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Rites of Passage of the Engram: Reconsolidation and the Lingering Consolidation Hypothesis

Review

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Memory consolidation refers to the progressive stabilization of items in long-term memory as well as to the memory phase(s) during which this stabilization takes place. The textbook account is that, for each item in memory, consolidation starts and ends just once. In recent years, however, the notion that memories reconsolidate upon their reactivation and hence regain sensitivity to amnestic agents has been revitalized. This issue is of marked theoretical and clinical interest. Here we review the recent literature on reconsolidation and infer, on the basis of the majority of the data, that blockade of reconsolidation does not induce permanent amnesia. Further, in several systems, reconsolidation occurs only in relatively fresh memories. We propose a framework model, which interprets reconsolidation as a manifestation of lingering consolidation, rather than recapitulation of a process that had already come to a closure. This model reflects on the nature of consolidation in general and makes predictions that could guide further research.

Memory consolidation refers to the progressive postacquisition stabilization of long-term memory, as well as to the memory phase(s) during which such presumed stabilization takes place (McGaugh, 2000; Dudai, 2004). The notion that fresh memories require time to stabilize and that such traces are prone to interference by physical or chemical agents, which lose their effectiveness with the passage of time, is an ancient one (e.g., Quintillian, *Institutio Oratoria*, 1C AD). The systematic investigation of this phenomenon, however, gained momentum only at the beginning of the last century (Muller and Pilzecker, 1900; Burnham, 1903). In so doing, it received more attention in mainstream neurobiology than in mainstream psychology of memory (Dudai, 2004; Wixted, 2004). From its outset, the generic idea of consolidation referred to two dissociable temporal domains: fast, completed within minutes to hours after training, and slow, lingering many days or weeks afterward. This dissociation culminated in what is currently referred to as "synaptic," or "cellular consolidation," apparently a primitive of biological memory machines, and "systems consolidation," which characterizes memories subserved by corticohippocampal circuits (McClelland et al., 1995; Dudai and Morris, 2000). As indicated below, this type-dichotomy now deserves renewed scrutiny.

The notion of consolidation, despite occasional surges of blasphemy (discussed in Dudai, 2004), consolidated rather well in the collective memory of the neuroscience community and practically attained the status of a tenet. The textbook account of cellular consolidation goes like this: in the course of training or immediately afterward, molecular cascades triggered by new experience induce synaptic and cell-wide alterations, which render the engram immune to the consequence of molecular turnover, hence permitting it to persist in the long term; the road to persistence is assumed to pass through posttranslational modifications, modulation of gene expression, and probably morphological synaptic remodeling (Goelet et al., 1986; Dudai, 2002a). Furthermore, so goes the Zeitgeist, for any memorized item, consolidation starts and ends just once. This assumption is currently the focus of a heated debate in the neurobiology of memory. The resolution of this debate is of profound relevance not only to fundamental issues in memory research, e.g., the nature of memory persistence, but also to potential applications, e.g., targeted erasure of stubborn traumatic memories.

The hypothesis that memories reconsolidate, hence that the aforementioned "one-item one-consolidation" assumption is invalid, was born almost 40 years ago (Misanin et al., 1968; Schneider and Sherman, 1968). It drew much energy from prominent research teams for about a decade, until practically demoted by the majority vote. For years it remained the topic of only a very modest stream of publications (reviewed in Sara, 2000; Dudai, 2004). But ultimately the debate was revitalized. This occurred mainly as a consequence of a report in a high-visibility journal that consolidated, long-term conditioned fear in the rat can be blocked again upon its retrieval by microinfusion of a consolidation blocker, the protein synthesis inhibitor anisomycin, into the brain circuit assumed to encode the memory (Nader et al., 2000). Although the protocol and outcome of this experiment did share much in common with earlier reconsolidation reports, this time, the experiment involved targeted perturbation of an identified neural circuit that subserves a well-characterized learning task. Since then, times have changed for reconsolidation: whereas in the period 1990–1999, only six papers mentioned the term in their title, keywords, or abstract, no less than 45 did so in the period 2000–2004, and 2004 is not yet over (admittedly, about 30% of these are reviews, commentaries, and discussions—a statistics unfortunately only reinforced by the present discussion, yet this still leaves over 30 new research reports). This accumulating body of new data renders it pertinent to ask: Is reconsolidation real? If so, what does it mean? And can we indeed use consolidation blockers to wipe out old memories after their reactivation?

