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Consolidation and Reconsolidation: Two Lives of Memories?

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Most studies on memory consolidation consider the new information as if it were imposed on a tabula rasa, but considerable evidence indicates that new memories must be interleaved within a large network of relevant pre-existing knowledge. Early studies on reconsolidation highlighted that a newly consolidated memory could be erased after reactivation, but new evidence has shown that an effective reactivation experience must also involve memory reorganization to incorporate new learning. The combination of these observations on consolidation and reconsolidation highlights the fundamental similarities of both phenomena as the integration of new information and old, and it suggests reconsolidation = consolidation as a neverending process of schema modification.

Memories evolve over time, and many have come to consider that memories have two extended ''lives'' after the initial encoding of new information. The first, called consolidation, involves a prolonged period after learning when new information becomes fixed at a cellular level and interleaved among already existing memories to enrich our body of personal and factual knowledge. The second, called reconsolidation, turns the tables on a memory and involves the converse process in which a newly consolidated memory is now subject to modification through subsequent reminders and interference. Here we propose that the time has come to join the literatures on these two lives of memories, toward the goal of understanding memory as an ever-evolving organization of the record of experience.

Consolidation

Since the pioneering studies on retrograde amnesia, it has been accepted that memories undergo a process of consolidation (Ribot, 1882; Müller and Pilzecker, 1900; Burnham, 1903). Immediately after learning, memories are labile, that is, subject to interference and trauma, but later they are stabilized, such that they are not disrupted by the same interfering events. It is well recognized that memory consolidation involves a relatively brief cascade of molecular and cellular events that alter synaptic efficacy as well as a prolonged systems level interaction between the hippocampus and cerebral cortex (McGaugh, 2000; Dudai, 2004). Here we will focus mainly on the latter. Linkage between the hippocampus and consolidation began with the earliest observations by Scoville and Milner (1957) on the patient H.M., who received a resection of the medial temporal lobe area including the hippocampus and neighboring parahippocampal region at age 27. H.M.'s amnesia was characterized as a severe and selective impairment in ''recent memory'' in the face of spared memory for knowledge obtained remotely prior to the surgery. Tests on H.M.'s memory for public and personal events have shown that his retrograde amnesia extends back at least eleven years (Corkin, 1984), and more recent studies of patients with damage limited to the hippocampal region also report temporally graded retrograde amnesia for factual knowledge and news events over a period extending up to ten years (Manns et al., 2003; Bayley et al., 2006). There remains debate about whether there is a temporal gradient for retrograde amnesia after hippocampal damage for all categories of memory (see below). However, it is consensual that damage restricted to the hippocampal region results in temporally retrograde graded amnesia for semantic information.

A major limitation on studies of retrograde amnesia in humans is that there is no control over the extent of exposure to events during acquisition, as well as no control over how often the memories for those events are re-experienced or remembered. This problem has been addressed in several prospective studies on amnesia in animals, where hippocampal damage occurs at different time points after learning and temporally graded amnesia emerges across multiple species and memory tasks (reviewed in Milner et al., 1998; but see Sutherland and Lehmann 2011). The duration of the systems consolidation period is highly variable across species and tasks, and hippocampal neurogenesis may also control its time course (Kitamura et al., 2009). The evidence for temporally limited hippocampal involvement is compelling; however, this observation does not provide direct evidence on what brain areas support memory when the hippocampus is no longer necessary.

Insights about the relative engagement of other brain areas over the course of consolidation have come from recent experiments that have measured brain activation during memory retrieval at different times after learning in humans and animals. In humans, activation of the hippocampus during accurate memory retrieval in normal subjects was maximal for the most recent news stories and declined over approximately nine years, parallel with the course of retrograde amnesia (Smith and Squire, 2009). Conversely, activation of widespread cortical areas was lowest for the most recent accurately remembered events and increased for more remote memories (see also Haist et al., 2001; Douville et al., 2005; Bayley et al., 2006). Recent prospective studies using functional imaging have identified greater activation of the hippocampus during recall of recently over remotely studied paired associations and the opposite temporal gradient

in cortical areas (Yamashita et al., 2009; Takashima et al., 2009). In the latter study, over time following learning, functional connectivity between the hippocampus and cortical areas decreased, whereas connectivity within the cortical network increased.

