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Hippocampal-Neocortical Interactions in Memory Formation, Consolidation, and Reconsolidation

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Abstract

This review, focusing on work using animals, updates a theoretical approach whose aim is to translate neuropsychological ideas about the psychological and anatomical organization of memory into the neurobiological domain. It is suggested that episodic-like memory consists of both automatic and controlled components, with the medial temporal mediation of memory encoding including neurobiological mechanisms that are primarily automatic or incidental. These ideas, in the cognitive and behavioral domain, are linked to neurophysiological ideas about cellular consolidation concerning synaptic potentiation, particularly the relationship between protein synthesis-dependent long-term changes and shorter-lasting post-translational mechanisms. Ideas from psychology about mental schemas are considered in relation to the phenomenon of systems consolidation and, specifically, about how prior knowledge can alter the rate at which consolidation occurs. Finally, the hippocampal-neocortical interactions theory is updated in relation to reconsolidation, a process that enables updating of stored memory traces in response to novelty.

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BACKGROUND

Memory is fundamental to human life. Qualitatively distinct types of memory enable us to acquire and use a repository of knowledge, to change our behavior in response to experience, to recollect events from the past, and to plan for the future. The use of memory is changing, with a great deal of human knowledge now externalized and then sought on-demand through the use of search engines on the Web. Nonetheless, the loss of memory remains greatly feared. The inability to recollect the events of our life can develop from a minor irritation to a condition that undermines normal existence and even aspects of personal identity. Given its central role in cognition, a grand challenge for neuroscience is to understand the neural mechanisms of the capacity to encode, store, consolidate, and retrieve information. Over recent years, there has been an explosion of research that is gradually revealing the underlying psychological processes and neural mechanisms of memory, such as consolidation and reconsolidation, now thought to depend on an interaction of cellular and systems-level mechanisms.

Different forms of memory include the fundamental dissociation between short-term and long-term (Baddeley 2001) memory and the qualitatively distinct systems of long-term memory (LTM). Different theoretical frameworks of LTM distinguish perceptual representations, semantic and episodic memory (Schachter & Tulving 1994), declarative memory (Squire 1992), spatial memory (O'Keefe & Nadel 1978), emotional memory (LeDoux 2007), and the learning of actions and habits

(Everitt & Robbins 2005, Schultz & Dickinson 2000). Cutting across these distinctions is the issue of whether memory expression is explicit or implicit—a distinction easier to make in humans than in animals (Graf & Schacter 1985, Griffiths et al. 1999). These memory systems operate semi-independently, involving distinct but overlapping brain networks that interact to realize the apparently seamless control of cognition and behavior.

This review is largely built around a specific neurobiological hypothesis about memory encoding, consolidation, and memory schemas (Morris 2006), emphasizing the importance of interactions between the hippocampal formation and cortical regions in which associative memory traces are stored. We relate our experimental work to other recent studies and develop the hypothesis further with reference to reconsolidation. We restrict our focus to animal work because it is only in animals that we can perform prospective interventions that can definitively reveal causal mechanisms.

THEORETICAL OVERVIEW: HIPPOCAMPAL-NEOCORTICAL INTERACTIONS THEORY

From its clinical origins (such as the phenomenon of amnesia), a diverse field of memory research has developed. Much of this has been concerned with the role of the hippocampus (HPC) and adjacent structures in the formation and consolidation of explicit memory. The mammalian hippocampal formation (HF) is a set of brain structures including the entorhinal cortex (EC), the dentate gyrus (DG), the individual CA fields of the HPC proper, and the subicular complex (SUB). Importantly, the HF does not work in isolation but rather together with subcortical networks (such as neuromodulatory systems involving cholinergic and catacholaminergic afferents) and with cortical networks where it is widely believed that long-term memory traces are stored (Osada et al. 2008). A comprehensive review of the various neurophysiological, neuropsychological, and computational models of the mechanisms and functions of the HF in memory, together with a detailed description of its extrinsic and intrinsic anatomy (human, monkey and rat), has recently been presented in *The Hippocampus Book* (Andersen et al. 2007).

