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A Synaptic Reinforcement-Based Model for Transient Amnesia Following Disruptions of Memory Consolidation and Reconsolidation

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ABSTRACT: The observation of memory recovery following post-training amnestic interventions has historically caused controversy over the meaning of this finding, leading some authors to question the paradigm of a consolidation period for memories. Similarly, recent demonstrations of transient amnesia caused by interventions following memory reactivation have been used to question the existence of a retrieval-driven reconsolidation process. The present work aims to approach the phenomenon of transient amnesia following disruptions of consolidation and reconsolidation, discussing how memory recovery might be explained within a framework of systems consolidation, persistent synaptic reinforcement, and multiple memory traces. With these concepts in mind, we propose that long-term consolidation processes can underlie recovery from amnesia, demonstrating the feasibility of such a hypothesis in a two-structure computational model of learning in which consolidation is dependent upon synaptic reentry reinforcement. On the basis of this, we suggest that prolonged consolidation can account for experimental findings of transient amnesia, in a way that explains differences between disruptions of consolidation and reconsolidation without the need to dwell into the discussion between storage- and retrieval-based explanations for memory impairment. © **2008 Wiley-Liss, Inc.**

KEY WORDS: hippocampus; systems consolidation; memory recovery; synaptic reentry reinforcement; connectionist network

INTRODUCTION

The concept of memory reconsolidation—that is, the idea that retrieval of a memory increases its lability to a variety of amnestic agents—was initially proposed almost 40 years ago (Misanin et al., 1968; Schneider and Sherman, 1968). However, it was cooled off by the mainstream view of memory consolidation at the time, and did not return to the spotlight until the end of the 20th century, when a new wave of studies dealing with the effect of amnestic agents after re-exposure to a learning context (Przybyslawski et al., 1999; Nader et al., 2000; Taubenfeld et al., 2001) set off a heated debate among researchers in the memory field, which has sparked considerable interest ever since (Dudai and Eisenberg, 2004; Dudai, 2006; Alberini, 2007; Nader, 2007; Tronson and Taylor, 2007). An extensive body of evidence has since been brought forward either in favor of or against the so-called "reconsolidation hypothesis": support for the hypothesis usually came from studies demonstrating the amnestic effects of post re-exposure interventions—especially injections of protein synthesis inhibitors (Nader et al., 2000; Milekic and Alberini, 2002)—while evidence against it arose from works showing either no such effects (Biedenkapp and Rudy, 2004; Cammarota et al., 2004) or opposite effects related to memory extinction (Berman and Dudai, 2001; Vianna et al., 2001).

At this point, the field seems to be somewhat more settled in the conclusion that, at least under some circumstances or "boundary conditions" (Dudai, 2006; Nader, 2007; Tronson and Taylor, 2007), some kind of postreactivation labilization can indeed occur. Moreover, many of these conditions have begun to be described: the occurrence of reconsolidation after exposure to the original memory context has been shown to depend on duration of exposure to the original context (Eisenberg et al., 2003; Pedreira and Maldonado, 2003; Suzuki et al., 2004), on the absence of significant extinction (Eisenberg et al., 2003) and on the encoding of new information at the time of retrieval (Pedreira et al., 2004; Morris et al., 2006; Rossato et al., 2006, 2007). The molecular requirements of such a reconsolidation process have also begun to emerge, and have been shown to be similar but not identical to those of the initial consolidation process (Taubenfeld et al., 2001; Lee et al., 2004; Alberini, 2005; Tronson and Taylor, 2007). Finally, temporal constraints on the susceptibility of memories to postreactivation amnestic interventions (Milekic and Alberini, 2002; Eisenberg and Dudai, 2004; Suzuki et al., 2004; Boccia et al., 2006; Frankland et al., 2006) have led some authors to propose that reconsolidation phenomena may be part of a prolonged phase of consolidation (Dudai and Eisenberg, 2004; Dudai, 2004; Alberini, 2007), reconciling the phenomenon with some aspects of traditional consolidation theory.

Nevertheless, various controversies remain in the reconsolidation field. Perhaps the most significant of these controversies at this time is the fact that many

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studies have shown the effects of "reconsolidation blockade" to be transient or reversible (Mactutus et al., 1979; Judge and Quartermain, 1982; Lattal and Abel, 2004; Power et al., 2006; Amaral et al., 2007). This has led some authors (Cahill et al., 2001; Power et al., 2006) to suggest that the effect of post re-exposure interventions is not related to blockade of a putative reconsolidation process, but to some form of temporary retrieval impairment, reigniting a decades-old controversy on whether experimental amnesia should be attributed to storage or retrieval impairments (Miller and Matzel, 2006; Nader and Wang, 2006; Riccio et al., 2006; Squire, 2006). On the other hand, other studies have failed to observe memory recovery following disruptions during the reconsolidation period (Duvarci and Nader, 2004; Lee et al., 2004; Boccia et al., 2005; Bustos et al., 2006; Tronel and Alberini, 2007), and many authors have tended to view transient amnesia in this situation as being unrelated to reconsolidation blockade, attributing it instead to spontaneous recovery after facilitated extinction (Fischer et al., 2004; Cai et al., 2006; Alberini, 2007) or other phenomena.

In this article, we propose a model which tries to explain the recovery of memories after disruptions of consolidation and reconsolidation in a way that reconciles the apparently conflicting data on the transience or permanency of amnesia without the need to assume fundamental dissimilarities between its mechanisms in both cases. With this objective in mind, we will begin by briefly reviewing some issues on transient amnesia, as well as concepts concerning systems consolidation and synaptic reinforcement, which will be relevant for understanding the model.

TRANSIENT AMNESIA AND MEMORY RECOVERY

Evidence for transient amnesia bothering a seemingly peaceful turf in the memory field is nothing new. In fact, before causing controversy in the reconsolidation field, it was used to argue against consolidation theory back from as early as the 1960s (Zinkin and Miller, 1967; Lewis et al., 1968). From then up to the 1980s, various reports showed that amnesia induced by post-training interventions such as electroconvulsive shock (ECS) (Zinkin and Miller, 1967; Lewis et al., 1968; Quartermain et al., 1970) or protein synthesis inhibitors (Quartermain and McEwen, 1970; Squire and Barondes, 1972) was reversible. This reversal was usually demonstrated by means of some kind of reinforcement, such as a reminder stimulus (Quartermain et al., 1970; Miller and Kraus, 1977) or a pharmacological injection either before training (Gold and Sternberg, 1978) or before testing (Bradley and Galal, 1988); nevertheless, in some cases memory recovery was also shown to occur spontaneously (Quartermain and McEwen, 1970; Serota, 1971; Squire and Barondes, 1972). Evidence for transient amnesia has also been described in humans following transient insults such as closed head injury (Russell and Nathan, 1946), ECS (Squire et al., 1975), and transient global amnesia (Kritchevsky and Squire, 1989). In these cases, temporally graded amnesia usually ensues but gradually "shrinks" due to the recovery of more remote memories, while a residual memory deficit for recent memory usually persists over time (Squire, 2006).

Findings of transient or reversible amnesia were used by some authors to argue that memory deficits caused by post-training interventions were not due to blockade of a consolidation process, but rather due to other factors such as nonspecific, long-lasting effects (Serota, 1971), inhibition of the formation of retrieval links despite storage of the memory representation (Miller and Springer, 1973), or modulatory effects related to state dependence (Hinderliter et al., 1975). Nevertheless, others argued that reversibility of amnesia with reminders reflected potentiation of residual memory traces after storage disruption to a point at which they were behaviorally expressed (Gold et al., 1973; Gold and King, 1974). The zeitgeist ended up favoring the consolidation theorists (Dudai, 2004; Squire, 2006), and the discussion eventually quieted down, but full agreement on the issue was never reached (Millin et al., 2001; Miller and Matzel, 2006). This is largely due to the fact that, at least using traditional methods, this debate appears unsolvable: it is impossible to prove through behavioral observation that a memory has not been stored, while it is impossible to disprove the alternate hypothesis that it has been stored but cannot be retrieved (Nader and Wang, 2006). This has led the discussion over the matter to become polarized, with great difficulty in bridging these two diametrically opposed views of amnesia due to the limitations of currently available methods (Nader and Wang, 2006; Squire, 2006).

The possibility of some form of retrieval impairment underlying amnesia has occasionally returned in the literature since then (Miller and Matzel, 2000; Millin et al., 2001; de Hoz et al., 2004); however, it regained force recently after a reasonable number of studies confirmed older findings (Mactutus et al., 1979; Judge and Quartermain, 1982) that amnesia following so-called "reconsolidation blockade" (postretrieval intervention of amnestic agents) was transient or reversible (Litvin and Anokhin, 2000; Vianna et al., 2001; Anokhin et al., 2002; Szapiro et al., 2003; Eisenberg and Dudai, 2004; Fischer et al., 2004; Lattal and Abel, 2004; Salinska et al., 2004; Power et al., 2006; Prado-Alcalá et al., 2006; Salinska, 2006; Amaral et al., 2007; Luft et al., in press) (Table 1). On the other hand, a similarly large number of studies which did test for amnesia persistence after variable periods did not observe such recovery effects (Child et al., 2003; Pedreira and Maldonado, 2003; Boccia et al., 2004, 2005, 2006; Debiec and LeDoux, 2004; Duvarci and Nader, 2004; Lee et al., 2004; Suzuki et al., 2004; Miller and Marshall, 2005; Tronel et al., 2005; Bustos et al., 2006; Lin et al., 2006; Rossato et al., 2006; Valjent et al., 2006; Jin et al., 2007; Tronel and Alberini, 2007) (Table 2).

