the molecules and brain regions involved in memory consolidation are already known, a direct approach to determine whether consolidation and reconsolidation are similar or distinct processes is to re-examine whether the same molecules and brain regions are also implicated in reconsolidation. Indeed, several laboratories investigated the effect of protein synthesis inhibitors administered in selected brain areas and/or tested the role of specific molecules and molecular pathways. The results of these studies appear to point to contrasting conclusions (Tables 2 and 3). One of the first findings supporting the hypothesis that reconsolidation is distinct from consolidation was provided by Taubenfeld *et al.* [21], showing that inhibitory avoidance (IA) memory can be disrupted by protein synthesis inhibitors administered systemically after memory reactivation. Furthermore, the authors examined the role of the transcription factor CCAAT enhancer binding protein β (C/EBPβ) in the dorsal hippocampus during consolidation and reconsolidation. The results showed that when the expression of hippocampal C/EBPβ is transiently blocked by antisense injections into the dorsal hippocampi after IA training, memory is impaired; by contrast, if C/EBPβ expression is inhibited after reactivation, memory remains unaffected. However, Taubenfeld *et al.* [21] also found that, in the dorsal hippocampus, protein synthesis is crucial for consolidation but not reconsolidation of IA memory. Therefore, they concluded that the two processes are different in that they require either different molecular mechanisms or different brain areas.

The notion that distinct brain areas might mediate the two processes was confirmed by many other studies. Salinska *et al.* [22], using a passive avoidance task in chick, reported that protein synthesis and glycosylation requirements, as well as induction of the transcription factor c-fos after training and reactivation, are anatomically and temporally different. The strongest differences were found in the intermediate medial hyperstriatum ventrale and lobus parolfactorius. Bahar *et al.* [23], using localized inhibition of protein synthesis, found that

Table 1. Systemic or ICV administration of protein synthesis inhibitors after memory reactivation

Finding	Inhibitor application[a]	Species	Refs
Contextual fear conditioning memory is disrupted by protein synthesis inhibitors administered either after training or after reactivation	IP	Mouse	[51]
Transcription and translation are required for both consolidation and reconsolidation of a classical conditioning task	Bath	Mollusk (*Hermissenda*)	[31]
Protein synthesis is required for both consolidation and reconsolidation	Pericardial sac	Crab (*Chasmagnathus*)	[52]
Protein synthesis inhibitors impair passive avoidance memory after recall	ICV	Chick	[42]
Both consolidation and reconsolidation of a contextual fear memory require protein synthesis	IP	Mouse	[32]
A reactivated inhibitory avoidance memory is disrupted by protein synthesis inhibition	IP	Rat	[21]
Passive avoidance memory is disrupted by a protein synthesis inhibitor administered after reactivation	ICV	Chick	[36]
A reactivated passive avoidance memory is disrupted by protein synthesis inhibitors (this also occurs after training)	SC	Mouse	[4]

[a]Abbreviations: ICV, intracerebroventricular; IP, intraperitoneal; SC, subcutaneous.

Table 2. Differences between consolidation and reconsolidation[a]

Finding	Species	Refs
Young, weak memories are more sensitive to disruption by protein synthesis inhibitors (IP application) after reactivation of contextual fear conditioning than are older, stronger memories	Mouse	[37]
Requirement for protein synthesis and glycosylation as well as induction of c-fos after training or reactivation of passive avoidance are anatomically and temporally different	Chick	[22]
Protein synthesis in the central nucleus of the amygdala is required for consolidation but not for reconsolidation of conditioned taste aversion	Rat	[23]
A reactivated contextual fear memory is only temporarily disrupted by protein synthesis inhibitors (IP application)	Mouse	[51]
New memories are more susceptible to disruption by protein synthesis inhibitors (SC application) after reactivation than are old memories	Rat	[35]
Protein synthesis inhibition (ICV application) after recall causes a temporary deficit of passive avoidance memory. The sensitive period after recall is shorter than after training	Chick	[42]
Protein synthesis is required in the nucleus accumbens for consolidation, but not for reconsolidation of instrumental learning	Rat	[24]
In auditory cortex, protein synthesis is required for consolidation but not for reconsolidation of a tone discrimination task	Gerbil	[53]
c-Fos expression is induced in different brain areas during consolidation and reconsolidation of an odor–reward association	Rat	[25]
Hippocampal protein synthesis is required for consolidation but for not reconsolidation of inhibitory avoidance memory	Rat	[54]
Hippocampal protein synthesis and C/EBPβ are required for inhibitory avoidance consolidation, but not for reconsolidation	Rat	[21]
Different areas are activated during encoding and retrieval of episodic memory	Human	[27]