Studies on animals have employed 2-deoxyglucose (2DG) uptake and immediate early gene (IEG) activation as measures of neural activity in brain areas during memory retrieval for recently and remotely acquired memories. Bontempi et al. (1999) reported greater 2DG uptake in hippocampal area for recently acquired spatial discriminations, and conversely greater activation of frontal and temporal cortical areas for remotely acquired spatial memories. Similar patterns of decreasing hippocampal activation and increasing widespread cortical activation were observed using IEG expression as a reflection of neural activation in a contextual fear paradigm (Frankland et al., 2004; Maviel et al., 2004). Whereas the latter studies have focused on the medial prefrontal area as a key site for postconsolidation spatial memory, other studies have localized greater activation of olfactory recipient cortical areas for remote social-olfactory memories (Ross and Eichenbaum, 2006), and greater activation of a higher-order auditory cortical area for remotely acquired tone-cued fear conditioning (Sacco and Sacchetti, 2010). The overall findings on cellular imaging studies in rodents impressively parallel the findings from functional imaging in humans, providing compelling evidence of systems consolidation characterized by early greater involvement of the hippocampus and later greater involvement of the task-relevant cortical areas.

Additional evidence for cortical-hippocampal interactions during consolidation comes from studies on hippocampal "replay" of memories during sleep and other offline states, suggesting that the strengthening of cortical linkages depends on inputs from the hippocampus (e.g., Wilson and McNaughton, 1994; reviewed in Carr et al., 2011). These interactions were highlighted in a study where, during sleep following maze running, populations of simultaneously recorded hippocampal and visual cortical cells fired in coordinated replays of the sequences of activity observed during awake behavior (Ji and Wilson, 2007). Additional support for the idea that hippocampal replay drives memory consolidation came from a report that replay following new spatial learning predicts subsequent memory performance (Dupret et al., 2010) and from findings that stimulation-produced suppression of hippocampal sharp waves, when most replay events occur, impairs subsequent spatial memory, whereas stimulation at other times has no effect (Girardeau et al., 2009; Ego-Stengel and Wilson, 2010; see also Nakashiba et al., 2009).

Other studies have focused on the cerebral cortex and shown development of a coordinated cortical neural network activation following learning (Alvarez and Eichenbaum, 2002; Takehara-Nishiuchi and McNaughton, 2008; Sakai and Miyashita, 1991) and cortical reorganization that depends upon an early tag within the regions that subsequently support the memory (Lesburguères et al., 2011).

Models of Memory Consolidation within the Cortical-Hippocampal System

These recent findings support the classic idea that a newly acquired memory depends initially on the hippocampus and eventually on widespread areas of the cerebral cortex. The classic and new observations have generated three current hypotheses about different aspects of the consolidation process (see Figure 1).

Consolidation as Linking Cortical Representations

There are several variations of the hypothesis that the hippocampus rapidly stores critical information for linking cortical representations and that during multiple iterations of cortical-hippocampal interaction, connections within the cortex are strengthened and eventually support these associations in the absence of hippocampal function (Marr, 1971; Squire et al., 1984; Teyler and DiScenna, 1986; Damasio, 1989; Squire, 1992). Each of these models proposes that, during learning, information from cortical areas that are activated in perceptual processing and working memory is sent through inputs to the hippocampus, which encodes a "sketch" or "conjunction" of that information or "index" of loci within the cortex that contain the detailed information. During the consolidation period, memory cues that replicate partial information from the learning experience reach the hippocampus, activating the hippocampal representation or index, which, via back projections to the cortex, reactivates the complete pattern of activations in cortical networks that were generated during learning (Figure 1A). Each time this reactivation occurs, intracortical connections between the disparate, active cortical networks are gradually strengthened. After many such reactivations the intracortical connections are sufficiently strong to support reactivation of the entire set of cortical networks without assistance from the hippocampus (Figure 1B). Under this model, blocking consolidation prevents the strengthening of the intracortical connections for a newly acquired memory but leaves pre-existing memories intact (Figure 1C).