Characterization of what causes this disparity has been lacking. Duration and/or degree of protein synthesis inhibition have been shown to correlate with amnesia persistence in two recent studies in rats (Milekic et al., 2006) and snails (Solntseva et al., 2007). Both of these studies found that a single injection of cycloheximide following reactivation of a memory caused transient amnesia, while two or three injections spaced over a few hours (or a higher dose of the drug, in the later study) had

TABLE 1.

Studies Showing Transient Amnesia Due to Interventions Following Memory Reactivation

Reference	System	Intervention	Time of disruption (from training)	Time of amnesia (from disruption)	Time of recovery (from disruption)	Reminder
Mactutus et al., 1979	Step-through inhibitory avoidance, rats	Hypothermia	1 day	1 day	2 days	No
Judge and Quartermain, 1982	Approach avoidance, mice	Anisomycin, systemic	3 hours	3 hours	4 days	No
Litvin and Anokhin, 2000	Passive avoidance, day-old chicks	Cycloheximide, IMM	2 h/1 day/ 3 days	1 h	3 h–2 days[a]	No
Vianna et al., 2001	Step-down inhibitory avoidance, rats	Anisomycin, hippocampus	1 day	1 day	2 days	Optional
Anokhin et al., 2002	Passive avoidance, day-old chicks	Anisomycin/2-deoxygalactose, IMM	2 h	1 h	3 h–1 day	No
Szapiro et al., 2003	Step-down inhibitory avoidance, rats	AP5/Rp-cAMPs/ PD098059, hippocampus	1 day	1 day	2 days	No
Eisenberg and Dudai, 2004	Fear conditioning, *Medaka* fish	MS222, systemic	1 day	2 days	2 days (w/reminder)	Required
Fischer et al., 2004[b]	Contextual fear conditioning, mice	Anisomycin, hippocampus	1 day	1 day	6 days (w/reminder)	Required
Lattal & Abel, 2004	Contextual fear conditioning, mice	Anisomycin, systemic	1 day	1 day	21 days	No
Salinska et al., 2004	Passive avoidance, day-old chicks	Anisomycin, IMM	1 day	6 h	1 day	No
Power et al., 2006	Step-through inhibitory avoidance, rats	Anisomycin, hippocampus	6 h	2 days	6 days	Optional
Prado-Alcalá et al., 2006	Step-through inhibitory avoidance, rats	Tetrodotoxin, hippocampus/ amygdala	2 days	2 days	6 days	No
Salinska, 2006	Passive avoidance, day-old chicks	MPEP, IMM	2 h	15 min	6 h	No
Amaral et al., 2007	Step-down inhibitory avoidance, rats	Muscimol, hippocampus	1 day	1 day	2 days	No
Luft et al., in press	Step-down inhibitory avoidance, rats	RC-3095/AP5, hippocampus	1 day	1 day	2 days	No
Cai et al., 2004[b]	Classical fear conditioning, mice	Corticosterone, systemic	2 days	1 day	3 days (1 day w/reminder)	Optional
Milekic et al., 2006	Morphine-conditioned place preference, rats	Cycloheximide, systemic (single injection)	1 week (from last session)	1 day	1 week	No
Solntseva et al., 2007	Food aversion conditioning, snails	Cycloheximide (single low dose)/ anisomycin, systemic	1 day	2.5 h	5.5 h	No

Indicated in the first three columns are the study, behavioral task, species, drug (or other intervention) and form of administration/targeted brain structures for the treatment used. "Time of disruption" column refers to the interval between training and the time at which memory is reactivated and disrupted. "Time of amnesia" refers to the interval between memory disruption and the time at which behavioral testing first indicates amnesia. "Time of recovery" refers to the interval between memory disruption and the first behavioral test indicating recovery from amnesia. "Reminder" column indicates if reminders were tested in the study, and if they were required or optional for recovery to occur ("no" indicates that reminders were not tested in the study). The last three studies show evidence of both transient and permanent effects of different interventions (see text), and are therefore also included in Table 2. Mechanisms of action of drugs: anisomycin and cycloheximide, protein synthesis inhibitors; 2-deoxygalactose, glycoprotein fucosylation inhibitor; AP5, *N*-methyl-D-aspartate (NMDA) receptor antagonist, Rp-cAMPs, protein kinase A inhibitor; PD098059, mitogen-activated kinase kinase (MEK) inhibitor; MS222 and tetrodotoxin, Na^+-channel blockers; MPEP, metabotropic glutamate receptor type 5 (mGluR5) antagonist; muscimol, GABA-A receptor agonist; RC-3095, gastrin-releasing peptide receptor antagonist. IMM, intermediate medial mesopallium (formally known as intermediate medial ventral hyperstriatum).

[a]Time of recovery dependent on time of intervention: for further discussion of this result, see text and Fig. 5.

[b]Results attributed to accelerated extinction.

TABLE 2.

Studies Showing Amnestic Effects Persisting Over Multiple Trials After Post-Reactivation Interventions

Reference	System	Intervention	Time of disruption (from training)	Time of initial test (from disruption)	Time of last test (from disruption)	Reminder
Child et al., 2003	Pavlovian conditioning, *Hermissenda*	Anisomycin, systemic	4 h	4 h	3 days	No
Pedreira and Maldonado, 2003	Contextual conditioning, crabs	Cycloheximide, systemic	1 day	1 day	2 days	No
Suzuki et al., 2004	Contextual fear conditioning, mice	Anisomycin, systemic	1 day	1 day	1 week	No
Duvarci and Nader, 2004	Contextual fear conditioning, rats	Anisomycin, amygdala	1 day	1 day	24 days	Yes
Debiec and LeDoux, 2004	Auditory fear conditioning, rats	Propranolol, systemic	1 day/ 2 months	2 days	16 days/ 1 month[a]	Yes
Lee et al., 2004	Contextual fear conditioning, rats	Zif-268 antisense ODN, hippocampus	1 day	1 day	6 days	No
Boccia et al., 2005	Step-through inhibitory avoidance, mice	Interfering task (hole-board habituation)	1 day	1 day	3 days	Yes
Miller and Marshall, 2005	Cocaine-conditioned place preference, rats	U0126, nucleus accumbens	2 days (from last session)	1 day	14 days	No
Tronel et al., 2005	Step-through inhibitory avoidance, rats	Anisomycin, systemic	2 days	1 week	1 week	No
Bustos et al., 2006	Contextual fear conditioning, rats	Midazolam, systemic	1 day	1 day	11 days	Yes
Rossato et al., 2006	Morris water maze, rats	Anisomycin, hippocampus	1 day/5 days (from last session)	1 day	5 days	No
Boccia et al., 2006	Step-through inhibitory avoidance, mice	Hemicholinium, ICV	2 days/7 days/ 14 days	1 day	5 days/19 days[b]	No
Lin et al., 2006	Pavlovian fear conditioning, rats	WIN55212-2, amygdala	1 day	1 day	7 days	Yes
Valjent et al., 2006	Drug-conditioned place preference, mice	SL327, systemic	2 days (from last session)	1 day	2 days/15 days[c]	Yes
Tronel et al., 2007	Step-through inhibitory avoidance, rats	RU 38486, amygdala	2 days	2 days	10 days	Yes
Jin et al., 2007	Auditory fear conditioning, rats	RU486, amygdala	1 day	1 day	6 days	No
Rossato et al., 2007	Object recognition, rats	Anisomycin, hippocampus	1 day	1 day	6 days	No
Cai et al., 2004	Classical fear conditioning, mice	Anisomycin, systemic	2 days	1 day	3 days	Yes
Milekic et al., 2006	Morphine-conditioned place preference, rats	Cycloheximide, systemic (2 injections); anisomycin, hippocampus/ amygdala/nucleus/ accumbens	1 week (from last session)	1 day	4 weeks (for cycloheximide/ 1 week (for anisomycin)	For anisomycin only
Solntseva et al., 2007	Food aversion conditioning, snails	Cycloheximide, systemic (high dose or 3 injections)	1 day	2.5 h	1 month	No

Indicated in the first three columns are the study, behavioral task, species, drug (or other intervention) and form of administration/targeted brain structures for the treatment used. "Time of disruption" column refers to the interval between training and the time at which memory is reactivated and disrupted. "Time of initial test" refers to the interval between memory disruption and the time at which behavioral testing first indicates amnesia. "Time of last test" refers to the interval between memory disruption and the last behavioral test performed. Note that the time of the last trial varies between 2 days and 1 month following disruption. "Reminder" column indicates if the effect of reminders after post-reactivation amnesia was tested in the study. The last three studies show evidence of both transient and permanent effects of different interventions (see text), and are therefore also included in Table 1. Mechanisms of action of drugs: anisomycin and cycloheximide, protein synthesis inhibitors; propranolol, β-adrenoreceptor antagonist; U0126 and SL327, mitogen-actived protein kinase kinase (MEK) inhibitors; midazolam, benzodiazepine; hemicholinium, choline uptake inhibitor; WIN 55212-2, cannabinoid CB1 receptor antagonist; RU 38486 and RU486, glucocorticoid receptor antagonists. ODN, oligodeoxynucleotide; ICV, intracerebroventricular.

[a]Group where disruption occurred at 2 days tested 16 days later, group where disruption occurred at 2 months tested 1 month later.

[b]Test at 19 days performed only in the group where disruption was performed at 2 days (other groups tested only at 5 days).