[a]Abbreviations: C/EBPβ, CCAAT enhancer binding protein β; ICV, intracerebroventricular; IP, intraperitoneal; SC, subcutaneous.

specific amygdala circuits are selectively required for consolidation but not reconsolidation of taste aversion memory. Hernandez *et al.* [24] demonstrated that *de novo* protein synthesis within the nucleus accumbens is necessary for the consolidation, but not the reconsolidation, of appetitive instrumental memories (lever-pressing for food). Using c-fos as an activity marker, Tronel and Sara [25] showed that, although the frontal cortex and the basolateral amygdala are activated following training of an odor–reward association, retrieval of this memory does not seem to activate the same regions. Specifically, the amygdala is not engaged after retrieval, whereas the lateral habenula shows strong activation. Kelly *et al.* [26] found that distinct hippocampal circuits activate MAP kinase following either training or reactivation of an object recognition task. Nyberg *et al.* [27], using positron emission tomography in humans during initial encoding and subsequent retrieval of information revealed the existence of distinct encoding and retrieval networks for episodic memory.

Finally, another level of distinction between consolidation and reconsolidation was suggested by a recent report by Lee *et al.* [28], providing evidence that the consolidation and the reconsolidation of contextual fear conditioning depend on distinct molecular mechanisms within the same region (the hippocampus). Using a localized antisense injection-based approach, these authors demonstrated that if the hippocampal expression of brain-derived neurotrophic factor is blocked, consolidation but not reconsolidation is impaired. Conversely, when the hippocampal expression of the transcription factor zif268 is blocked, reconsolidation is impaired but consolidation remains unaffected.

In contrast to this body of work, it has been suggested by other researchers that consolidation and reconsolidation are similar processes. Nader *et al.* [7] and Debiec *et al.* [11] reported that in rat, protein synthesis is required in the amygdala for both consolidation and reconsolidation of cued fear conditioning, and required in the hippocampus

Table 3. Similarities between consolidation and reconsolidation[a]

Finding	Species	Refs
Hemicholinium-3 (inhibitor of the high-affinity choline uptake) injected ICV impairs both consolidation and reconsolidation of inhibitory avoidance	Mouse	[55]
As with consolidation, reconsolidation of conditioned taste aversion requires protein synthesis in insular cortex	Rat	[56]
Zif268 is required for both consolidation and reconsolidation of object recognition task	Mouse	[33]
Protein synthesis is required in the same cell for consolidation and reconsolidation of an operant conditioning task	Pond snail (*Lymnaea stagnalis*)	[29]
Hippocampal MAPK is required for both consolidation and reconsolidation of an object recognition task	Rat	[26]
Amygdala PKA is required for reconsolidation of conditioned taste avoidance	Rat	[30]
CREB is required for both consolidation and reconsolidation of contextual fear conditioning	Mouse	[32]
As with consolidation, hippocampal protein synthesis is required for reconsolidation of contextual fear conditioning	Rat	[11]
Amygdala protein synthesis is required for both consolidation and reconsolidation of auditory fear conditioning	Rat	[7]
The β-adrenoceptor antagonist propanolol impairs both consolidation and reconsolidation of inhibitory avoidance	Rat	[57]
As with consolidation, the β-adrenoceptor antagonist timolol blocks reconsolidation of a radial-arm-maze memory	Rat	[58]

[a]Abbreviations: CREB, cAMP-response-element-binding protein; ICV, intracerebroventricular; MAPK, mitogen-activated protein kinase; PKA, protein kinase A.

for both consolidation and reconsolidation of contextual fear conditioning. Moreover, Sangha *et al.* [29] showed that in the pond snail *Lymnea stagnalis*, protein and RNA syntheses are required in the same cell for both consolidation and reconsolidation of a classical conditioning task.