In this paper, we will first briefly review the recent literature on reconsolidation. We do not intend to critically analyze individual studies. Rather, we will attempt to extract a few general conclusions. It would be only fair to advise the reader from the outset that, in this highly dynamic field, disagreement on conclusions and even on methodology is fairly common and sometimes loud; yet, we do think that overall the data so far justify

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Table 1. Blockade of Reactivated Long-Term Memory by Protein Synthesis Inhibitors

System	Reactivation, Time Posttraining	Inhibitor	Drug Administration	Reference
Elemental fear conditioning, rat	1, 14 days	anisomycin	lateral and basal amygdala	1
Contextual fear conditioning, rat	3, 15, 45 days	anisomycin	hippocampus	2
Contextual fear conditioning, mouse	24 hr	anisomycin, puromycin	hippocampus	3[a]
As above	24 hr	anisomycin	s.c.	4
As above	24 hr	anisomycin	i.p.	5
Passive avoidance, rat	48 hr	anisomycin	i.p.	6
As above	2, 7 days[b]	anisomycin	s.c.	7
Passive avoidance, chick	2, 24, 48 hr[c]	cycloheximide, anisomycin	intracerebrally	8, 9
Conditioned taste aversion, rat	3 days[d]	anisomycin	insular cortex	10
As above	3 days	anisomycin	basolateral amygdala	11
Spatial learning, mouse	24 hr	anisomycin	i.p.	5
Classical conditioning, *Hermissenda*	4 hr	anisomycin	bath application	12[e]
Contextual fear conditioning, *Chasmagnathus*	24 hr	cycloheximide	pericardial sac	13[f]

In this as well as in the tables below, for the sake of brevity, only data published since the year 2000 are compiled; see text. References: 1, Nader et al., 2000; 2, Debiec et al., 2002; 3, Fischer et al., 2004; 4, Lattal and Abel, 2004; 5, Suzuki et al., 2004; 6, Taubenfeld et al., 2001; 7, Milekic and Alberini, 2002; 8, Litvin and Anokhin, 2000; 9, Anokhin et al., 2002; 10, Eisenberg et al., 2003; 11, Bahar et al., 2004; 12, Child et al., 2003; 13, Pedreira et al., 2002.

[a] Fischer et al. interpret their results as enhanced extinction.

[b] Memory reactivated 14 and 28 days after training was unaffected; see text and Table 3.

[c] A reminder given 2 hr after training was considered in this system to tap into a process relevant to reconsolidation. The effect 48 hr after training was smaller, see text.

[d] Reconsolidation was apparent only after training that did not promote experimental extinction, see text.

[e] Memory was considered consolidated 4 hrs posttraining in this system

[f] Reconsolidation was apparent only after training that did not promote experimental extinction, see Pedreira and Maldonado (2003).

the conclusions we make. We will then proceed to propose a framework model, which addresses the aforementioned questions and is intended to serve as a heuristic platform for further research.

The Basic Re-Findings

Reports of reconsolidation from the late 1960s until a few years ago were recently reviewed (Sara, 2000; Nader, 2003; Dudai, 2004) and need not be rereviewed here. Instead, we will focus on the more recent studies. The well-established, standard type of consolidation blocker used in memory consolidation experiments is a protein synthesis inhibitor (Davis and Squire, 1984). Anisomycin is the most popular, being considered a relatively specific inhibitor that blocks the peptidyl transferase reaction on the ribosome; other inhibitors are also occasionally used, including puromycin, whose site of action overlaps that of anisomycin, and cycloheximide, which blocks the translocation reaction on the ribosome. None of these agents is completely specific (e.g., Kyriakis et al., 1994).