With regard to the functional imaging studies described above, it is notable that these models do not explicitly predict that the hippocampus should be less activated during effortful recall of remote memories. Indeed, a recent experiment showed increased c-*fos* expression in the hippocampus for older memories for the escape location on the Morris water maze (Lopez et al., 2011). Furthermore, these models predict that the relevant cortical networks should be activated for both recent and remote memories, even though those activations might be generated differentially through the hippocampus for recent memories and directly for remote memories. There is also strong evidence that the hippocampus is engaged during any memory processing that involves combinations of detailed associative and contextual information (see below) and evidence that cortical networks that are engaged during encoding are re-engaged during recall even shortly after the learning experience (e.g., Buckner et al., 2001; Polyn et al., 2005; Hannula et al., 2006; Danker and Anderson, 2010). These issues remain to be resolved for models of the hippocampus as temporarily linking cortical representations.

Consolidation as Semantic Transformation

The multiple trace theory, frequently opposed with the cortical linkage view, proposes that memories are qualitatively transformed from episodic memories into semantic memories during the consolidation period (Nadel and Moscovitch, 1997; Winocur et al., 2010). In this view, memories that are initially stored in cortical-hippocampal circuitry are episodic, defined as context

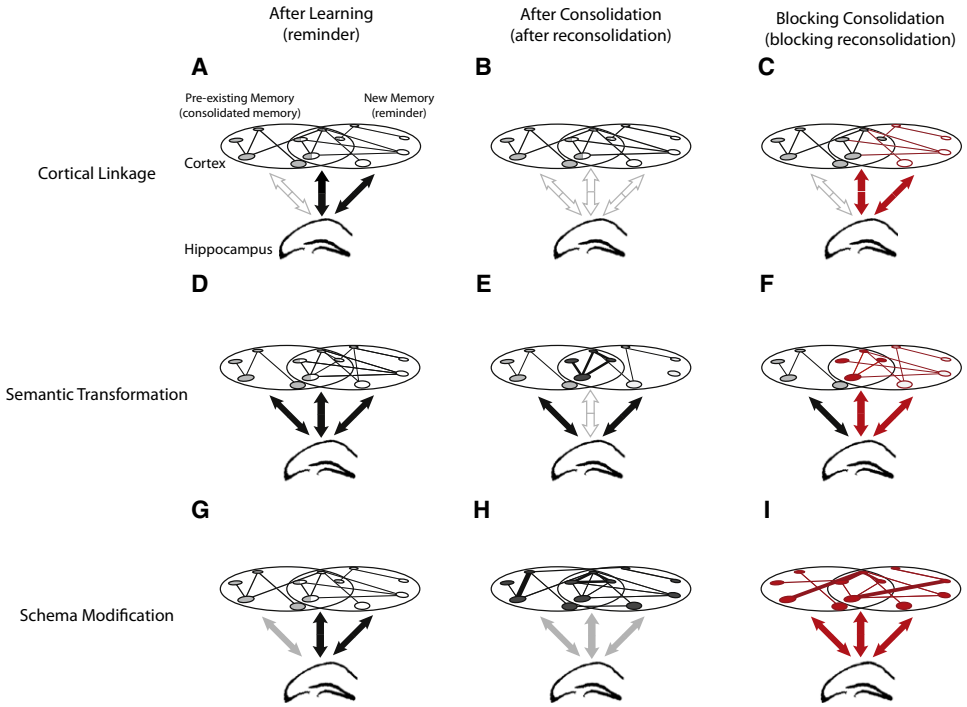

Figure 1. Three Models of Systems Consolidation, Each of Which Also Supports Aspects of Reconsolidation

The hippocampus and an idealized network of connections among nodes (neurons) in the cortex represent a pre-existing memory (gray nodes), a newly acquired memory (white nodes), and shared components (gray/white nodes). The thickness of lines between cortical nodes reflects the strengths of intracortical connections. The dependence of cortical networks on the hippocampus is indicated by the arrows (dark = strong; gray = weak; open = no dependence). Throughout, red indicates a network disrupted by amnesic agents.

(A–C) The cortical linkage model. (A) Immediately after learning, the pre-existing memory has strong connections (thick lines) between nodes, whereas connections in the newly acquired memory network are weak (thin) and hippocampal dependent (dark arrows). (B) Consolidation is accomplished by strengthening intracortical projections (thick lines) and eventually the hippocampal connections are not required (open arrows). (C) Blocking consolidation prevents cortical strengthening of the new information (red, thin lines), leaving those cortical regions still dependent on the hippocampus (red arrow). Pre-existing memories (thick lines) that are supported by cortical networks are spared.