[c]Group undergoing cocaine-conditioned place preference tested up to 2 days later; group undergoing morphine-conditioned place preference tested up to 15 days later.

persistent amnestic effects lasting many weeks. In another study, a systemic injection of anisomycin during reconsolidation caused persistent amnesia, while an injection of corticosterone in the same protocol had a transient effect, although the authors attributed the latter to facilitated extinction (Cai et al., 2006). Finally, differences among behavioral protocols are also likely to play a role, as even though both transience and persistence of amnesia have been reported by different groups for similar drugs in the same kind of tasks, such as inhibitory avoidance (Tronel et al., 2005; Power et al., 2006) and contextual fear conditioning (Lattal and Abel, 2004; Suzuki et al., 2004), results from specific laboratories using a fixed behavioral protocol have tended to yield consistent results of either persistent (Tronel et al., 2005; Boccia et al., 2005, 2006; Tronel and Alberini, 2007) or transient (Vianna et al., 2001; Szapiro et al., 2003; Salinska et al., 2004; Salinska, 2006; Amaral et al., 2007) effects using a variety of treatments.

Nevertheless, the fact that there is ample evidence showing that either transient or persistent amnesia can result from both post-training and post re-exposure interventions suggests the need for a model which can encompass both possibilities, as parsimony suggests that the transience or permanency of memory impairments should not lead one to invoke more than one mechanism for amnesia in these situations (Nader, 2007). With this in mind, new ways of looking at transient amnesia seem to be important to allow the field to move forward without becoming trapped once again in the "storage versus retrieval" debate. In this sense, we believe that a few conclusions can be obtained from the currently available evidence to be used as a starting point to understand how memory recovery might occur after amnestic interventions during the consolidation and reconsolidation periods.

One important point is that, in many studies in which transient amnesia was observed after postreactivation interventions (Vianna et al., 2001; Anokhin et al., 2002; Szapiro et al., 2003; Lattal and Abel, 2004; Power et al., 2006; Prado-Alcalá et al., 2006; Amaral et al., 2007), the same treatments which caused transient effects on reconsolidation caused persistent amnesia when applied in the consolidation period. Therefore, even though both transient and persistent amnesia have been described to occur following blockade of either consolidation or reconsolidation, the possibility of spontaneous recovery following reconsolidation blockade appears to be significantly greater in a variety of protocols.

Moreover, while some studies showed memory recovery after amnesia to occur only in the presence of reminders (Eisenberg and Dudai, 2004; Fischer et al., 2004), in many others it was shown to occur spontaneously (Vianna et al., 2001; Szapiro et al., 2003; Lattal and Abel, 2004; Amaral et al., 2007). This fact (i.e., that memories can recover with no stimulus other than the passage of time) suggests that late, dynamic processes occurring endogenously in the absence of behavioral manipulations are likely to be involved in the mechanisms underlying memory recovery. Since such long-term processes have also been proposed to be linked to reconsolidation (Dudai and Eisenberg, 2004; Alberini, 2007), we will now move on to review some data concerning late events which happen to memory traces after the initial consolidation period.

SYSTEMS CONSOLIDATION, SYNAPTIC REINFORCEMENT AND LATE EVENTS ON THE LIFE OF MEMORIES

Although extensive research has yielded a large body of knowledge concerning the initial few hours of memory consolidation (McGaugh, 2000), significantly less is known about what happens to memories afterwards. And, although traditional memory research has sometimes tended to view memory as "consolidated" after a few hours (the timeframe in which so-called "synaptic" or "cellular" consolidation is thought to occur), it is well demonstrated that mnemonic traces undergo changes long after this period is over (Dudai, 2004). By far the most studied of these late phenomena in memory consolidation is "systems consolidation," the process which leads the retrieval of declarative memories to become independent of the hippocampus, putatively as a result of the establishment of a permanent neocortical representation (Wiltgen et al., 2004; Frankland and Bontempi, 2005). This is supported mostly by the finding of temporally graded retrograde amnesia in hippocampal lesion studies (Squire and Alvarez, 1995; Rempel-Clower et al., 1996), as well as by some functional imaging (Bontempi et al., 1999) and gene expression (Ross and Eichenbaum, 2006) studies showing different patterns of brain activation for recent and remote memories.

Other things also happen to memories on the long run, however. Memory traces become less dependent on context, for example (Kim and Fanselow, 1992; Winocur et al., 2007), which is probably analogous to the "semantization" of memory we experience in everyday life (in which semantic memory for facts persists while the contextual, episodic information used for building it is frequently lost). Differential sensitivity of recent and remote long-term memories to specific interventions, such as late protein synthesis inhibition, has also been shown to exist (Bekinschtein et al., 2007). Finally, a number of recent studies has suggested that older memories become less sensitive to the amnestic effects of reconsolidation blockade (Milekic and Alberini, 2002; Eisenberg and Dudai, 2004; Suzuki et al., 2004; Boccia et al., 2006; Frankland et al., 2006). While this finding has not been universally replicated (Debiec et al., 2002; Debiec and LeDoux, 2004), it has brought important support to the view that memory reconsolidation occurs predominantly during the timeframe in which systems consolidation is occurring, suggesting that the two processes could be interrelated (Dudai and Eisenberg, 2004; Alberini, 2007).

Intrinsic to the nature of systems consolidation is the idea that declarative memories are supported by multiple systems during their long-term existence, initially relying on the hippocampal formation for storage and retrieval and later on neocortical connections which allow retrieval independently of the

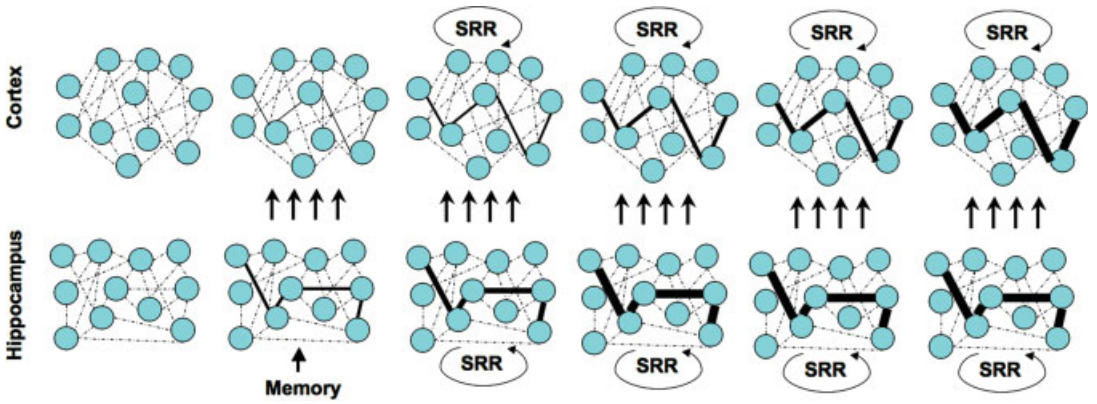

FIGURE 1. Schematic representation of learning in the SRR model as proposed by Wittenberg and Tsien (2002). Diagrams represent interconnected networks of hippocampal and cortical neurons (connected circles) and their respective connection strengths (black lines, with line thickness representing connection strength). Memory formation initially occurs through strengthening of specific connections (left column) in the hippocampus and cortex. Each reactivation of the memory (subsequent columns) leads to strengthening of the trace in both structures. Strengthening of the trace occurs rapidly in the hippocampus, but is much slower in the cortex, as proposed in previous models (Alvarez and Squire, 1994; McClelland et al., 1995). Therefore, for a period of time, both memory retrieval and trace strengthening in the cortex depend on hippocampal reactivation of the trace (middle columns). After a sufficient number of cortical reactivations, the cortical trace consolidates to full strength (right column) and can retrieve the trace independently of the hippocampus, bringing systems consolidation to an end. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

hippocampus. Theoretical models (Alvarez and Squire, 1994; McClelland et al., 1995) have argued that the existence of such a "dual" system allows fast learning to occur in the hippocampus without interfering with existing structured knowledge, which is slowly extracted by the cortex based on replay of hippocampal traces. There are different views to explain this duality: the hippocampal trace has been proposed to be an index to cortical areas underlying the representation of a memory (Teyler and DiScenna, 1986; Morris, 2006), or alternately as containing a compressed version of the memory which will eventually be consolidated in the cortex (McClelland et al., 1995). Controversies over the role of the hippocampus on the retrieval of episodic memories have also led some to propose changes in this model, such as the "multiple trace theory" (Nadel and Moscovitch, 1997; Moscovitch et al., 2006), which argues that long-term memory stability should be supported by proliferation of multiple memory traces within the medial temporal lobe (along with their respective neocortical connections). Nevertheless, there is usually agreement on the fact that long-term consolidation of memory is brought about by the gradual formation of a more distributed memory trace.

Independently of the explanation, the concept that at least some memories eventually become independent of the hippocampus for retrieval leads to the natural assumption that some form of prolonged communication between the hippocampus and the neocortex is necessary to achieve a cortical representation (Marr, 1971; Wang et al., 2006). The most obvious of these forms of communication is conscious retrieval of the memory (McClelland et al., 1995; Alberini et al., 2007), a fact which is supported by the enhancing effect of context re-exposure on memory persistence (Parvez et al., 2006). Another frequently invoked form of communication, however, is the spontaneous replay of hippocampal firing patterns, which has been shown to occur both shortly after learning in the awake state (Lin et al., 2005; Foster and Wilson, 2006) and during slow-wave and rapid eye movement (REM) sleep after a learning episode (Pavlides and Winson, 1989; Wilson and McNaughton, 1994; Louie and Wilson, 2001; Ribeiro et al., 2004).