Table 1 lists the new wave of experimental evidence, accumulated since the year 2000, on blockade of long-term memory by inhibition of protein synthesis immediately after memory reactivation. Most of the studies used anisomycin. In only a few cases was the level of protein synthesis inhibition measured in situ, but local microinfusion of similar concentrations established inhibition of >90% at the target (e.g., Rosenblum et al., 1993). The outcome of systemic administration is more problematic. All in all, since different inhibitors were used, the common denominator of which is protein synthesis inhibition, it is reasonable to assume that the effect on behavior is indeed a direct or indirect consequence of this inhibition. It can be seen that (1) a substantial number of laboratories find that, upon reactivation in retrieval, performance guided by specific items in memory is markedly suppressed by the application of the protein synthesis inhibitors, leading to what could be considered, for the sake of discussion, postreactivation amnesia; (2) this phenomenon is reported for a variety of species, ranging from invertebrates to primitive vertebrates to rodents to humans; (3) all the studies listed in Table 1 are based on punishment or aversive training (but see Table 2). (4) Memory reactivation time was commonly a day after training (reflection of the cellular biological belief that memory at 24 hr is already long-term, discussed in Dudai, 2002b), but some studies sampled memory a few days or even weeks after training. Even without delving into the specifics of each study, given the latest surge of reports, let alone combined with earlier studies, the phenomenology clearly deserves further scrutiny.

Cellular and Molecular Signatures

Although in the neurobiology of memory blockade of long-term memory by transient inhibition of protein synthesis is used as a defining criterion for consolidation, many other molecular targets are involved. Other inhibitors could therefore be used to block consolidation or postulated reconsolidation (Dudai, 2004). In recent years, attempts have been made to identify molecular mechanisms of reconsolidation by using inhibitors of cellular targets ranging from receptors and channels to intracellular signal transduction cascades, transcription factors, and immediate early genes (Table 2). Most interesting

Table 2. Cellular and Molecular Signatures of Consolidation and Reconsolidation

System	Molecular Process or Entity	Role in Consolidation	Role in Reconsolidation	Reference
Multiple	protein synthesis	required	required	many groups, see text
Passive avoidance, young chick, cerebrum	glycoprotein synthesis	required	required[a]	1
Instrumental respiratory behavior, identified neuron, *Limnaea stagnalis*	RNA synthesis	required	required	2
Classical conditioning, *Hermissenda*, systemic	RNA synthesis	required[b]	required[b]	3
As above	CAMs	required[b]	required[b]	3
Contextual fear conditioning, genetically engineered mouse	CREB	required	required	4
Inhibitory avoidance, rat hippocampus	C/EBPβ	required	not required	5
Contextual fear conditioning, rat hippocampus	BDNF	required	not required	6
As above	Zif268	not required	required	6
Object recognition, Zif269 mutant mouse	Zif268	required	required	7
Object recognition, rat brain, systemic	ERK	required	required	8
Inhibitory avoidance, mouse brain, systemic	HACU	required	required	9
Conditioned taste aversion, rat basolateral amygdala	PKA	required	required	10
Contextual fear conditioning, *Chasmagnathus*, systemic	NMDAR	required	required	11
Contextual fear conditioning, mouse, systemic	NMDAR	required	required	12
As above	CB1, LVGCC	not required	not required[c]	12

Abbreviations: BDNF, brain-derived neurotrophic factor; CAMs, cell adhesion molecules; CB1, cannabinoid receptor 1; C/EBPβ, CCAAT enhancer binding protein β; CREB, cAMP-response element-binding protein; ERK, extracellular signal-regulated kinase; HACU, high-affinity choline uptake; LVGCC, L-type voltage-gated calcium channel; NMDAR, N-methyl D aspartate receptor; PKA, protein kinase A; Zif268, zinc finger binding protein 268. References: 1, Anokhin et al., 2002; 2, Sangha et al., 2003; 3, Child et al., 2003; 4, Kida et al., 2002; 5, Taubenfeld et al., 2001; 6, Lee et al., 2004; 7, Bozon et al., 2003; 8, Kelly et al., 2003; 9, Boccia et al., 2004; 10, Koh and Bernstein, 2003; 11, Pedreira et al., 2002; 12, Suzuki et al., 2004.

[a] More sensitive to blockade than consolidation.

[b] Memory at 4 hr posttraining was considered consolidated in this system.

[c] Required for extinction.

in this context are those studies that identify differences between the two phenomena. Hence, C/EBPβ plays a role in consolidation but not reconsolidation (Taubenfeld et al., 2001), and there is double dissociation of the roles of BDNF and Zif268 (Lee et al., 2004). It is not yet firmly determined, however, whether such differences are fundamental to the consolidation and reconsolidation or emerge only in the specific memory type and protocol used (e.g., Zif268 was found to be essential for consolidation of object recognition but not of contextual fear conditioning; Table 2). At first approximation, the pharmacological and molecular data suggest that consolidation and reconsolidation share many mechanistic components, yet reconsolidation is not a faithful mechanistic recapitulation of consolidation.