This review builds upon neuropsychological foundations with the aim of extending to anatomical and physiological levels of analysis. These foundations include Tulving's serial, parallel, independent (SPI) framework (Schachter & Tulving 1994) and the idea that hippocampal memory includes the ability to remember events and episodes (Aggleton & Brown 1999, de Haan et al. 2006, Eichenbaum 2004). It recognizes that other brain structures also contribute to episodic memory via their role in executive function and working memory (Fletcher & Henson 2001), but this aspect of episodic-like memory processing is not discussed in detail.

Four key ideas of this theory (**Table 1**) on which we focus are (*a*) the automaticity of aspects of episodic encoding in the HF (Miyashita 2004), (*b*) the role of synaptic tagging and capture in the neural mechanisms of cellular consolidation (Frey & Morris 1997), (*c*) the critical role of mental schemas in systems consolidation (Tse et al. 2007), and (*d*) memory updating as a key factor for memory reconsolidation in the HF. We refer to the theory as the hippocampal-neocortical interactions theory, as it attempts to map existing neuropsychological ideas about the determinants of episodic-like memory onto the neural circuits and synaptic processes in both hippocampus and neocortex that have been identified as relevant to memory formation.

If events are encoded automatically on-line (Marr 1971), there must exist physiological mechanisms for capturing information about them as they happen (**Table 1**, Proposition #1). For context/event associations that are critical for episodic memory, area CA1 is critical. Anatomically, CA1 receives (*a*) an excitatory input from layer III of EC, which could carry information pertaining to familiar spatial locations at which new events are occurring (Morris 2006, Witter & Moser 2006);

Hippocampus (HPC): a brain area in the medial temporal lobe that is involved in memory encoding and retrieval

HF: hippocampal formation

Neuromodulatory: describes a class of neurotransmitter systems with diffuse projections in areas of the forebrain that modulate the actions of excitatory and inhibitory neurotransmission

Episodic-like memory: a term used to describe episodic memory as studied in animals, in which it is not possible to examine the sense of the self as revealed in verbal reports by humans

Synaptic tagging and capture: a physiological process by which local changes at synapses can, through tagging in association with potentiation or depression, capture diffusely transported gene products that stabilize synaptic change

Table 1 Elements of the hippocampal/neocortical interactions theory of memory formation (updated from Morris 2006)

Proposition #1. Encoding and recall: Activity-dependent hippocampal synaptic potentiation is critical for the automatic recording of attended events (a component of episodic-like memory formation). The memory traces in hippocampal formation (HF) are likely indices of locations in the neocortex where more detailed sensory/perceptual features of information are stored and normally activated during recall.
Proposition #2. Cellular consolidation: The flipside of automaticity is the rapid decay of HF memory traces to avoid the saturation of distributed associative storage. However, index traces in HF can persist for longer if encoding happens around the time of the synthesis, distribution, and synaptic capture of plasticity-related proteins at tagged synapses.
Proposition #3. Systems consolidation: These HF traces enable, through indirect association, a systems consolidation process that builds connections between relevant modules in cortex. Importantly, this can be very rapid when consolidation involves an interaction with activated associative schemas previously stored in the neocortical networks.
Proposition #4. Retrieval and reconsolidation: Retrieval activates the index traces in HF that in turn reactivate cortically stored memory traces. This will re-engage cellular mechanisms responsible for trace stabilization in circumstances in which there is new information occurring at the time of retrieval that is to be assimilated into existing memory traces (memory updating).

Cellular consolidation: intracellular mechanisms, such as signal-transduction and transcriptional activation, by which cell-biological mechanisms give rise to lasting changes in the structure or function of a neuron with respect to information storage

Mental schemas: frameworks of knowledge, built up through paired-associations and the establishment of transitive and other relationships

Systems consolidation: intercellular and interregional mechanisms by which the activity in one brain area can influence that of another in relation to information storage

(*b*) separate excitatory inputs via the Schaffer collaterals from CA3, which could involve index representations of events; (*c*) neuromodulatory inputs from subcortical regions, such as the dopaminergic input from the ventral tegmental area (VTA); and (*d*) numerous inhibitory inputs (projection and intrinsic) that regulate the timing of neural events and the opportunity for plasticity (Dudai 2004). The paired-association of spatial information and event information could be realized automatically by hippocampal N-methyl-D-aspartate (NMDA) receptor–dependent synaptic plasticity at CA1 synapses, subject to modulation via other afferents. Assessed via the phenomenon of long-term potentiation (LTP), this plasticity exhibits many physiological properties that are suitable for memory, provided it is embedded into appropriate distributed-associative anatomical circuitry such as that of areas CA3 and CA1. A growing body of evidence supports this aspect of the synaptic plasticity and memory (SPM) hypothesis (Bliss et al. 2007, Martin et al. 2000).