Experimental evidence suggesting that late hippocampal activity is necessary for permanent memory storage has been brought forward in recent years. Late disruptions of the hippocampus targeting glutamatergic receptors (Riedel et al., 1999; Shimizu et al., 2000), protein kinases (Wang et al., 2003; Pastalkova et al., 2006) and transcription factors (Taubenfeld et al., 2001) have been shown to impair memory even when started later than 24 h after training. This data suggests that some form of late replay of synaptic activity initially involved in learning is crucial to the maintenance of long-term memory, and led Wittenberg and Tsien (2002) to formulate the concept of "synaptic reentry reinforcement" (SRR). Using computational models, they have suggested that synaptic reactivation in neuronal ensembles could underlie not only maintenance of a memory trace within a network itself (e.g., within the hippocampus) but also lead to the consolidation of the trace in areas connected to the network (such as the neocortex) (Wittenberg et al., 2002) (for a schematic representation of this principle, see Fig. 1). More recently, the same group has provided evidence arguing that the same kind of *N*-methyl-D-aspartate (NMDA) receptor induced reinforcement could also underlie long-term maintenance of the trace in the cortex (Cui et al., 2004), a fact which is also supported by the recent demonstration that injection of a protein kinase M zeta inhibitor in the insular cortex can apparently erase a memory acquired many weeks before (Shema et al., 2007). Such long-term, endogenous reinforcement processes might conceivably be related to memory recovery in models of transient amnesia, as the spontaneous

nature of recovery in many of these models (Squire and Barondes, 1972; Vianna et al., 2001; Lattal and Abel, 2004; Amaral et al., 2007) suggests that an endogenous process would be required to account for such an effect.

CAN THE SLOW SYNAPTIC CHANGES OF SYSTEM CONSOLIDATION ACCOUNT FOR MEMORY RECOVERY FROM TRANSIENT AMNESIA?

The extensive data on transient amnesia after disruptions of consolidation and reconsolidation suggests that a plausible model to explain memory recovery should account for the following features:

1. Either transient or permanent amnesia can result both from interventions in the initial consolidation period (i.e., consolidation blockade) and from interventions during episodes of memory reactivation (i.e., reconsolidation blockade), depending on the experimental protocol used.
2. Transient amnesia seems to occur more frequently after interventions following memory reactivation (i.e., during reconsolidation) than after interventions occurring in the initial consolidation period, which usually result in permanent effects.
3. Memory recovery, when it occurs, can be driven by experimental manipulations (i.e., reminders, cues, context reexposure), but can also happen spontaneously, particularly after postreactivation interventions.

The finding that transient amnesia can be induced by pharmacological manipulations leads to the natural assumption that the memory trace is being partially disrupted by these interventions, in the sense that memory expression is initially impaired, but a part of the trace is left intact and is able to drive retrieval later on. This could be due either to partial disruption of a single memory trace or to disruption of one "version" of the trace if memory traces are assumed to be dual or multiple. The fact that recovery from amnesia can occur spontaneously, meanwhile, strongly suggests that endogenous, long-term processes occurring to memory traces might be responsible for this phenomenon. By assuming that partial disruption of the trace might occur due to the coexistence of different, distributed representations of a memory, and by attributing the spontaneous recovery of memories to the slow, systemic consolidation phenomena underlying the formation of a permanent trace, such as SRR, we will now discuss at least three possible mechanisms through which the experimental findings on transient amnesia might be accounted for.

Partial Damaging of Hippocampal Traces, Followed by Local Synaptic Reinforcement

The simplest explanation for spontaneous memory recovery, which has been proposed in a limited extent by some authors (Nader and Wang, 2006; Tronson and Taylor, 2007) is that reconsolidation blockade could cause partial disruption of a memory trace, but that the network could somehow "rebuild" the original trace from its remaining parts in a later period. In the hippocampus, this has been suggested to involve the CA3 region's capability for pattern completion when partial cues about a learned context are presented (Nakazawa et al., 2002; Nader and Wang, 2006). And, although this rebuilding potential has not been specifically related to long-term consolidation mechanisms, it seems feasible that processes such as SRR occurring in the hippocampus over time could lead to such an effect (Fig. 2A).

Evidence in favor of partial disruptions of the trace underlying transient amnesia comes from the recent demonstration that increasing the number of injections or the dose of a protein synthesis inhibitor after memory reactivation can tip the balance from a transient to a persistent effect (Milekic et al., 2006; Solntseva et al., 2007), suggesting that greater disruption of the trace is associated with permanency of amnesia. The finding that persistence of amnesia can depend on the amnestic agent used, using the same reconsolidation protocol (Cai et al., 2006), might also be explained by different degrees of disruption. It is also noteworthy that almost all studies showing transient memory deficits after reconsolidation disruption in mammals—with a single exception up to our knowledge (Prado-Alcalá et al., 2006)—have used either hippocampal or systemic interventions (which could be thought of as preferentially affecting the hippocampus), while the vast majority of reconsolidation studies involving other structures, particularly the amygdala, have yielded persistent effects (see Tables 1 and 2). Therefore, a central role of the hippocampus in transient amnesia (and possibly in memory recovery) seems to be supported by the literature. Finally, if the degree of trace damage determines the possibility of memory recovery, an interesting possibility to explain the greater persistence of the impairments induced by consolidation blockade, when compared with those induced by reconsolidation blockade, would be that only parts of the original trace might be made labile in reconsolidation, leading to more limited disruption and greater possibility of recovery (Riccio et al., 2006).

The main limitation of such a hypothesis is that it is unclear how a partially damaged network could "find" its missing parts by itself. Rebuilding of the trace could be feasibly aided by cues or reminders, such as re-exposure to the memory context; however, the possibility of spontaneous recovery is not as readily accounted for. Still, if we think of the hippocampus as an index to distributed cortical representations forming a memory trace (Teyler and DiScenna, 1986; Morris, 2006), it is possible that reactivation of separate parts of the trace might eventually lead to a new representation of the ensemble. Alternately, if parts of the trace are weakened but not completely erased, SRR acting on those synapses might also lead to memory recovery. However, the possibility of SRR-induced recovery, especially after postreactivation amnesia, could also be explained by the presence of a partially consolidated cortical trace, as will be discussed in more detail below.