Similarities between the two processes were also suggested by investigations examining the requirement for specific molecules. These studies revealed: (i) that inhibition of the MAP kinase pathway by ICV injection of a specific inhibitor affects both consolidation and reconsolidation of an object recognition task (however, as already mentioned, the activation of MAP kinase occurred in distinct hippocampal subregions [26]); (ii) that inhibiting protein kinase A in the amygdala affects both consolidation and reconsolidation of conditioned taste aversion [30]; (iii) that inhibiting bond formation between cell-adhesion molecules blocks both processes in pavlovian conditioning [31]; (iv) that temporally regulated knockout of the transcription factor cAMP-response-element-binding protein (CREB) impairs both consolidation and reconsolidation of contextual fear conditioning [32]; and, finally, (v) that knock-out of zif268 results in deficits in both consolidation and reconsolidation of an object recognition task [33].

Sorting through the outcomes of the studies already described here, some interesting parallels emerge from the apparently conflicting results. First, with the exception of some studies (e.g. those of Nader *et al.* [7] and Debiec *et al.* [11]), brain regions required or activated in consolidation are not engaged in reconsolidation. The results of Nader *et al.* and Debiec *et al.* probably indicate that, although the network involved in consolidation and reconsolidation seems to be different, some brain regions could participate in both. Second, with the exception of the work of Lee *et al.* [28], most of the findings provide evidence that the same molecular mechanisms and pathways mediate both consolidation and reconsolidation. Indeed, it is not surprising that the molecular requirements for consolidation and reconsolidation largely overlap, as it is likely that the induction and the maintenance of a memory use common mechanisms of long-term synaptic plasticity. Nevertheless, it should be pointed out that most of the studies that investigated the role of specific molecules or pathways targeted the whole brain (using ICV injections, systemic injections and/or knock-out) and, therefore, did not provide any information about the role of specific molecules in specific brain areas. Thus, more experiments that test specific mechanisms in specific brain regions are needed to identify the discrete molecular circuitry underlying either consolidation or reconsolidation.

Therefore, consolidation and reconsolidation share common molecular mechanisms but are distinct processes because they require, with some degree of overlap, the activation of different brain areas and circuits. In most cases, regions involved in consolidation are not required for reconsolidation. However, because the reverse has yet to be shown, it is possible that a subset of regions is involved in both processes. Should we expect to find that the reconsolidation of different kinds of memory uses common circuits? Probably not, because consolidation and retrieval of distinct forms of memories are also known to use discrete memory systems [12,13,34].

Temporal requirements of reconsolidation

Further distinctions between the two processes became evident when the temporal requirements for protein synthesis during reconsolidation were analyzed. In IA, the protein synthesis requirement induced by recall is a function of the age of the memory, with recent (2- and 7-day-old) but not remote (14- and 28-day-old) memories becoming sensitive to protein synthesis inhibitors upon reactivation [35]. Similar results, indicating a temporally graded requirement for protein synthesis after recall, have been reported by other groups who have used different model systems, including chick passive avoidance [36], Medaka fish fear conditioning (Y. Dudai, pers. commun.) and mouse contextual fear conditioning [37]. Importantly, Suzuki *et al.* [37] also showed that the temporal dynamics of memory reconsolidation depend on both the strength of the memory and the strength of reactivation. Thus, a weaker memory is more susceptible to become labile, and the stronger the reactivation of the learned experience, the more labile the memory becomes.

These results could explain the findings of Nader *et al.* [7] and Debiec *et al.* [11] who, using cued and contextual fear conditioning in rats, found that 2-week-old or even 45-day-old memories still become sensitive to protein synthesis inhibitors after recall. These authors suggested that, independently of its age, each time a memory is reactivated it becomes labile. However, in several different species and learning paradigms (including fear conditioning), the gradient of protein synthesis requirement is very clear. Hence, it is reasonable to believe (and also testable) that, as suggested by Suzuki *et al.* [37], the gradient for protein synthesis requirement shifts according to the strength and number of reactivation events and could vary with the nature of the memory test itself. Consistent with this hypothesis, Bozon *et al.* [33] have shown that during recall of an object recognition memory, neither contextual information nor the exposure to previously presented objects in a different context is alone sufficient to destabilize the memory. In fact, to induce the need for zif268, the objects had to be recalled in the previously associated context. Similar results had been obtained using electroconvulsive shock [38] and, recently, using morphine-conditioned place preference (M. Milekic and C. Alberini, unpublished). In this study, the animals formed an association between a context and the rewarding effects of morphine. Protein synthesis inhibitors administered after reactivation disrupted an established conditioned place preference if the reactivation included the re-experience of both training context and morphine, but not if it included the re-experience of context or morphine alone (M. Milekic and C. Alberini, unpublished).