Propositions #2 and #3 relate to the persistence of encoded traces. Most automatically encoded traces will fade and be lost. It is vital that only some memory traces persist, the flipside of automaticity being the need to guard against saturation of distributed associative memory. The psychological determinants of trace selection include information content, the novelty or emotional significance of an event (linked to VTA dopamine upregulation), and that of others happening in the same spatio-temporal context. The relevance of ongoing events to the existing knowledge structures is also critical for consolidation.

Mediating these psychological processes of persistence are two neural mechanisms of memory consolidation (Dudai & Morris 2000): (*a*) cellular consolidation mechanisms that include the synthesis and synaptic capture of plasticity-proteins that stabilize memory traces within neurons at the level of the individual synapse, perhaps involving calcium-calmodulin kinases, such as calcium-calmodulin-dependent protein kinase (CaMKII), together with the products of mRNA activation at the soma or locally in the dendrites; and (*b*) systems consolidation mechanisms that reflect a dynamic interaction between populations of interconnected neurons within hippocampus and neocortex. The products of cellular consolidation are stable memory indices in HPC that last long enough for the slower systems consolidation process to work selectively. Cellular consolidation provides an initial filter on what could potentially be retained at the systems level. The synaptic tagging and capture (STC) hypothesis of cellular consolidation makes a number of behavioral predictions, which we discuss here.

We outline a new approach to systems consolidation. The standard theory holds that it is a process that involves a dynamic interaction

between the HPC and cortex that gradually—over weeks or months—enables a stable associative network of traces that are later used for memory retrieval (Squire 1992). Multiple trace theory asserts, in contrast, that some long-lasting traces remain in HPC, e.g., for spatial memory (Nadel & Moscovitch 1997). However, our recent data suggest that the cortex can be both a fast learning system and a fast consolidating system (Tse et al. 2007). For associative memory, the cortex makes immediate but transient changes in connectivity that decay rapidly unless the new hippocampally processed information is interleaved within existing, activated cortical frameworks (schema). HF index traces, retained by cellular consolidation mechanisms, guide the process by which new information is subject to systems consolidation, possibly by altering the synaptic weights of initially 'silent' connections to allow for rapid incorporation of new information in schema. Such intercortical connections may take time to develop (Chklovskii et al. 2004). However, once built, relevant new information can be assimilated into schema very rapidly. Put simply: we rapidly remember what interests us, but what interests us takes time to develop.

Although novelty-detection in HPC followed by the activation of dopaminergic neurons in the VTA—which, in turn, provides a reward signal for new learning that is projected to various networks (Lisman & Grace 2005)— and/or a temporary shutdown of certain inhibitory interneurons (Paulsen & Moser 1998) may together aid new memory encoding and trace persistence, we need to consider circumstances in which new memories supplant, interact, or assimilate with earlier consolidated memories. Thus, Proposition #4 provides a way to incorporate the new concept of reconsolidation—the idea that the act of retrieving previously consolidated memories can, in certain situations, put those memory traces back into a labile state such that they are again sensitive to the inhibition of protein synthesis and that they might be strengthened, overridden, or incorporated with new information. This is what Dudai (2004) and others (Alberini 2005, Sara 2000) have referred to as memory updating.

AUTOMATIC ASPECTS OF EPISODIC-LIKE MEMORY ENCODING IN ANIMALS

The Concept of Automatic Memory Encoding

A longstanding concept in human cognition is the distinction between automatic and controlled processes (Schneider & Shiffrin 1977). Is this distinction relevant to episodic-like memory formation in animals? And, if so, how and in what neural circuits do these ostensibly distinct processes operate?