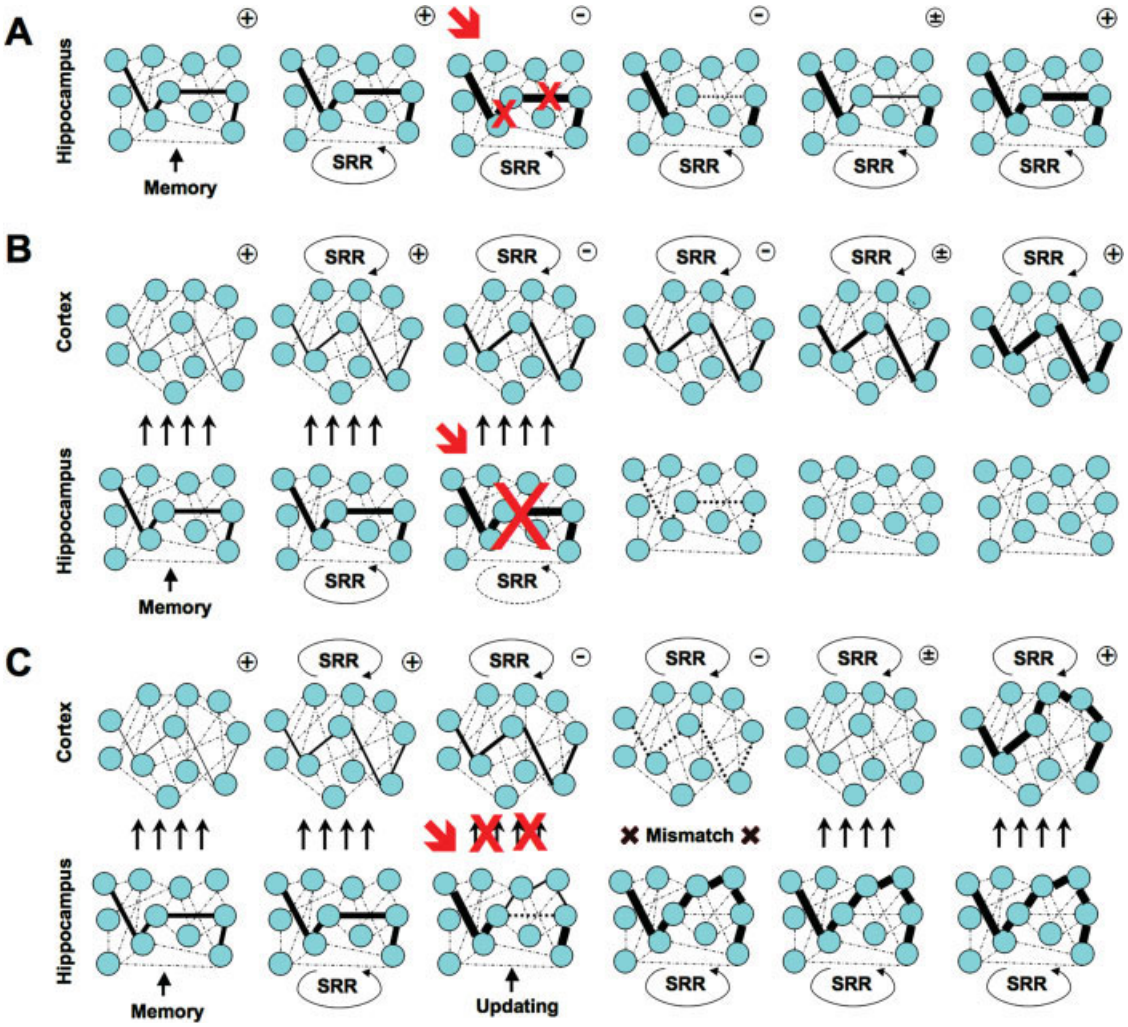

FIGURE 2. Schematic representation of possible mechanisms for transient amnesia. A: Partial damaging of hippocampal traces, followed by local synaptic reinforcement. Represented in the figure is a schematic network of hippocampal neurons (connected circles) encoding a memory trace through a specific pattern of strengthened connection weights (black lines, with line thickness representing connection strength). Capability of the network to retrieve the trace is represented by circles containing "+" (adequate retrieval), "±"; (partial retrieval) or "−" (absent retrieval) signs. The pattern is initially encoded in the left column and rapidly strengthened through local SRR. Disruption of the trace occurs in the third column (large arrow), leading to weakening of part of the pattern (crosses) and impaired retrieval (fourth column). However, local SRR in the network gradually restores the missing connections and leads to memory recovery (sixth column). B: Disruption of the hippocampal trace, with persistence of a partially consolidated cortical representation. Represented are two connected neuronal networks, representing hippocampal (bottom line) and neocortical neurons (top line) encoding a memory trace in their connection weights. The pattern representing the trace is initially encoded in both structures, but while strengthening of the pattern through SRR is rapid in the hippocampus, it progresses more slowly in the neocortex (see Fig. 1). Disruption of the hippocampal trace (third column) causes amnesia – however, a partially consolidated trace persists in the cortex. This trace is initially incapable of driving adequate retrieval due to its weak connection strengths (fourth column); however, through local SRR, it slowly strengthens itself to the point where memory recovery occurs (sixth column). C: Transient hippocampal disruption leading to abnormal hippocampocortical communication and disruption of the cortical trace. Hippocampal and cortical networks are represented, and initial learning occurs as in (B). In the third column, transient disruption of the hippocampus during memory updating impairs adequate transfer of updated information to the neocortex, creating mismatch between the two traces, which leads to decay of the cortical trace and impaired retrieval (fourth column). The hippocampal trace itself remains intact, however, and is able to start consolidation of a new cortical trace through SRR after the drug effect is over (fifth column), eventually leading to recovery of retrieval capability in the cortex (sixth column). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Complete or Partial Damaging of the Hippocampal Trace, With Persistence of a Partially Consolidated Cortical Representation

Another interpretation which has been used to account for transient amnesia findings, albeit usually in other timeframes and settings, is the postulation of dual memory systems. Transience of amnesia in some situations has been used as evidence, for example, that short-term and long-term memory are mechanistically separate, on the basis that it is possible to block formation of short-term memory (lasting only a few hours) while leaving long-term memory intact (Izquierdo et al., 1998, 1999). Transient impairments of retrieval of this type are usually attributed to the fact that different systems—a short-term one depending on post-translational modifications and a long-term one depending on protein synthesis, for example—are responsible for memory expression in each time point. It seems feasible, therefore, to invoke a similar view to explain transient amnesia occurring on a longer time scale, by assuming the existence of a more transient, rapidly consolidating trace (probably dependent on the hippocampus) and a permanent, slowly consolidating one (probably dependent on the neocortex).

Such an explanation has indeed been postulated, although somewhat infrequently, to explain findings of transient amnesia induced by blockade of consolidation (Squire and Barondes, 1972) and reconsolidation (Dash et al., 2004; Amaral et al., 2007). In this case, transient amnesia could occur due to interventions which disrupt the hippocampal trace (which is initially required for memory retrieval) but leave intact a cortical trace which is able to consolidate on its own and eventually reach a point which allows memory retrieval independently of the hippocampus (Fig. 2B). This view accounts well for the evidence indicating that interfering with reconsolidation is more likely to cause a transient memory deficit than blocking the initial period of consolidation, as cortical consolidation could have to reach a threshold point for this effect to happen; therefore, the later the intervention occurs, the more likely it is that memory recovery can occur. It is also compatible with findings showing that biochemical and gene expression changes in the cortex start to occur shortly (i.e., minutes to hours) after a memory is acquired (Izquierdo et al., 1997; Vazdarjanova et al., 2002), and with the view that local SRR occurs in the cortex and is important for memory maintenance (Cui et al., 2004). Finally, it also fits well with the fact that the majority of studies observing transient amnesia have involved interventions targeted at the hippocampus (or systemic interventions which might affect this structure preferentially), as discussed above.

One important point arguing against this hypothesis is the fact that memory recovery usually occurs in a few days, or even hours, in most studies showing transient reconsolidation blockade (Litvin and Anokhin, 2000; Anokhin et al., 2002; Power et al., 2006; Salinska, 2006; Amaral et al., 2007). This is substantially shorter than the length of time systems consolidation is usually thought to require; it may be unlikely, therefore, that the cortical trace should be fully consolidated so quickly, although the fact that the duration of systems consolidation varies considerably among tasks and studies (McClelland et al., 1995) and the finding that it can be sped up to a single day by the existence of preexisting knowledge or "schema" (Tse et al., 2007) make this inconsistency a relative one. Additionally, one might argue that the notion of independent cortical consolidation also goes against the evidence showing that late hippocampal activity (Riedel et al., 1999; Shimizu et al., 2000; Wang et al., 2003; Tse et al., 2007) and communication between the hippocampus and neocortex (Remondes and Schuman, 2004) are vital to long-term consolidation.

Nevertheless, this mechanism can be better reconciled with current views of systems consolidation if one assumes that completion of cortical consolidation can be helped by remaining parts of the hippocampal trace; therefore, partial disruption of the hippocampus could make memory recovery in the cortex more likely and/or faster. This hypothesis, therefore, can extend the previously described one (partial hippocampal disruption) by providing a means for the trace to be reformed; namely, that the cortical trace already exists in a partially consolidated version, and that its interaction with a partially damaged hippocampal trace provides the basis for consolidation of a fully independent cortical memory. Such a view accommodates the possibility of permanent or transient amnesia following injection of amnestic agents, depending on the extent of trace damage and on the timepoint in which disruption occurs. This temporal dependence, on its turn, accounts for the distinction between the usually persistent amnesia induced by consolidation blockade and the frequently transient amnesia induced by reconsolidation blockade without having to resort to mechanistic distinctions between the two phenomena.

Transient Hippocampal Disruption Leading to Abnormal Hippocampo-Cortical Communication and Disruption of the Cortical Trace

If we judge it possible that memory recovery in transient amnesia occurs through consolidation of a cortical trace after disruption of the hippocampus, it is natural that the opposite hypothesis—namely, that the cortical trace could be disrupted and rebuilt on the basis of an intact hippocampal trace—should also be examined. At first glance, this may seem less likely, as much of the evidence of transient amnesia deals with pharmacological manipulation of the hippocampus. However, if reconsolidation occurs while systems consolidation is taking place, it is possible that, even though interventions are directed at the hippocampus, what is disrupted is not the hippocampal trace per se, but the updating of the cortical trace which occurs when the hippocampus encodes new aspects of a memory.

A view of this kind has been expressed in a recent editorial by Eichenbaum (2006), who proposed that reconsolidation blockade might disturb interleaving of new information within a previously established cortical trace, leaving the cortical network susceptible to "catastrophic interference" (McClelland et al., 1995) and corruption of the trace. Although the phenomenon of transient amnesia was not considered in this case,

it seems feasible that corruption of the cortical trace could occur with partial or complete sparing of the hippocampal trace, which could eventually lead to memory recovery. For instance, injection of an amnestic agent in the hippocampus when it is engaged in updating a memory could lead it to send erroneous output to the neocortical network underlying the memory, thus disturbing the cortical trace and disrupting retrieval. Alternately, amnesia could occur due to interference with the cortical representation as it tries to integrate the original (intact) memory trace with the new (corrupted) memory encoded at the time of the amnestic intervention. Finally, updating of the trace could occur in the hippocampus without this information adequately reaching the cortex due to the action of the pharmacological agent; this would create mismatch between the representations in the hippocampus and cortex and might also lead to corruption of the cortical trace (Fig. 2C). In any of these cases, the original hippocampal trace might remain intact and could start the process of systems consolidation anew over time, eventually leading to memory recovery.

Although feasible, this account of transient amnesia seems harder to explain from a cellular point of view, as it is not clear how amnestic agents such as protein synthesis inhibitors would interfere with hippocampo-cortical communication at a cellular level without disrupting the hippocampal trace significantly. Another thing to consider is that, for such a view to account for the possibility of persistent amnesia following blockade of consolidation or reconsolidation, one would probably have to assume that the hippocampal trace itself is disrupted in these cases, but not in those of transient amnesia, which does not represent a particularly parsimonious explanation (especially when one considers that the pharmacological agents can be the same in both cases). Nevertheless, the possibility of cortical trace corruption during interleaving of information should be taken into account as a possible mechanism involved in reconsolidation blockade, as it can also help to explain other data in the reconsolidation field, such as the requirement of memory updating for reconsolidation blockade to occur (Eichenbaum, 2006; Morris et al., 2006) and the possibility of reconsolidation of remote memories in some studies (Debiec et al., 2002; Debiec and LeDoux, 2004).