(D–F) The semantic transformation model. (D) Immediately after learning, hippocampal connections are critical (dark arrows) for pre-existing episodic memories as well as for the newly acquired memory. (E) Consolidation involves strengthening (very thick lines) of intracortical connections shared by overlapping nodes to create a system that differs from either the first or second network (black nodes) and no longer depends upon the hippocampus (open arrow). Network elements that represent unique (episodic) portions of those memories remain weakly connected (thin lines) and dependent on the hippocampus (dark arrows). (F) Blocking consolidation prevents the formation of a new episodic memory stored within the hippocampal-cortical networks (red thin lines) and also the strengthening of the overlapping portion of the cortical network, leaving the newly formed network (red arrow), as well as the pre-existing cortical networks, hippocampal dependent (dark arrows).

(G–I) The schema modification model. (G) Immediately after learning, the hippocampus is essential for supporting connections within the newly acquired memory, and important for the full elaboration of details of episodic memories (gray arrow). (H) During consolidation, the hippocampus supports both increases (thick lines) and decreases (thin lines) in connection strengths within the networks for pre-existing and new memories, resulting in an interleaving of the memories into a composite network (black nodes) that remains dependent on the hippocampus for the full range of detailed information (gray arrows). (I) Blocking consolidation after learning not only disrupts the consolidation of the newly acquired memory, but also corrupts the synaptic weight changes that support the interleaving of networks (reconsolidation), resulting in an altered set of cortical networks (red) still partially dependent on the hippocampus (red arrows).

Parentheses indicate references to the text.

specific, and repeated ''offline'' reactivations create multiple distinct traces (Figure 1D, ''New Memory'') from which the common information is extracted and integrated within pre-existing semantic networks in the cortex. Eventually the cortical representations that are common among memories, i.e., semantic memories free of episodic/contextual detail (Figure 1E, thick lines), do not depend on the hippocampus (Figure 1E, empty arrow), but retrieval of episodic details continues to depend upon cortical-hippocampal connections (Figure 1E, black arrows). In this model, blocking consolidation prevents the strengthening of intracortical connections that support semantic transformation, leaving new as well as remotely acquired episodic memories dependent on the hippocampus (Figure 1F, red).

In support of this view are reports that amnesic patients show temporally ungraded retrograde impairment for episodic memories (e.g., Rosenbaum et al., 2001; Steinvorth et al., 2005). However, contrary to the view that episodic and contextual memories always depend on the hippocampus, there are also findings of spared remote autobiographical memories in patients with medial temporal lobe damage (Bayley et al., 2003; reviewed in Squire and Bayley, 2007) and it is argued that flat retrograde gradients for episodic memory occur only following damage extending beyond the hippocampus into cortical areas (Reed and Squire, 1998). However, functional imaging studies have consistently reported that the hippocampus is activated for both recently and remotely acquired episodic and autobiographical

memories (Ryan et al., 2001; Maguire et al., 2001; Piolino et al., 2004; Addis et al., 2004; Gilboa et al., 2004; Viard et al., 2007). These findings contrast with the above-described observations of declining hippocampal activation during retrieval of famous faces and names and of news events, i.e., semantic memories (Smith and Squire, 2009; Haist et al., 2001; Douville et al., 2005). A possible reconciliation of these observations is that the hippocampus is consistently engaged whenever detailed associative or contextual information is recalled (Piolino et al., 2008; Hoscheidt et al., 2010). Notably, the hippocampus is also involved even when people imagine detailed events that have never occurred (Hassabis et al., 2007; Addis et al., 2007). Thus, observations of hippocampal activation during relational processing may fit the expectation that the hippocampus becomes engaged by cues that generate an extensive memory search, regardless of the age or even the existence of a memory.