Circuit Signatures

A few studies have compared the neural circuits that subserve consolidation and reconsolidation, respectively. A dissociation has been reported in the role of amygdalar nuclei in conditioned taste aversion: whereas protein synthesis in the central amygdala nucleus is required for acquisition but not extinction, and in the basolateral amygdala for extinction but not acquisition, neither of these nuclei is essential for reconsolidation (Bahar et al., 2004). In passive avoidance in the rat, hippocampus is required for consolidation, but not for reconsolidation, as judged by the lack of the postreactivation effect of intrahippocampal anisomycin; in contrast, systemic (i.p.) anisomycin did impair reconsolidation (Taubenfeld et al., 2001), suggesting dissociation of the role of hippocampus in consolidation and reconsolidation. (See also lack of protein synthesis-dependent reconsolidation in hippocampal place cells, which require protein synthesis for consolidation; Agnihotri et al., 2004.) In passive avoidance in the young chick, metabolic brain maps of deoxyglucose or c-Fos following memory reactivation differed from those obtained after the initial training (Salinska et al., 2004). In other systems, ranging from rat (Tronel and Sara, 2002) to human (Nyberg et al., 1996), circuits activated in or after retrieval differ from those activated in acquisition and consolidation, but it is yet unclear how much of this activity is related to reconsolidation.

System Signatures

Differences between consolidation and reconsolidation in the temporal response of the behavioral system, and

in the susceptibility to blockers, were noted already over 30 years ago. These included both increased and decreased sensitivity of reconsolidation to blocking agent, faster onset of amnesia in reconsolidation blocking, and a shorter time window of susceptibility to blocking (reviewed in Dudai, 2004). Differences in system response were also found in more recent studies. The dose of anisomycin used to block initial consolidation had no effect on reconsolidation in passive avoidance (Taubenfeld et al., 2001), but double the dose affected fear conditioning (Debiec et al., 2002). In taste learning, the time window of postretrieval consolidation in an extinction protocol (see below), as determined by susceptibility to inhibition of protein synthesis in the insular cortex, was shorter than that of the initial consolidation (Berman and Dudai, 2001). And in passive avoidance in the chick, a significantly lower dose of anisomycin or 2-deoxygalactose was required to induce postreactivation amnesia compared to postconsolidation amnesia (Anokhin et al., 2002).

The Relevance of Reconsolidation to Extinction

When a memory item is retrieved, multiple related traces may come to compete for the control of behavior, including new traces formed by the retrieval experience (Berman et al., 2003). Application of a consolidation blocker at that point in time could affect any of these traces. Of special interest in this respect is experimental extinction, i.e., the decline in frequency or intensity of the conditioned response as a consequence of testing in the absence of the reinforcer. Inhibition of protein synthesis immediately after retrieval, the same procedure employed to block consolidation, blocks extinction (Berman and Dudai, 2001; Vianna et al., 2001). Several groups have noted a functional link between extinction and reconsolidation; reconsolidation was detected only in the absence of significant extinction (Eisenberg et al., 2003; Pedreira and Maldonado, 2003; Suzuki et al., 2004). Some authors interpret this as an indication of competition of extinction and reconsolidation for shared cellular resources (Nader, 2003), others as reflecting a basic rule of brain function, that among multiple traces, the memory that retains or gains control over behavior is the one that becomes susceptible to consolidation blockers (Eisenberg et al., 2003). The mutual exclusiveness of extinction and reconsolidation may explain some conflicting reports on the presence or absence of reconsolidation in some systems (Eisenberg et al., 2003). The nature of the interrelationship of extinction and reconsolidation is, however, still an open question. Note also that blockade of reconsolidation and enhancement of extinction both yield apparent amnesia of the original memory. Since extinction is relearning, not unlearning (see also below), it is difficult to see how consolidation blockers enhance extinction; yet, given that behavioral performance could be the outcome of the activity of competing traces (Berman et al., 2003; Eisenberg et al., 2003), such possibility should not be discarded (e.g., Hernandez et al., 2002).