A GENERAL MODEL FOR TRANSIENT AMNESIA

Independently of which of the mechanisms above is judged more likely to account for transient amnesia, a model in which memory recovery in hippocampus-dependent tasks is based on the reinforcement processes underlying systems consolidation basically predicts that the extent of memory disruption and the time at which it occurs during the course of memory consolidation (taken here to include both synaptic and systems consolidation) should be central factors in determining the probability of recovery of an impaired memory trace. Therefore, the specific predictions of such a model for interventions in different time points during the life of a memory trace would be the following:

1. Early disruptions of the hippocampus—such as those occurring during the initial consolidation period—will usually cause permanent damage, either because (a) the whole hippocampal trace, and not parts of it, is labile at that time or because (b) a cortical representation of the trace will also be prevented from forming at such an early time period. Nevertheless, the possibility of partial disruption with residual memory traces leading to recovery is not excluded; therefore, results suggesting that amnesia after consolidation blockade can be transient, especially in the presence of reminders, can still be accounted for.
2. Disruptions of the hippocampus at an intermediate period (i.e., within the duration confines of systems consolidation) require the trace to be reactivated and made labile to have an effect, as shown by virtually all reconsolidation studies. Once this effect is achieved, both permanent and transient amnesia are possible: the probability of memory recovery in this case will depend both on the extent of trace disruption (with greater damage leading to a greater probability of permanency) and on the extent of consolidation of a long-term memory trace at the time of disruption (with more advanced consolidation leading to a greater probability of recovery). This accounts for the apparently contradictory data on the transience or persistence of amnesia following reconsolidation blockade. Moreover, differences between the results of interventions during consolidation and reconsolidation concerning the persistence of amnesia are explained by the greater extent of trace consolidation at the time points in which reconsolidation blockade is performed.
3. Late disruptions of the hippocampus (i.e., after systems consolidation is complete) will usually have no effect, as a cortical representation of the trace is consolidated and sufficient for retrieval at this time. This has indeed been the case in most studies which evaluated the effect of memory age on reconsolidation sensitivity (Milekic and Alberini, 2002; Eisenberg and Dudai, 2004; Suzuki et al., 2004; Boccia et al., 2006; Frankland et al., 2006), although it is worth noting that post-reactivation interventions as late as 45 days after training (Debiec et al., 2002) have occasionally been shown to cause amnesia. The possibility of such remote effects can conceivably be due to the variation in the timeframe of systems consolidation across different tasks, species and training conditions (McClelland et al., 1995) – with the latter, at least, having already been shown to influence such a "reconsolidation gradient" (Suzuki et al., 2004; Frankland et al., 2006). Alternately, the possibility of disrupting more remote memories could also be related to the degree to which encoding of new information makes the cortical trace labile and prone to corruption, as suggested previously (Debiec et al., 2002; Eichenbaum, 2006).

As a proof of principle that our general model fits into currently accepted views of systems consolidation, we have used an

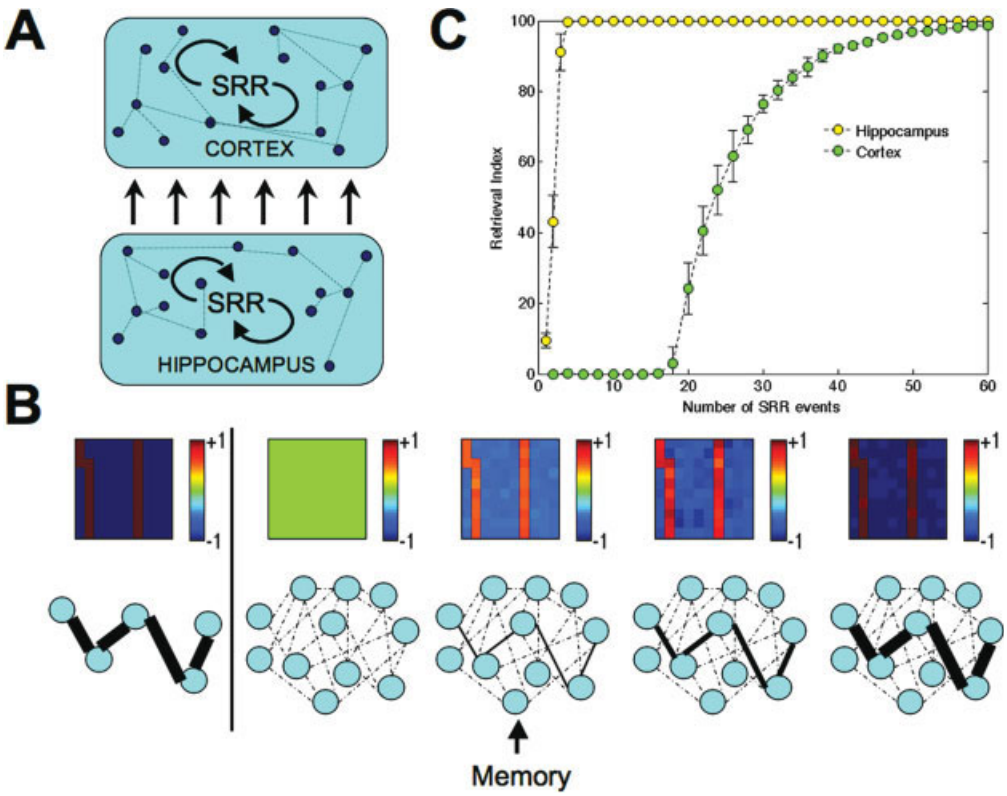

FIGURE 3. An outlook of the model used in the computational simulations. A: General view of the model, adapted from the original SRR model by Wittenberg et al. (2002). The network consists of two interconnected connectionist networks of 100 neurons, representing the hippocampus and neocortex, respectively, which encode a memory trace in their connection weights. After initial memory acquisition, SRR occurring in each subsequent reactivation of the network is responsible for progressive strengthening of the trace in both structures. Hippocampal neurons are initially responsible for retrieval due to their faster learning rate, and gradually help to strengthen the trace onto the cortex through reactivation. B: Learning in the model. An activation pattern, representing the activation states of a 10 × 10 neuron matrix (left of the black line) is initially presented to the network at its initial, resting state (first column to the right of the black line), changing the connection weights among neurons (bottom row). On each subsequent random initialization of the network (subsequent columns to the right), altered connection weights tend to bring the network to an activation state approaching the one initially presented. Each reactivation strengthens subsequent retrieval of the trace (top row) by causing further strengthening in the connection weights of activated neurons. After a certain number of reactivations, the retrieved pattern is very similar to the one initially presented (right column). C: Learning rates in the model. *X*-axis represents the number of reactivations of the network, while *Y*-axis represents independent retrieval of the pattern in the hippocampal and cortical networks, as measured by a retrieval index (described in the appendix). Circles and error bars represent mean ± standard deviation (SD) for 20 simulations with random initial conditions. Because of differential learning rates, connection strengths in the hippocampal network evolve faster and reach optimal retrieval at about five reactivations. Strengthening of the trace in the cortical network is much slower, meanwhile, taking about 50–60 reactivations to evolve to full strength; therefore, during an initial period, the cortical network is dependent on hippocampal activity for retrieval of the pattern and SRR to occur. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

adaptation of the SRR computational model originally described by Wittenberg et al. (2002) to test whether the two proposed variables (extent of trace disruption and time of intervention) can affect the transience or permanency of amnesia resulting from disruption of the hippocampal trace in this model. Briefly, the model consists of two interconnected connectionist networks (Hopfield, 1982, 1984; Cohen and Grossberg, 1983) representing hippocampal and cortical neurons (Fig. 3A). A memory trace is initially "burned" into the hippocampal network by the presentation of an activation pattern, which strengthens the connections between simultaneously activated neurons. This change in connection weights attracts the hippocampal network to the learned pattern at each subsequent initialization of the network, with reinstatement of the pattern in the hippocampus also attracting the cortical network to the same pattern. Retrieval of the pattern at each initialization cause further strengthening of synaptic weights in both networks, and therefore allows retrieved patterns in both structures to get closer to the original one after each subsequent reactivation (Fig. 3B). This strengthening process happens rapidly in the hippocampus, but takes much longer in the cortex, where learning rates are slower; therefore, the model allows for a period of "systems consolidation" in which the hippocampus is needed to drive retrieval