Rodent studies also support the view that consolidation involves the semantic transformation of memories. In these studies, a memory that generalizes to testing conditions that differ from original training is typically considered an animal model of semantic memory. Parallel to the human literature, several experiments have shown that remote contextual memories become more generalized and independent of the hippocampus (Wiltgen and Silva, 2007; Wiltgen et al., 2010; Winocur et al., 2007; see also Lehmann et al., 2010; but also Weinberger et al., 2009). Conversely, hippocampal damage results in ungraded retrograde amnesia for spatial memories (Clark et al., 2005a, 2005b; Martin et al., 2005; Winocur et al., 2005a), except under circumstances of extensive and varied experience in environments wherein remote spatial memories are spared following hippocampal damage in both humans (Teng and Squire, 1999) and rats (Winocur et al., 2005b). Notably, these findings are also consistent with a simpler view that details of memories and information not repeated or contradicted across repeated experiences are most likely to be forgotten or overwritten, which also would be expected to result in a residual and strengthened semantic memory.

Consolidation as schema modification

A distinct idea on memory transformation argues that newly acquired memories are not stored in isolation. Instead, they are gradually incorporated into a ''schema,'' an organization of related knowledge that contains semantic knowledge *as well as* episodic details. Unlike the semantic transformation view, schemas do not distinguish episodic and semantic memories. Rather, they interleave all memories via common elements, and, unlike the focus on semantic transformation of multiple hippocampal traces, schemas involve the interleaving of new learning initially with previously acquired memories and subsequently with future memories. The schema idea, originally proposed by Bartlett in 1932 (Bartlett, 1932), was extended from the perspective of consolidation theory by McClelland et al. (1995), who contrasted rapid synaptic modification in the hippocampus with slowly modified connections within the cortex and suggested that that the hippocampus supports memory for a brief period after learning, during which system reactivations integrate the new information via modifications of a pre-existing schema that connects related memories (Figures 1G and 1H). In this model, blocking consolidation disrupts the reorganization of pre-existing cortical representations and leaves newly acquired memories corrupted and dependent on the hippocampus (Figure 1I).

In support of this model, Tse et al. (2007) demonstrated that rats develop a schema of locations where different foods are buried by showing that once several food/location associations had been formed, new ones could be added within a single trial; however, in a different environment, the learning of new associations was much more gradual. Moreover, when new associations could be integrated within a pre-existing schema, hippocampal lesions after 3 hr, but not 48 hr, impaired subsequent performance, revealing a consolidation gradient considerably steeper than those reported in studies in which learning did not benefit from an existing schema.

By examining the organization of related memories that is the foundation of schemas, Bunsey and Eichenbaum (1996) showed that normal rats link overlapping paired associates and make new inferences about indirectly related elements, and that this capacity depends on the hippocampus. The same finding was extended to a schema that involved a hierarchical organization of stimulus elements (Dusek and Eichenbaum, 1997). Consistent with these findings, Gupta et al. (2010) reported replays of spatial representations that comprised overlapping spatial trajectories that occasionally linked to form representations of routes that would be consistent with a navigational inference of related previous experiences. Many other studies in humans, monkeys, and rats have shown that hippocampal neurons encode both distinct experiences and their common overlapping features, consistent with the existence of networks of related memories (for review see Eichenbaum, 2004). In addition, fMRI studies have shown that the hippocampus is engaged as related memories are integrated to support novel inferences in tasks similar to those dependent on the hippocampus in rats (Preston et al., 2004; Zalesak and Heckers, 2009). Hippocampal activation is also observed as humans learn overlapping face-scene associations that they later can generalize across indirectly related elements (Shohamy and Wagner, 2008) and as they acquire conceptual knowledge that bridges across related experiences in predicting the outcomes of complex associations that have overlapping features (Kumaran et al., 2009). Reports of hippocampal ''preplay,'' where neural patterns recorded during behavior can be observed before the subject explores a well-learned (Louie and Wilson, 2001) or novel (Dragoi and Tonegawa, 2011) environment, suggest a potential mechanism by which retrieval at the time of learning can link past experience with present.

The three models of consolidation described above are not mutually exclusive. The hippocampus plays a key role in linking elements of memories processed in the cortex, including links that compose representations of discrete events and representations of episodes composed of sequences of events (Eichenbaum, 2004). Memories interact through ''nodal'' representations of features common to multiple experiences. Importantly, these common nodal elements characterize information that is not bound to a particular event or episode and is consistent across experiences, and in that sense they underlie a ''semantic transformation.'' Also, it is precisely via the nodal elements that memories are connected and therefore underlie the structure

of schemas. The evidence presented above suggests a critical role for the hippocampus in the establishment of the cortical nodes that link and relate disparate experiences. As illustrated in Figure 1, the different models of consolidation may best be viewed as focusing on different aspects of the larger process by which memories are interleaved during consolidation.