With respect to episodic-like memory, unexpected neural events happen and it may be important for an animal to encode what, where, and perhaps when they have occurred—and to do so irrespective of whether episodic-like memory is engaged in some other purposeful activity. Attention will be momentarily diverted and, even though the animal had no intention of remembering this unexpected information nor was motivated to do so, it nonetheless encodes something about it. This is automatic or incidental encoding. Conversely, the animal may be engaged in some very specific goal-seeking activity when novel stimuli arise that are directly relevant to the task underway. This would engage intentional or controlled processing that is both task- and goal-related. The automatic versus controlled distinction does not map easily onto classical animal learning concepts, such as those of classical and instrumental conditioning, primarily because there is no obvious role for reinforcement in automatic processing. However, the idea does have echoes in classical phenomena such as latent learning, in which laboratory animals are shown to learn about the layout of a maze during exploration that occurs prior to being made hungry and the availability of food at the goal. It recently has been shown that the EC and HPC are engaged in different aspects of latent learning and goal-place associations, respectively (Gaskin & White 2007).

Memory reconsolidation: the process by which the act of memory retrieval appears to destabilize previously stored memory traces and thereby enable them to be strengthened or to incorporate new information

CA1: one subregion (the others are CA3, DG, EC, SUB) of the hippocampal formation containing different cell types and local circuits and interconnected by largely unidirectional circuitry

VTA: ventral tegmental area; a small brain area containing dopaminergic neurons

NMDA: N-methyl-D-aspartate

LTP: long-term potentiation

CaMKII: calcium-calmodulin-dependent protein kinase; an enzyme located at synapses widely believed to play a critical role in early stages of synaptic change at the time of memory formation

VPC: visual paired comparison task; an incidental memory task as used in human and nonhuman primate studies

SOR: spontaneous object recognition task, which does not involve food reward or other apparent reinforcer; the equivalent task to VPC for work with rodents

Various lines of evidence in nonhuman primates (Miyashita 2004) and rodents (Floresco et al. 1997, Seamans et al. 1998) are consistent with the automatic/controlled distinction, although it is not always expressed in such terms. Moreover, with respect to automatic and controlled aspects of encoding and retrieving experience, the supposition is that the medial temporal lobe is involved primarily in automatic encoding. This is not to deny that the prefrontal lobe can play a critical role in episodic memory encoding as well—it is only to assert that it does so when subjects engage in a more deliberate or prospective attempt to remember events.

Relevant Data

It is unclear what constitutes an incidental episodic-like learning paradigm for animals, as we cannot directly ask to what stimulus information they are consciously attending. The basic requirements are that encoding should be fast (e.g., one trial), lack explicit motivation or incentive for learning (e.g., explicit reward), and not require elaborate task planning of a prospective nature.

One example is the diverse family of visual paired comparison (VPC) and visual object recognition (VOR) tasks. In a spontaneous object recognition (SOR) task, introduced by Ennaceur & Delacour (1988), animals are first habituated to a test arena and then are merely exposed to toy objects placed within it for a short period of time and given the opportunity to investigate them. Rats and mice typically do this by cautiously approaching the objects and then engaging in sniffing and tactile behavior. After a memory delay, the animals are placed back into the arena containing duplicates of some of these objects, with one or more of the originals replaced by one or more novel objects. The animals typically explore the novel object(s) more than the familiar one(s). There is no apparent reinforcement for this exploration—it just happens. The differential sensitivity of various versions of VPC/VOR to hippocampal, perirhinal, and parahippocampal lesions (and other interventions) has been debated extensively in recent years (Aggleton & Brown 1999, Eichenbaum et al. 2007, Mumby 2001, Squire et al. 2007), with a number of studies revealing conflicting results (contrast Ainge et al. 2006 with Broadbent et al. 2004). A key idea is that the episodic-like character of some of these recognition tasks derives from protocols in which there is more than mere object recognition at stake—namely memory for object-place, object-context, and object-context-place associations—with impairments after localized HF lesions seen in these variations of the VPC/SOR task. A familiar object may be moved to a new location in the arena, or the arena context in which testing takes place may be changed, but the location of the objects within it remain the same—and other permutations. Eichenbaum et al. (2007) suggest that the HPC is essential for those variants of the task that require associations between objects and places, the parahippocampal cortex is important for place memory, while the perirhinal cortex subserves object familiarity.