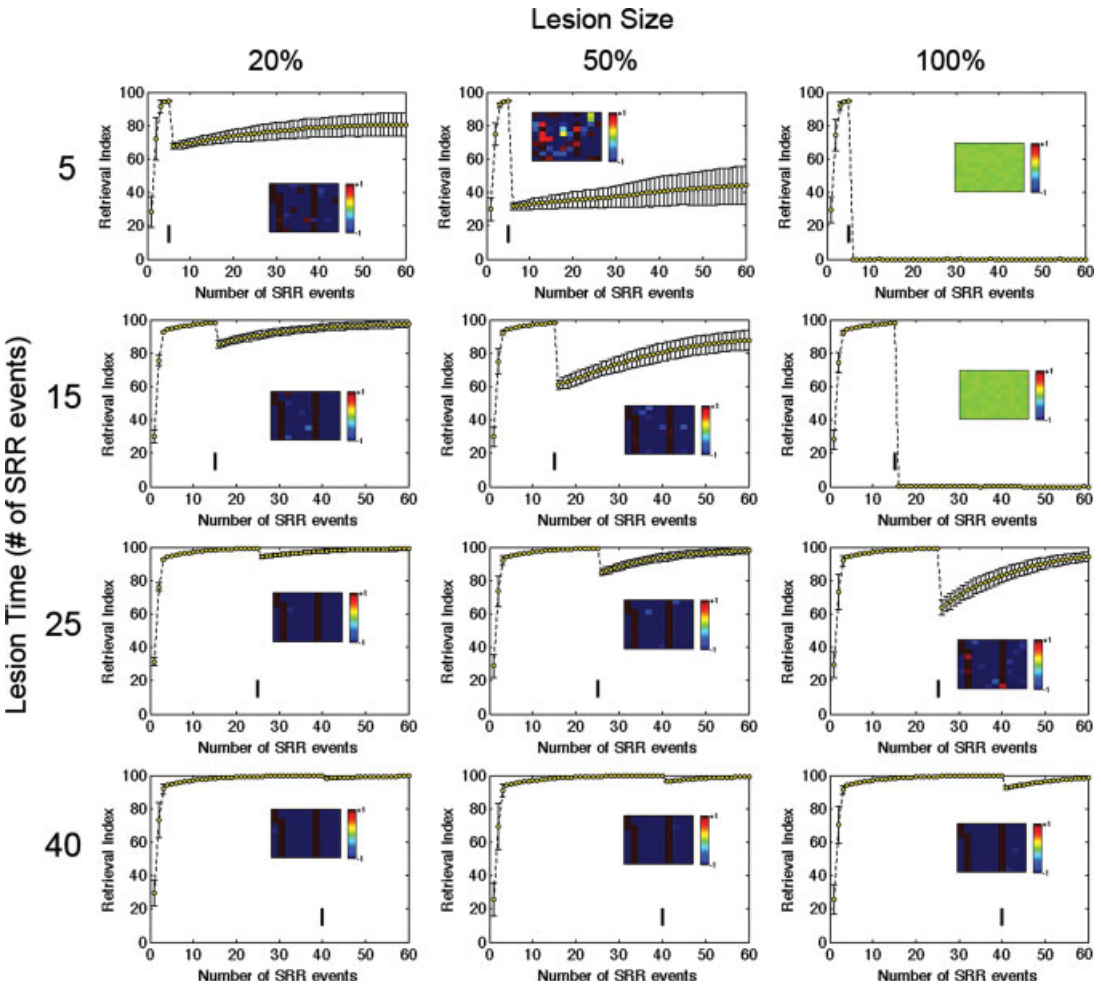

FIGURE 4. Results of learning simulations in the computational model using different time points and extents of hippocampal trace disruption. Learning in the model occurs as described in Figure 3, with successful retrieval indicated by the cortical network reaching the pattern shown in Figure 3B. Rows indicate lesions (disconnection of part of the hippocampal neurons from the rest of the network) at different times after initial learning, as measured by number of SRR events before the lesion, while columns indicate the percentage of hippocampal neurons disconnected for each simulation. *X*-axis in each graph represents time as measured by number or reactivations, while *Y*-axis represents the retrieval index of the cortical network (see Appendix). Dots represent mean ± SD of retrieval indexes at each time point obtained from 20 simulations with random initial conditions. Black lines represent the time point in which hippocampal disruption occurs in each case. Also shown within each graph is the retrieved pattern after 60 reactivations for a representative simulation in that condition. Results indicate that, for early disruptions, occurring near the end of the hippocampal consolidation period (after five reactivations, top row), little recovery occurs, except for a small improvement in some (but not all) cases after very small lesions (20%). On the other hand, at a late time point (after 40 reactivations, bottom row) hippocampal disruptions of all magnitudes have little effect, as cortical consolidation is already at an advanced stage. Intermediate disruptions after 15 reactivations can cause reversible or irreversible impairments in retrieval, depending on the extent of disruption, while retrieval impairments caused by disruptions after 25 reactivations are always reversible, with smaller lesions leading to smaller dips in retrieval and faster recovery. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of the trace in the cortical network (consequently strengthening the cortical trace) (Fig. 3C). Hippocampal "lesions" in the model are simulated by cutting off a percentage of the hippocampal neurons from the rest of the network at various time points, and retrieval is measured after each initialization by comparing the pattern reached by the cortical network with the original pattern. For further methodological details on the computational model, we refer the reader to the appendix.

Data originating from computer simulations are presented in Figure 4. As can be seen in the figure, our results largely confirm the predictions made earlier concerning the effects of hippocampal trace disruptions at different time points. Early interventions occurring during or shortly after the hippocampal consolidation period (e.g., after five reactivations) cause retrieval impairments which show little recovery, except for a limited range of initial conditions in small disruptions (e.g., 20% of hippocampal neurons). Hippocampal disruptions occurring at

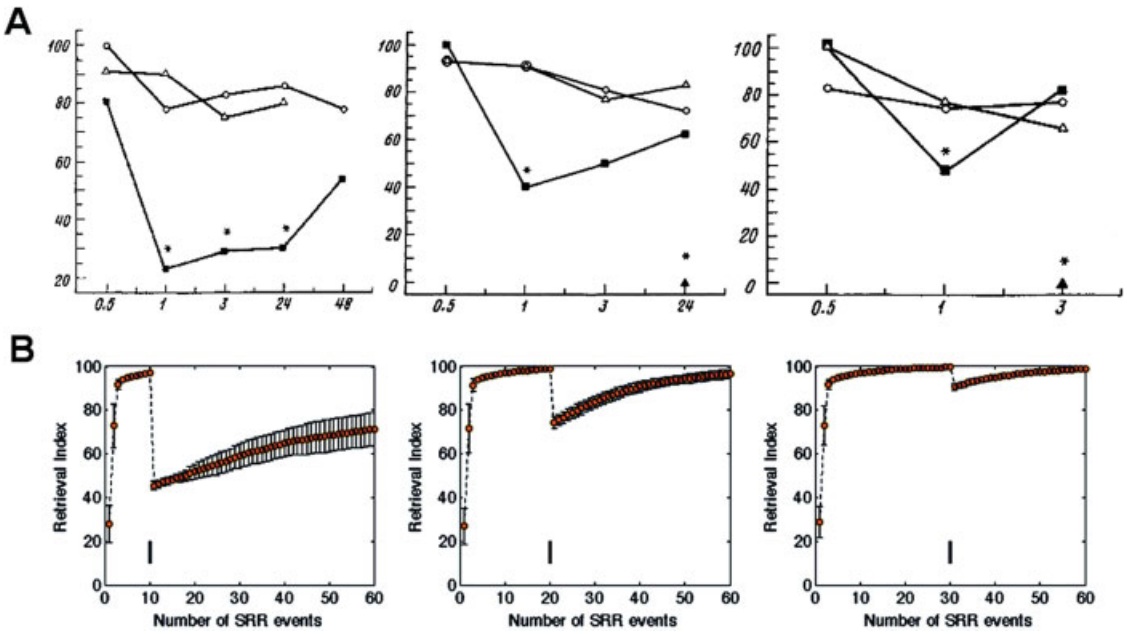

FIGURE 5. Effect of the interval between training and post-reactivation interventions on the time course of transient amnesia. A: Effect of postreactivation injections of cycloheximide in the intermediate medial mesopallium (IMM, formerly known as the intermediate ventral medial hyperstriatum) of day-old chicks on performance in a passive avoidance task (shown in the *Y*-axis as percent of animals presenting avoidance behavior) at various times after the injection (shown in the *X*-axis as hours). The three graphs show task performance in animals receiving postreactivation cycloheximide (black squares), postreactivation saline (white circles) or cycloheximide with no reactivation (white triangles) at 2 h (left graph), 24 h (middle graph), and 48 h (right graph) after training. Impairments induced by early reconsolidation blockade (2 h) in the postreactivation cycloheximide group show partial recovery 48 h after the intervention, while those induced by intermediate blockade (24 h) recover in 24 h and those induced by late blockade (48 h) are mild and short-lasting, recovering fully after 3 h (reproduced from Litvin OO, Anokhin KV, Neurosci Behav Physiol, 2000, 30, 671–678. © Springer Science and Business Media, reproduced by permission). These results correlate well with the general trend observed in our computational results, shown below for comparison. B: Computer simulations showing the effect of disconnecting 50% of hippocampal neurons (as was performed in Fig. 4) after 10, 20, or 30 reactivations, respectively. Partial recovery from amnesia is observed in the earliest lesion, nearly complete recovery is observed in the second case and full recovery occurs in the third case. As in the experimental results, both the degree of amnesia and the time for memory to recover are inversely proportional to the interval between training and the amnestic intervention. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the time when "systems consolidation" in the model is nearing completion (e.g., after 40 reactivations), on the other hand, have little effect on subsequent retrieval, irrespective of their magnitude. Finally, interventions at intermediate time points (e.g., after 15 reactivations), consistent with the timeframe in which reconsolidation blockade is usually performed experimentally (i.e., between the end of the hippocampal—or "synaptic"—consolidation period and the end of the cortical—"or systems"—consolidation period), can cause either transient or permanent amnesia, depending on the extent and time of disruption, with larger and earlier disruptions leading to a greater probability of permanent effects.