Reconsolidation

The standard consolidation theories described above characterize consolidation as a one-time event, after which a memory is impermeable to subsequent disruption. However, this view was challenged in the late 1960s by studies reporting that presentation of a ''reminder'' cue made a completely consolidated memory again labile to the same agents that would block consolidation (Misanin et al., 1968; Schneider and Sherman, 1968). In 2000, Nader and colleagues raised this challenge again in experiments that targeted the known role of the amygdala in synaptic consolidation of the Pavlovian association of a tone (CS) with a shock (US; Falls et al., 1992; Duvarci et al., 2006), showing that a CS alone reminder presented long after consolidation was complete re-engaged the temporary susceptibility of the memory. These findings were interpreted as evidence that the reminder reactivated the original memory trace, making it necessary to ''reconsolidate'' the memory, or else suffer erasure of the memory (Sara, 2000; Nader et al., 2000). Over the last decade, many experiments have supported the observation of memory susceptibility following reminders and these findings have been reviewed extensively in recent papers (Nader and Hardt, 2009; Dudai and Eisenberg, 2004; Lee, 2010; Alberini, 2011; Sara, 2010).

Results supporting the existence of reconsolidation have been reported in several species across a broad range of learning tests, and using a variety of manipulations to block memory (e.g., Rose and Rankin, 2006; Pedreira et al., 2002; Eisenberg et al., 2003; Frankland et al., 2006; Lee et al., 2005; Hupbach et al., 2007; Monfils et al., 2009; Schiller et al., 2010). Despite broad support for the generality of reconsolidation (Nader and Hardt, 2009), several studies have failed to find that amnesic agents block memory in the reconsolidation paradigm (Biedenkapp and Rudy, 2004) or have observed that the memory deficits are temporary (Lattal and Abel, 2004, Power et al., 2006), leading to the idea that the reconsolidation phenomenon has ''boundary conditions'' (Eisenberg et al., 2003; Milekic and Alberini, 2002; Morris et al., 2006). Several experimental parameters have been shown to be important in determining whether reconsolidation occurs, including how memories are reactivated (Debiec et al., 2006; Tronel et al., 2005), whether novelty is introduced during memory reactivation (Pedreira et al., 2004), and the age and strength of a memory (Eisenberg et al., 2003; Milekic and Alberini, 2002). We consider two main categories of boundary conditions: which memory is active at the time of amnesic treatment and whether the reminder generates new learning.

Early in the recent series of studies on reconsolidation there were conflicting reports on whether reminders reinstated lability of memories for classical aversive conditioning. Several studies (Berman et al., 2003; Vianna et al., 2001; Koh and Bernstein, 2003; Pedreira and Maldonado, 2003) noted that, in the Pavlovian conditioning studies, presentation of the CS alone can have two opposing effects: it can act as a reminder to engage the original memory trace, and it can generate extinction, which involves development of a new and competing memory trace. Based on the dual roles of CS alone presentation, Eisenberg et al. (2003) suggested that the effects of amnesic agents differ depending on whether the original memory trace or the newly developed memory for extinction was dominant at the time of amnesic treatment. To test the trace dominance theory, subjects were given either more initial CS/US training or more CS-alone trials after initial conditioning, with the assumption that more initial training would cause the fear memory to dominate during the reminder, while extinction memory would dominate after more sessions with the CS alone. Consistent with the trace dominance hypothesis, more CS/US pairings resulted in disrupted reconsolidation of the original aversive memory whereas more CS-alone presentations resulted in subsequent loss of extinction and preserved fear memory, in different species and different memory tests. These findings can also explain why extensive training and/or specific time periods between initial training and reminder could result in strong, original memory traces that are reactivated as dominant following a reminder (Suzuki et al., 2004; Wang et al., 2009; Milekic and Alberini, 2002; Eisenberg and Dudai, 2004; Robinson and Franklin, 2010, but see Duvarci et al., 2006) and why effective reminders must be presented for reconsolidation of the original memory (Bozon et al., 2003).