In summary, age of the memory, task specificity, strength of initial learning, and strength and number of reactivation events all make important contributions to the process evoked by recall.

Concluding remarks and future directions

The knowledge accumulated so far indicates that reconsolidation of a reactivated memory and consolidation of an initial learning are characterized by distinctive features. First, they involve different brain areas and circuits.

Consolidation appears to require several areas that are not essential for reconsolidation and, as will be suggested in this section, reconsolidation might involve mostly modulatory systems. Second, consolidation and reconsolidation also differ in their temporal dynamics. Training always induces a labile phase during which memory can be disrupted, whereas reactivation does not always result in a labile memory. A stronger and older memory is less labile; a more intense reactivation is more destabilizing.

However, both consolidation and reconsolidation seem to use similar molecular mechanisms, the same ones that are known to mediate long-term synaptic plasticity. Perhaps what these findings on the labile nature of a reactivated memory reveal is that reactivation of the memory trace is an integral aspect of a single, extended consolidation process. In other words, it is possible that what is currently defined as reconsolidation is a phase of the consolidation process.

The following is a working model that could explain the results thus far provided by the reconsolidation studies:

(i) Learning creates a memory trace. This trace resides within a circuit, which includes a network of brain areas required to process and integrate the learning experience. The trace is activated by a modulation event that stabilizes the trace itself (modulation phase). Indeed, it has been proven that modulation is essential for memory consolidation [39].

(ii) Modulation events are evoked by both initial learning and subsequent memory reactivations, which can be either implicit (internal reactivation) or explicit (cued recall). Indeed, it has been shown that memory is impaired if modulation is blocked after its reactivation [40].

(iii) The stabilization of the memory trace is a function of the duration and number of modulation events that it receives. In other words, each training and reactivation event contributes to a gradient of stabilization that gradually increases and eventually results in a fully consolidated trace that is insensitive to disruption. However, during the gradient, the still-unstable trace can become labile if activated by a modulation event.

(iv) Reactivations, whether implicit or explicit, have at least two functions: they are necessary for memory stabilization and they allow integration of new information with old memories.

(v) At late times, when memory is stable, a modulation event induced by reactivation can add to or modify the trace but can no longer disrupt it.

This model would explain why: (i) older memories are more stable [35,37], (ii) the labile nature of a memory can be overcome by various reminder manipulations [41–44], (iii) modulation can promote retrieval from retrograde amnesia [45], repetition increases memory stability, and (iv) during sleep, memory seems to consolidate via internal re-activation of the trace [46–50]. The nature of the modifications that over time stabilize the memory is still unclear. A possible explanation is, as suggested previously [35] and discussed here, that memories gradually change the anatomical localization of the trace [12,15–17].

More studies are needed to determine the nature of the fascinating process induced by memory recall. Specifically, it is important that we gain a more detailed understanding of the anatomical and temporal dynamics of the molecular and systems changes required after training as well as after memory reactivation. Only with this knowledge will we have a clearer understanding of how a memory is formed and preserved. Perhaps then, a more precise definition of what is currently defined as 're'-consolidation will emerge.

Acknowledgements

I thank Maria Milekic and Stephen Taubenfeld for helpful comments and discussions.