On Reversibility and Transiency of Reconsolidation Blockade

Whether the amnesia induced after blockade of reconsolidation is permanent or only transient is a cardinal issue in reconsolidation research. Lack of reversal of amnesia could support storage deficit interpretations, similar to the type of deficit assumed to occur after consolidation blockade. In contrast, reversibility of amnesia favors retrieval or performance deficit interpretations. The tools used to tackle this question are the same ones used in the study of extinction. Extinction is considered relearning and not unlearning because of four phenomena (reviewed in Dudai, 2002b): spontaneous recovery, the return of the original memory in the absence of explicit retraining; saving, the facilitation of relearning; reinstatement, the reversal of amnesia by presentation of unpaired reinforcer; and renewal, the reappearance of the original memory in a context different from that in which extinction was practiced. It is noteworthy, however, that the power of these protocols is limited. Lack of spontaneous recovery, saving, unpaired-US reinstatement, or renewal, does not definitively prove obliteration of the trace. This is because, first, it is inherently problematic to reach decisive conclusions on the basis of negative findings. Second, these phenomena could be construed as the summation of new experience with residues of the damaged trace (e.g., Gold et al., 1973). Distinction between storage and retrieval deficits might in the future benefit from identification of specific neural signatures and systems in which such signatures could be matched with specific learning (e.g., Hasselmo et al., 2002). In the meantime, trace-seeking protocols such as those used in the study of extinction are still the best we have.

Taking the above caveat into consideration, several groups have identified spontaneous recovery and reinstatement of reconsolidation-blocked memory (Table 3). This was taken to favor blocked retrieval or performance interpretations and contrasted with the common storage deficit interpretation of blocked consolidation. This conclusion should, however, be taken as a heuristic only, because even if an identical protocol is run on consolidation and reconsolidation in the same system, by definition, the history of the subject is different, hence the comparison is far from being satisfactory. Furthermore, there used to be a time when retrieval and performance deficit interpretations of consolidation blockade were also quite popular (reviewed in Dudai, 2004).

Another findings that should be taken into account in interpreting reconsolidation is that, in several studies, the amnestic effect depended on the age of the reactivated memory (Table 3). Young reactivated memory was prone to disruption by consolidation blockers, older memory was not (Litvin and Anokhin, 2000; Milekic and Alberini, 2002; M.E. and Y.D., 2004, Old fears in medaka do not reconsolidate, Soc. Neurosci., abstract). In yet another study, increasing the intensity of the reactivation cue overcame the inability of older fear memory to reconsolidate, but still, the old memory was significantly less susceptible than the younger one (Suzuki et al., 2004). This memory-age dependency of reconsolidation was reported so far only in protocols in which the consolidation blocker was applied systemically. The time to lack-of-effect of the postreactivation application of the blocker differed among studies. An appealing possibility is that the process manifested in reconsolidation itself consolidates, and that the temporal window in which this happens depends on the system and protocol.

Table 3. Reversibility and Transiency of Amnesia Induced by Blockade of Reconsolidation

System	Spontaneous Recovery[a]	Reinstatement	Amnesia Limited by Memory Age[b]
Passive avoidance, young chick, protein synthesis inhibitors, intracranial	1, 2, 3		1
Inhibitory avoidance, rat, anisomycin s.c.			7
Contextual fear conditioning, mouse, anisomycin s.c.	4		
Contextual fear conditioning, mouse, intrahippocampal		5[c]	
Elemental fear conditioning, medaka fish, anesthetic, systemic		6	6

References: 1, Litvin and Anokhin, 2000; 2, Anokhin et al., 2002; 3, Salinska et al., 2004; 4, Lattal and Abel, 2004; 5, Fischer et al., 2004; 6, M.E. and Y.D., 2004, Old fears in medaka do not reconsolidate, Soc. Neurosci., abstract; 7, Milekic and Alberini, 2002.

[a] Spontaneous recovery was not detected after blockade of reconsolidation by anisomycin in fear conditioning in the rat (Debiec et al., 2002) and in conditioned taste aversion in the rat (Eisenberg et al., 2003).

[b] Older memories were found to undergo reconsolidation in fear conditioning in the rat (Nader et al., 2000; Debiec et al., 2002) and in the mouse (Suzuki et al., 2004; longer reminder duration was however required to induce reconsolidation of old memory in this system).