In a new development in this field, reversible manipulations such as drugs that inactivate neural activity offer an opportunity to dissociate the contributions that the HF or perirhinal/parahippocampal cortex make to object recognition by giving the drugs at the time of encoding, the start of the consolidation period, or the time of retrieval (Barker & Warburton 2008, Winters et al. 2008). The use of such procedures is a conceptual improvement on classical lesion approaches that cannot easily dissociate distinct memory processes such as encoding and retrieval, but there are disadvantages. The spread of a drug may be incomplete within a target brain area, or it may pass beyond a cytochemical boundary and affect a different region. Histological data is rarely available to detect such imprecision. The use of drug manipulations with the VOR family of tasks is also less successful for studying consolidation because long-term memory traces are either not formed or relatively weak.

A related strand to thinking about episodic-like memory has been interest in the distinction between a hippocampal-independent

familiarity component of memory retrieval and a hippocampal-dependent recollection component—with signal-detection theory and receiver operating characteristic (ROC) procedures developed to help make this distinction (Haskins et al. 2008). The curvilinear component of the ROC curve is held to reflect familiarity, whereas a step-function at the origin is thought to reflect recollection. In animal experiments in which experimental lesions of the hippocampus (Fortin et al. 2004) or medial prefrontal cortex (Farovik et al. 2008) have been examined, a partial dissociation of familiarity and recollection is observed, supporting the two-process models of recognition memory (Eichenbaum et al. 2007). This work could, subject to the caveats raised above, be developed further through drug manipulations to establish whether the familiarity/recollection distinction operates at the time of encoding or retrieval (or both). For example, the claim that the hippocampus mediates recollection is really a claim about the phenomenological experience at the time of memory retrieval. Does this experience only require the HPC to be active at the time of retrieval? Or does it also require hippocampal-mediated encoding as well?

Although the ROC approach to distinguishing familiarity and recollection is intriguing, the analytic adequacy of this approach has been questioned (Wixted & Squire 2008) and, with it, the possibility that the ostensibly qualitative distinction between recall and familiarity actually reflects a distinction between strong and weak memories. Might there be other ways of making the distinction in animals that are qualitative rather than quantitative? In a new development, it has been suggested that VOR paradigms be supplemented by procedures that require recall rather than recognition of object-place associations (Eacott & Easton 2007). For example, in a study that used an E-shaped maze in which rats have to make a choice of which way to turn at a choice point without being able to see the target objects, fornix lesions were observed to disrupt choice behavior without affecting the relative time investigating novel and familiar objects found at the ends of the maze (Easton et al. 2009). This suggests that such lesions disrupt recollection without affecting familiarity, consistent with the work of the Eichenbaum group and the theoretical distinctions developed by Aggleton & Brown (1999).

Other tasks have been introduced as models of episodic-like memory in avian species (Clayton & Dickinson 1998). The idea was that the what-where-when triad of episodic memory might be addressed by specific behavioral protocols in animals. Initial attempts to show the same in rodents were unsuccessful, but recent work has established that rats can show integrated what-where-when in food-finding, replenishment, and degrade paradigms when appropriately trained in the radial maze (Babb & Crystal 2006, Naqshbandi et al. 2007). The sensitivity of these tasks to hippocampal dysfunction is unknown.

Paired-Associate Learning in an Event Arena

The event-arena protocols are a new set of procedures for rats that enable multiple, within-subject object-place associations to be encoded and stored across varying time periods (Day et al. 2003). In these procedures, the object is a flavored reward that can then be used as a cue for associative retrieval of place information. In addition, encoding is incidental in the sense that, on sample trials, the animal is engaged in securing a food reward with no imposed discrimination necessity for it to encode the location where the food was found (**Figure 1*A***). After a short delay, the animal is placed in a different start box and a second sample trial is run, now to a different sandwell containing a different flavor of food (**Figure 1*B***). An unexpected memory retrieval trial follows after a delay, ranging from minutes to hours, in which both sandwells are now available (**Figure 1*C***). The question is, what do the animals then do when the door opens? In practice, the animals display a tendency to revisit the location in the arena from which they earlier secured that food. In effect, the rat brings to mind the specific