References

1 Davis, H.P. and Squire, L.R. (1984) Protein synthesis and memory: a review. *Psychol. Bull.* 96, 518–559
2 Dudai, Y. (1996) Consolidation, fragility and the road to the engram. *Neuron* 17, 367–370
3 McGaugh, J.L. (2000) Memory – a century of consolidation. *Science* 287, 248–251
4 Judge, M.E. and Quartermain, D. (1982) Characteristics of retrograde amnesia following reactivation of memory in mice. *Physiol. Behav.* 28, 585–590
5 Misanin, J.R. *et al*. (1968) Retrograde amnesia produced by electroconvulsive shock after reactivation of consolidated memory trace. *Science* 160, 554–555
6 Mactutus, C.F. *et al*. (1979) Retrograde amnesia for old (reactivated) memory: some anomalous characteristics. *Science* 204, 1319–1320
7 Nader, K. *et al*. (2000) Fear memories requires protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* 406, 722–726
8 Sara, S.J. (2000) Retrieval and reconsolidation: toward a neurobiology of remembering. *Learn. Mem.* 7, 73–84
9 Dudai, Y. (2004) The neurobiology of consolidation, or, how stable is the engram? *Annu. Rev. Psychol.* 55, 51–86
10 Lewis, D.J. (1979) Psychobiology of active and inactive memory. *Psychol. Bull.* 86, 1054–1083
11 Debiec, J. *et al*. (2002) Cellular and systems reconsolidation in the hippocampus. *Neuron* 36, 527–538
12 Ambrogi Lorenzini *et al*. (1999) Neural topography and chronology of memory consolidation: a review of functional inactivation findings. *Neurobiol Learn. Mem.* 71, 1–18
13 Poldrack, R.A. and Packard, M.G. (2003) Competition among multiple memory systems: converging evidence from animal and human brain studies. *Neuropsychologia* 41, 245–251
14 Bontempi, B. *et al*. (1999) Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature* 400, 671–675
15 Frankland, P.W. *et al*. (2004) The involvement of the anterior cingulate cortex in remote contextual fear memory. *Science* 304, 881–883
16 Maviel, T. *et al*. (2004) Sites of neocortical reorganization critical for remote spatial memory. *Science* 305, 96–99
17 Anagnostaras, S.G. *et al*. (1999) Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: within-subjects examination. *J. Neurosci.* 19, 1106–1114
18 Brown, A.S. (2002) Consolidation theory and retrograde amnesia in humans. *Psychon. Bull. Rev.* 9, 403–425
19 Moser, M.B. *et al*. (1994) An increase in dendritic spine density on hippocampal CA1 pyramidal cells following spatial learning in adult rats suggests the formation of new synapses. *Proc. Natl. Acad. Sci. U. S. A.* 91, 12673–12675
20 Silva, A.J. (2003) Molecular and cellular cognitive studies of the role of synaptic plasticity in memory. *J. Neurobiol.* 54, 224–237
21 Taubenfeld, S.M. *et al*. (2001) The consolidation of new but not reactivated memory requires hippocampal C/EBPβ. *Nat. Neurosci.* 4, 813–818
22 Salinska, E. *et al*. (2004) Reminder effects: the molecular cascade following a reminder in young chicks does not recapitulate that following training on a passive avoidance task. *Eur. J. Neurosci.* 19, 3042–3047
23 Bahar, A. *et al*. (2004) Amygdalar circuits required for either consolidation or extinction of taste aversion memory are not required for reconsolidation. *Eur. J. Neurosci.* 19, 1115–1118