Moreover, the simulations performed yield at least one additional prediction, which is that the degree of retrieval impairment and the time for memory to recover following reconsolidation blockade (in the cases in which it is transient) should decrease as the time between training and the amnestic intervention increases (for an example, compare similar lesions at 15 and 25 reactivations in Fig. 4). To our knowledge, only one study in which transient amnesia was observed after reconsolidation blockade has tested the effect of performing this intervention at different times after training (Litvin and Anokhin, 2000). Remarkably, its findings (reproduced in Fig. 5A) are quite consistent with the prediction generated by our simulations (shown for comparison in Fig. 5B): blocking reconsolidation 2 h after training led to amnesia which recovered partially after 2 days, whereas the same intervention performed 24 or 48 h after training led to recovery in 1 day or 3 h, respectively. The degree of amnesia in this study was smaller with increasing memory age at the time of reconsolidation blockade, a fact which is also consistent with our results. Finally, memory recovery, irrespective of the time that reconsolidation blockade was performed, occurred at a relatively constant time interval from the original training session, a trend which is also compatible with our simulations, in which recovery occurs at a relatively constant number of network reactivations.

Other predictions of our model, such as the possibility of permanent and transient amnesia with similar interventions at

different time points, remain to be tested experimentally. For this to happen, however, the development of experimental models of reconsolidation blockade in which both persistent and transient amnesia can be observed depending on protocol variations - which up to now have been scarce (Cai et al., 2006; Milekic et al., 2006) is likely to be necessary.

CONCLUSIONS

In this article, we have proposed a model which can encompass the possibility of permanent or transient amnesia after disruptions of consolidation and reconsolidation in hippocampus-dependent tasks, based on the assumption that memory recovery is intrinsically linked to the mechanisms underlying systems consolidation. Although a more detailed explanation of the mechanisms of recovery is still under debate, and is likely to depend on greater knowledge about memory encoding on a systems level, the general framework of our model—namely, that the extent of trace disruption and the time in which it occurs are central factors in determining the possibility of memory recovery—seems to account well for much of the apparently contradictory data in the reconsolidation field concerning (a) the possibility of transient or permanent amnesia after reconsolidation blockade; (b) the greater possibility of memory recovery after reconsolidation blockade when compared with consolidation blockade and (c) the effect of memory age on sensitivity to reconsolidation. Moreover, although the proposed model is limited to memories processed by the hippocampus, this fact is in agreement with the finding that transient amnesia is usually observed after hippocampal or systemic interventions in hippocampus-dependent tasks, possibly because of the particular role played by this structure in the processes leading to long-term memory consolidation.

We believe that such a model has two significant advantages in that it (a) circumvents the "storage versus retrieval" debate, by viewing memory loss and recovery within the framework of distributed traces and endogenous reinforcement and (b) avoids the need to invoke different mechanisms for amnesia after consolidation and reconsolidation, therefore conforming to the principle of parsimony. We also believe that it reiterates the view that memory reconsolidation and consolidation should not be viewed as separate entities, as they are likely to represent different aspects or parts of the long-term processes underlying memory storage at the systems level. Therefore, studying reconsolidation and the possibility of recovery from its disruption, not as an artifact or caveat but as a real phenomenon, could provide a unique window to study these processes and further our understanding of long-term memory consolidation and storage.

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APPENDIX

Computational Model Description

The model we employed is very similar to the SRR model described by Wittenberg et al. (2002), with small adaptations. We refer the reader to this reference for further details about its functioning.

In this model, the process of memory consolidation happens as in the classical attractor memory model (Hopfield, 1982, 1984; Cohen and Grossberg, 1983), with some adaptations included to incorporate features of synaptic reinforcement processes. Thus, synaptic plasticity extending beyond initial memory acquisition is taken into account, as is the destabilizing effect on stored memory of the dynamic turnover of synaptic proteins (Wittenberg et al., 2002). The model architecture consists of a cortical and a hippocampal network, as shown schematically in Figure 3A, with each network consisting of 100 neurons.

In all simulations, each network evolves according to the following system of differential equations:

$$\tau \frac{du_{x,i}}{dt} = -u_{x,i} + \sum\nolimits_j w_{x,ij} V_{x,j} + I_{x,i} \quad \text{(A1)}$$

$$\Delta w_{x,ij} = -\gamma_x w_{x,ij} + \eta_x V_{x,i} V_{x,j} + \xi \quad \text{(A2)}$$

where $x = C$ or H labels cortical or hippocampal variables, $u_{x,i}$ represents the membrane potential of neuron i in network x, $V_{x,i} = \tanh(\beta u_{x,i})$ represents its firing rate and τ represents a time constant defining the time scale of changes in membrane potentials. According to the classical interpretation of this model, $V_{x,i}$ can be thought as a moving time average of the instantaneous firing rate, which is expressed as deviations from the basal firing rate, assuming both negative and positive values. The first term in Eq. (A1) ($-u_{x,i}$) causes the membrane potential to decay to its resting state (0 mV in this formulation). The second term, $\sum_j w_{x,ij} V_{x,j}$, represents the changes in the membrane potential due to the firing rate of presynaptic neurons, weighed by the strength of the synaptic connection ($w_{x,ij}$). Each network is modeled as being fully connected. The last term, $I_{x,i}$, represents synaptic inputs coming from the other network or from a sensory input. For simplicity, a one-to-one mapping between the hippocampus and the cortex was used; therefore, this term in the cortical network is represented by the following equation:

$$I_{C,i} = \alpha V_{H,i} \quad \text{(A3)}$$

The synaptic weight matrix in both networks is updated discretely after an attractor state has been reached, and this update occurs according to Eq. (A2). The first term in Eq. (A2) ($-\gamma_x w_{x,ij}$) represents synaptic turnover, which acts towards erasing the memory traces, whereas the second term ($\eta_x V_{x,i} V_{x,j}$) models the extended synaptic plasticity related to SRR. The last term (ξ) is a white noise process. Therefore, γ determines the rate at which changes in synaptic weights decay over time, while η represents the learning rate (i.e., the rate at which activity changes the synaptic weights).

In this formulation, there are two stages of hippocampal memory formation: initial memory acquisition and memory reactivation. Memory acquisition can be modeled by presenting

inputs to the hippocampal network (i.e., by setting $I_{H,i}$ properly), which is intended to model the presence of sensory inputs. This learning period causes initial changes in the hippocampal synaptic weight matrix ($w_{H,ij}$). After the initial learning period, all hippocampal inputs ($I_{H,i}$) are set to zero, and the growth of the memory trace is dependent on its continuous reactivation through SRR process. We note, however, that the learning period can be equivalently modeled by initializing the hippocampal network with the memory trace stored weakly as $w_{H,ij} = \varepsilon I_{H,i} I_{H,j}$, $I_{H,i} = -1$ or 1, which was the approach used in the present study. The cortical synaptic weight matrix is initialized with uniform random entries between $-\varepsilon$ and ε. After each SRR event, membrane potentials in the networks are randomly reinitialized, with $u_{x,i}$ chosen from a uniform distribution on the interval $[-0.5, 0.5]$.

Retrieval of the memory trace by the model is evaluated by a retrieval index (RI), which is defined by the following formulas:

$$\Psi(V_C) = \frac{1}{2N} \sum_{i=1}^{N} \| V_{C,i} - I_{H,i} \|$$

$$RI(V_C) = 100 + 400\Psi(V_C)(\Psi(V_C) - 1) \qquad \text{(A4)}$$

where N is the cortical network size ($= 100$), $I_{H,i}$ ($= -1$ or 1) is the pattern to be stored, and $V_C = (V_{C,1}, \ldots, V_{C,N})$ refers to the cortical network activity after achieving the steady state. RI approaches its maximum values when the term $V_{C,i} - I_{H,i}$ for each cortical neuron has a value of either 0 (perfect similarity between the achieved and desired activation states) or 2 (complete dissimilarity between both states). This is meant to circumvent the problem of eventual encoding of "mirror patterns" due to the fact that $V_{x,i}$ can assume both positive and negative values. Using the retrieval function described earlier, both solutions will yield a perfect RI of 100, while for random activation patterns the average value of the term $V_{C,i} - I_{H,i}$ for each neuron will be 1, leading to an expected RI value of 0. Therefore, successful retrieval in our model is defined as the cortical network being able to reach either the right attractor or its perfect mirror pattern.

To simulate the effect of hippocampal lesions on memory retrieval by the cortical network, we set $u_{H,i} = 0$ [instead of using Eq. (A1)] after the lesion time under study for a number of indexes i depending on the size of the lesion. To obtain independent retrieval indexes for the cortical network, as shown in Figure 3C, we have set $I_{C,i} = 0$ for all i at each time point studied. Retrieval indexes for the hippocampal network in the same figure were obtained by applying the RI function shown in Eq. (A4) to the hippocampal activity V_H.

Model parameters in the simulations were the following: $\tau = 1$, $\gamma_H = 0.02$, $\gamma_C = 0.008$, $\eta_H = 0.02$, $\eta_C = 0.0007$, $Var(\xi) = 0.0001$, $\beta = 1$, $\alpha = 2$, $\varepsilon = 0.0104$. As one can see, therefore, the cortical and hippocampal networks differ in two important aspects: (a) decay of synaptic weights is faster in the hippocampus than in the neocortex due to the differences in γ, and (b) the learning rate in the hippocampal network is much faster than in the cortex, in which synaptic weights are updated much more slowly. This kind of approach to differences between hippocampal and cortical learning has been used in previous models of two-structure learning (McClelland et al., 1995; Alvarez and Squire, 1994), as it allows the model to incorporate the main features of systems consolidation. More specifically, this causes memory retrieval in the model to be initially dependent on the attractor being reached by the hippocampal network, leading to retrieval in the cortex and strengthening of the cortical trace. After a number of reactivations, changes in cortical synaptic weights reach a point in which they can drive retrieval by themselves, leading the period of "systems consolidation" to a closure.

All simulations included in the article were performed using MATLAB 7.0 software by MathWorks, Inc.