The other major factor in determining the efficacy of amnesic agents in the reconsolidation protocol is whether the reminder event involves new learning in addition to recovery of the initial memory trace. One study reported that whereas original memories are blocked by an amnesic agent following a CS alone reminder, there was no loss of the original memory following reminder presentations that involve a combination of CS and US presentations, suggesting that CS alone reminder constituted a new learning experience (Pedreira et al., 2004). However, there are several examples of successful disruption of reconsolidation following presentation of both a CS and US (Duvarci and Nader, 2004; Rodriguez-Ortiz et al., 2008; Valjent et al., 2006). In these studies, it is not clear that performance was at asymptote, leaving open the possibility that new learning still occurred during the reminder event, a factor that proved critical in another study (Rodriguez-Ortiz et al., 2005). Also, Morris et al. (2006) directly compared reconsolidation following reminder trials in rats trained to asymptotic performance in standard (''reference memory'') water maze task versus a (''working memory'') variant of the task where new escape locations were learned daily and found that anisomycin was effective after reminders only in the condition of new learning each day. Also, in other studies on human declarative and motor memory, providing subjects with a reminder that involves new learning is key to alteration of existing memories (Walker et al., 2003; Hupbach et al., 2007, 2008, 2009; Forcato et al., 2007, 2009). These findings and several other studies indicate that learning during the reminder session is a critical boundary condition for reconsolidation (Winters et al., 2009; Robinson and Franklin, 2010; Lee, 2010).

The combination of requirements for dominance of the original memory and new learning suggest that the key conditions for blockade of reconsolidation involve a reactivated memory trace that is susceptible to modification and new, related learning that

occurs during the interfering event. Thus, the encoding of new information occurs within the context of retrieval, and the circuits that are modulated by new information are the ones that are activated by the reminder. At the same time, blockade of reconsolidation is only observed in conditions that favor new learning related to the reactivated memory (e.g., additional training, extinction), suggesting that reconsolidation involves some kind of reconciliation or integration of a vulnerable memory trace and new relevant information (Eichenbaum, 2006).

Reconsolidation and Systems Consolidation

The three models of systems consolidation introduced earlier differ in the nature of interactions between pre-existing and new memory networks and their dependence on the hippocampus. In the cortical linkage model, consolidated memories are independent of the hippocampus (Figures 1A and 1B). Therefore, in a reconsolidation protocol, amnesic agents delivered to the hippocampus could only affect the newly acquired network—that is, the reminder—but leave intact the previously consolidated memories (Figure 1C). This outcome is not consistent with the findings that even consolidated memories are affected by reminders and damage to the hippocampus (Debiec et al., 2002; Winocur et al., 2009). Theories that hypothesize elimination of hippocampal connectivity to cortical networks during systems consolidation must be somehow updated to incorporate the findings that even consolidated memories can regain hippocampal dependence after a reminder (systems reconsolidation).

In the semantic transformation model, newly acquired memories are overlaid with pre-existing semantic memory networks, such that the common elements and connections become hippocampal independent and semantic (Figures 1D and 1E). Reconsolidation has been suggested as having two roles: to potentiate intracortical connections to form semantic memories, and to strengthen episodic memories when new learning, or a reminder, re-engages the hippocampal networks active during original learning (Figure 1E; Hupbach et al., 2007; Winocur et al., 2009). In this scheme, hippocampal amnesic treatments after a reminder should block the retention of any new episodic memory, prevent new semantic memory formation, and disrupt reconsolidation of other, similar episodic memories (Figure 1F, red); pre-existing, semantic memories would be left intact. Initial support for these claims came from a study that found systemic, but not hippocampal, delivery of amnesic agents disrupted reconsolidation of remote fear memories, findings that were interpreted to be evidence of corrupted semantic memory (Frankland et al., 2006). However, other studies showed that hippocampal reconsolidation is necessary for consolidated memories (Debiec et al., 2002; Winocur et al., 2009), and a recent experiment on remote memories showed that the generalized, "semantic," fear responding that normally occurs in nonconditioned contexts was also dependent on hippocampal reconsolidation (Winocur et al., 2009). Therefore, somehow pre-existing semantic networks must become hippocampus dependent, a condition that counters predictions of the original theory (Nadel and Moscovitch, 1997).