[c] These authors interpret the effect of postreactivation application of the protein synthesis inhibitor as enhancement of extinction.

Interim Conclusions

Taken together, the data show that renewed transient susceptibility of reactivated long-term memory to consolidation blockers occurs in a variety of species and memory paradigms; reconsolidation shares attributes and molecular substrates with consolidation, but the processes are mechanistically nonidentical; the outcome of reconsolidation blockade may be interpreted as retrieval or performance deficit, but this is not a definitive conclusion; and there is evidence that the process that is manifested in reconsolidation itself consolidates.

A Framework Model

So, is "reconsolidation" a misnomer? At face value, if "re" implies faithful recapitulation, it is. But the question arises, first, should we expect faithful recapitulation at all, and second, at what level of analysis should the question be posed? It is questionable whether detailed comparison of consolidation in two different systems, or even two different protocols in the same system, would yield identical mechanistic descriptions. It is therefore risky to draw sweeping conclusions from mechanistic differences observed between consolidation and reconsolidation. As a matter of fact, many molecular components are shared by both phenomena (Tables 1 and 2). Given the inconclusiveness of the mechanistic comparison, it might be more informative to shift the debate to the functional level, or, borrowing terminology from Marr (1982), to the computational theory level. The question then becomes: do consolidation and reconsolidation share functional goals?

In our opinion, in spite of the aforementioned reservations concerning the limitation of current protocols that attempt to dissociate storage from retrieval deficits, the data so far do make a case for considering the amnesia caused by reconsolidation blockade as reflecting retrieval or performance deficit. Does this mean that the function of reconsolidation differs from that of consolidation? Not necessarily. Consolidation is indeed commonly considered to stabilize the neural representation of the specific information acquired in the learning session. It is worthwhile to emphasize, however, the likely possibility that, in many memory systems, its role is also, or even mainly, to create associations and retrieval links (The major exception perhaps being very simple modifiable reflexes or segments of such reflexes studied in isolation from the rest of the nervous system.). These links render the new memory item retrievable and hence usable (Dudai, 2004). The formation of retrieval links might be subserved by synaptic recruitment and growth, shown in some systems to correlate with long-term memory. In such a scenario, blockade of consolidation immediately after acquisition might prevent the formation of all retrieval links and render the memory item behaviorally undetectable. This would be practically indistinguishable from a storage deficit. We hence concur with the notion that the debate on the role of storage/retrieval deficits in retrograde amnesia deserves revisiting (e.g., Millin et al., 2001). Therefore, at the current state of the art, using storage/retrieval deficit criteria to differentiate between the functions of consolidation and reconsolidation is not very fruitful.

We propose a heuristic interpretational framework for the reconsolidation data that deviates from the chronic storage/retrieval debate. At the same time, it conforms to the maxim of parsimony, that entities should not be multiplied without necessity. Drawing particularly upon those studies that find reconsolidation in young but not old long-term memories (Table 3), we propose that reconsolidation is a manifestation of lingering consolidation. In this sense, it is not "re"consolidation, because consolidation did not come to a closure. In other words, the idea is that, generally, memory consolidates over much longer periods than so far assumed (see also Litvin and Anokhin, 2000).

The hypothesis goes as follows:

(A) In most memory systems, consolidation takes at least several days or weeks to complete. We hence challenge the accepted dogma that such a slow time course of consolidation is unique to corticohippocampal circuits. The time course of what is currently considered "cellular consolidation" does not reflect the time to completion of memory consolidation in the behaving subject.

(B) Shortly after their acquisition, memory items pro-

ceed to persist in an inactive state with intercalated reactivations (this assumption echoes models of system consolidation in corticohippocampal circuits, see McClelland et al., 1995; Shimizu et al., 2000; Louie and Wilson, 2001; Hoffman and McNaughton, 2002). "Active" means, in this context, actualization of the coherent spatiotemporal pattern of network electrical activity that encodes the internal representation of the item. We assume that this activation is both permissive and necessary for triggering behaviorally relevant plasticity in the network in vivo. Reactivations occur either endogenously in the course of maintenance, in which case they could promote consolidation, or in retrieval, in which case they control behavior but may still promote consolidation as well (Maintenance could involve rest and sleep, e.g., Louie and Wilson, 2001. No assumption is being made concerning the longest time interval in which a memory can survive without reactivation.).