24 Hernandez, P.J. *et al*. (2002) Early consolidation of instrumental learning requires protein synthesis in the nucleus accumbens. *Nat. Neurosci.* 5, 1327–1331
25 Tronel, S. and Sara, S.J. (2002) Mapping of olfactory memory circuits: region-specific c-fos activation after odor–reward associative learning or after its retrieval. *Learn. Mem.* 9, 105–111
26 Kelly, A. *et al*. (2003) Activation of mitogen-activate protein kinase/extracellular signal-regulated kinase in hippocampal circuitry is required for consolidation and reconsolidation of recognition memory. *J. Neurosci.* 12, 5354–5360
27 Nyberg, L. *et al*. (1996) General and specific brain regions involved in encoding and retrieval of events: what, where, and when. *Proc. Natl. Acad. Sci. U. S. A.* 93, 11280–11285
28 Lee, J.L. *et al*. (2004) Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science* 304, 839–843
29 Sangha, S. *et al*. (2003) 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
30 Koh, M.T. and Bernstein, I.L. (2003) Inhibition of protein kinase A activity during conditioned taste aversion retrieval: interference with extinction or reconsolidation of a memory? *NeuroReport* 14, 405–407
31 Child, F.M. *et al*. (2003) Memory reconsolidation in *Hermissenda*. *Biol. Bull.* 205, 218–219
32 Kida, S. *et al*. (2002) CREB required for the stability of new and reactivated fear memories. *Nat. Neurosci.* 5, 348–355
33 Bozon, B. *et al*. (2003) A requirement for the immediate early gene zif268 in reconsolidation of recognition memory after retrieval. *Neuron* 40, 695–701
34 Nadel, L. *et al*. (2000) Multiple trace theory of human memory: computational, neuroimaging, and neuropsychological results. *Hippocampus* 10, 352–368
35 Milekic, M.H. and Alberini, C.M. (2002) Temporally graded requirement for protein synthesis following memory reactivation. *Neuron* 36, 521–525
36 Litvin, O.O. and Anokhin, K.V. (2000) 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
37 Suzuki, A. *et al*. (2004) Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J. Neurosci.* 24, 4787–4795
38 DeVietti, T.L. and Holliday, J.H. (1972) Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace: a replication. *Psychon. Sci.* 29, 137–138
39 Izquierdo, I. and McGaugh, J.L. (2000) Behavioural pharmacology and its contribution to the molecular basis of memory consolidation. *Behav. Pharmacol.* 11, 517–534
40 Sara, S.J. (2000) Strengthening the shaky trace through retrieval. *Nat. Rev. Neurosci.* 1, 212–213
41 Brown, A.M. *et al*. (1985) The roles of information reactivation and nonassociative arousal in recovery from ECS-induced retrograde amnesia. *Physiol. Behav.* 35, 183–187
42 Anokhin, K.V. *et al*. (2002) 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
43 Hildreth, K. and Rovee-Collier, C. (2002) Forgetting functions of reactivated memories over the first year of life. *Dev. Psychobiol.* 41, 277–288
44 Millin, P.M. *et al*. (2001) Interpretations of retrograde amnesia: old problem redux. *Nat. Rev. Neurosci.* 2, 68–70
45 Mactutus, C.F. *et al*. (1980) Extending the duration of ACTH-induced memory reactivation in an amnesic paradigm. *Physiol. Behav.* 24, 541–546
46 Kali, S. and Dayan, P. (2004) Off-line replay maintains declarative memories in a model of hippocampal–neocortical interactions. *Nat. Neurosci.* 7, 286–294
47 Wilson, M.A. and McNaughton, B.L. (1994) Reactivation of hippocampal ensemble memories during sleep. *Science* 265, 676–679
48 Louie, K. and Wilson, M.A. (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron* 29, 145–156
49 Fenn, K.M. *et al*. (2003) Consolidation during sleep of perceptual learning of spoken language. *Nature* 425, 614–616
50 Walker, M.P. *et al*. (2003) Dissociable stages of human memory consolidation and reconsolidation. *Nature* 425, 616–620
51 Lattal, K.M. and Abel, T. (2004) Behavioral impairments caused by injections of the protein synthesis inhibitor anisomycin after contextual retrieval reverse with time. *Proc. Natl. Acad. Sci. U. S. A.* 101, 4667–4672
52 Pedreira, M.E. *et al*. (2002) 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
53 Kraus, M. *et al*. (2002) 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
54 Vianna, M.R. *et al*. (2001) Retrieval of memory for fear-motivated training initiates extinction requiring protein synthesis in the rat hippocampus. *Proc. Natl. Acad. Sci. U. S. A.* 98, 12251–12254
55 Boccia, M.M. *et al*. (2004) Memory consolidation and reconsolidation of an inhibitory avoidance response in mice: effects of i.c.v. injections of hemicholinium-3. *Neuroscience* 124, 735–741
56 Eisenberg, M. *et al*. (2003) Stability of retrieved memory: inverse correlation with trace dominance. *Science* 301, 1102–1104
57 Przybyslawski, J. *et al*. (1999) Attenuation of emotional and nonemotional memories after their reactivation: role of beta adrenergic receptors. *J. Neurosci.* 19, 6623–6628
58 Roullet, P. and Sara, S. (1998) Consolidation of memory after its reactivation: involvement of beta noradrenergic receptors in the late phase. *Neural Plast.* 6, 63–68