In the schema modification model, consolidation occurs by integrating the new memory into active, pre-existing memories via reorganization of common elements within the hippocampus and the cortex (Figures 1G and 1H). In reconsolidation experiments, the reminder determines which memories will be active during encoding and therefore which synapses will be affected by the new learning (Figure 1G). In this model, systemic amnesic treatment after a reminder would result in a partial integration of the newly learned information into the hippocampal and cortical networks, resulting in a corruption of the reorganizing network (Figure 1I, red). Manipulations limited to the hippocampus could cause disruption of cortical reconsolidation due to interrupted replay of the newly acquired learning (Eichenbaum, 2006) or errant discharges from a damaged hippocampus driving molecular changes in reorganizing cortical circuits (Rudy and Sutherland, 2008) or perhaps another mechanism that would affect cortical circuits undergoing plastic remodeling. While each of the models described here captures some of the phenomenology of reconsolidation experiments, none has compelling support, and this is likely to remain the case until we better understand the nature of neural representations in the hippocampus and cortex and how they change during consolidation and its breakdown.

Reconsolidation = Consolidation?

While the cellular substrates of consolidation and reconsolidation are largely shared, several studies have reported dissociations between these processes for particular plasticity molecules or for plasticity in general within certain brain regions (e.g., von Hertzen and Giese, 2005; Maroun and Akirav, 2009; Taubenfeld et al., 2001; Lee et al., 2004, Lee, 2008, 2010; reviewed in Alberini 2005). Furthermore, several reconsolidation studies have shown that as time passes memories become resistant to reconsolidation blockers (Milekic and Alberini, 2002; Suzuki et al., 2004; Eisenberg and Dudai, 2004), though others have found conflicting results (Debiec et al., 2002; Wang et al., 2009; Robinson and Franklin, 2010). The apparent differences between consolidation and reconsolidation can be expected due to the design of consolidation experiments. First, due to the importance of the active memory as a boundary condition, a difference in the predominance of the memory during initial learning versus following the reminder event could lead to a difference in susceptibility to interference (Alberini, 2005). Second, in many behavioral paradigms (especially aversive conditioning tasks), arousal is likely to be much larger during original learning than during the reminder, especially if the reminder is the CS alone. Since arousal plays a major role in consolidation (McGaugh, 2000), dissociations between consolidation and reconsolidation are expected. Third, given large differences in the duration of the consolidation period observed across paradigms (Milner et al., 1998), there is reason to expect differences in the durations of consolidation and reconsolidation even for the same memories. Fourth, there is a large literature, described above, suggesting that different brain areas or networks may support highly novel memories versus retrieval from well-integrated networks. These conditions may work in combination to underlie differences in the susceptibility of newly formed versus recently retrieved memories.

Taken together, the findings on blockade of reconsolidation following molecular interventions, hippocampal lesions, and interference has led several to suggest that reconsolidation

normally involves an ''updating'' of memories (Lewis, 1979; Sara, 2010; Morris et al., 2006; Lee, 2009, 2010; Dudai and Eisenberg, 2004). It has been suggested that updating can occur via two mechanisms, a destabilization of existing memory traces and modification of the contents of the original memory to add new related material (Lee et al., 2008; Lee, 2010). Common among these views is the idea that reconsolidation is the mechanism by which initially consolidated memories are changed with new learning.

We take a different view and propose that even initial consolidation occurs through a reorganization of pre-existing memories. Thus, while there is still much to be discovered about the mechanisms of consolidation and reconsolidation, we suggest that it would be valuable to consider that reconsolidation = consolidation. Dudai and Eisenberg (2004) adopted a very similar hypothesis, suggesting that reconsolidation is a manifestation of a ''lingering'' consolidation process. Here we take this idea one step further and suggest that reconsolidation is the neverending consolidation process. When we refer to consolidation, we cannot consider new learning to occur in a tabula rasa. Rather, the consolidation of new learning, the first life of a memory, is a reorganization (and therefore a ''re''-consolidation) of the existing schema. Correspondingly, after the new learning has been consolidated into the existing schema, reminders and new related experiences normally constitute memories that must be consolidated by further reorganization of the current relevant schema. By this view, the fundamental conclusion here is that new information is continually being integrated and thereby repeatedly consolidated in a never-ending reorganization of memory networks.

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