(C) Upon reactivation, synapses in the network might be further stabilized (but see (F) below), and the network is refined and integrates with other memories. The network hence comes to encode the "core representation," i.e., the encoding of the specific learning experience, which stabilizes first, as well as retrieval links to other representations. The latter require recruitment of new synapses and circuits (The model does not postulate core-trace migration, which is assumed by some authors to occur in corticohippocampal circuits.). In the process, as a consequence of reciprocal interactions, elements added to the representational network may transiently induce or enhance plasticity in some older elements.

(D) The memory network becomes susceptible to the memory disruption consequences of consolidation blockers only upon its activation or immediately afterward. This can occur either in acquisition or in maintenance or in retrieval. Specific blockers interfere with specific aspects and consequences of neural activity (e.g., formation of synaptic tags, modulation of gene expression, synaptic remodeling and growth). They may hence disrupt stabilization, integration, and formation of retrieval links. Windows of opportunity for consolidation blockers do not suffice, therefore, to delineate the onset and offset of consolidation of a memory item in the behaving subject; rather, they are time locked to a distinct period of network activity within the overall time window of progressive consolidation of that item and identify the recruitment of the specific cellular target that is a consequence of this activity. Indeed, consolidation windows described in the literature differ not only by the blocker used but also by the sampling time after acquisition (e.g., McGaugh, 1966; Grecksch and Matthies, 1980; Przybyslawski et al., 1999).

(E) The effect of the blocker on a given part of the system at a specific point in time reflects time-dependent balance between stability and plasticity; more extensive reactivation periods promote more extensive plasticity.

(F) Over time, provided new experiences do not mismatch experience-dependent expectations and destabilize the system anew, progressive stabilization reaches a stage at which the representational network becomes essentially stable. From this point on, the network is only minimally affected by reactivation. Although in real life the system may never reach a completely robust state, asymptotic proximity to such a state could be deemed as the closure of the consolidation window. The time to reach this is system and protocol dependent.

The above assumptions lead to several predictions:

(1) There should be recurrent time windows of susceptibility to consolidation blockers over days, weeks, and possibly more.
(2) This recurrent susceptibility should ultimately decay over time.
(3) The behavioral and neural signature of the outcome of consolidation blockade should vary as consolidation advances. This is because the role of attributes such as novelty or expectation differs between initial and later experience of a stimulus (e.g., Berman and Dudai, 2001) and because elements of the network stabilize with different kinetics (e.g., core representation versus retrieval links).
(4) Intensive retrieval session should create a better opportunity for the consolidation blocker to interfere with the reactivated memory, unless the protocol comes to promote experimental extinction, in which case the new learning (i.e., extinction), competing for cellular plasticity resources in at least part of the circuit, becomes the prime target of the blocker.
(5) It should be more difficult to detect reconsolidation in isolated synapses or small segments of circuits detached from system input, unless appropriate recurrent spatiotemporal input is mimicked in vitro.
(6) Consolidation blockers should damage memory upon its reactivation independent of behaviorally effective retrieval, e.g., in the course of background processing or sleep.

Results from several laboratories concur with predictions 1–4 (Tables 1–3). Prediction 2 is particularly in dispute (Debiec et al., 2002). Predictions 5 and 6 require testing.

This framework model is intended to serve as a trigger for tests of the above predictions as well as for proposing alternative conceptual frameworks. The latter should account for the susceptibility of reactivated but not nonreactivated long-term memories to amnestic agents and for the temporal gradient of this susceptibility.

In conclusion, we propose here that the phenomenon dubbed "reconsolidation" is a manifestation of lingering consolidation, not recapitulation of a process that had already come to a closure. Reconsolidation, as we interpret it, does not demote the concept of consolidation. It only expands it, taking into account that, in real life, synapses and their cell bodies do not reside in isolation, nor do they rest for the rest of their life after responding to a modifying experience. Rather, they are dynamic elements in circuits that keep interacting with the world and updating their models of it. The main issue here is not terminology. Although at the end of the day reconsolidation may prove to be good old consolidation in disguise, the revitalized research in this field is bound to clarify what consolidation is in the first place and result

in new insights into memory formation, persistence, and loss.

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