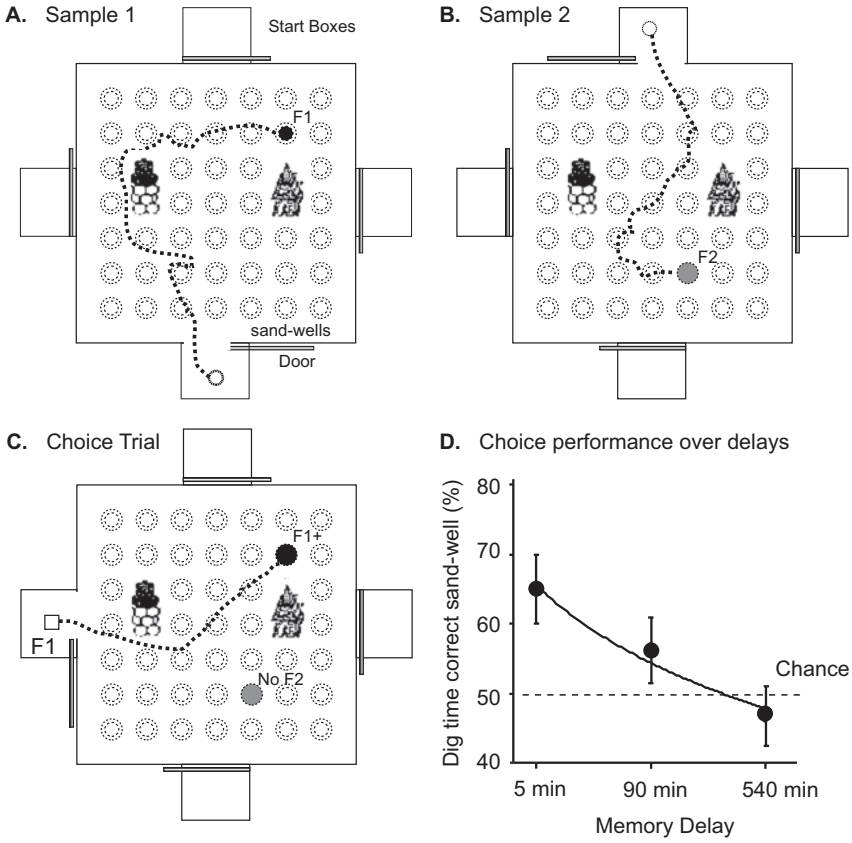

Figure 1

The event arena. (*A*) Schematic drawing of arena showing 7–7 array of possible sandwell locations, the two intra-arena landmarks, and the path of a rat from the south start-box to the single open sandwell containing food 1. (*B*) Path taken on the sample trial 2. (*C*) In the cued-recall choice trial, both sandwells used earlier are available, but the animal is cued with only one of the flavors (in this case, F1). The animal correctly takes a path to the sandwell that had previously contained this food. (*d*) Memory performance in the nonrewarded choice probe trials decays over a period of around 90 min.

location of the associated cue flavor and goes there. A contingency is arranged such that, if it goes there, it is rewarded by more of the same taste of food. Thus, it seems that the animals have automatically encoded the places where the food flavors had been located and, at retrieval, preferentially revisit the cued location. On the next day, a different pair of sandwell locations and flavors of food are used and the procedure is repeated, a process that can continue indefinitely across months of training. The task is thus an object-place task with one-trial automatic encoding, albeit supported by a contingency at the point of retrieval. Memory decays relatively rapidly (**Figure 1*D***).

The primary function of food in this unusual task is to act as a retrieval cue, although it also has the secondary role of acting as an incentive to the food-motivated animal. This renders performance less variable than is typical for VPC/SOR, but it creates an ambiguity regarding the automatic versus controlled dimension. Nonetheless, the results reveal effective single-trial information encoding, with rapid forgetting over a delay of around 90 min, that is sensitive to intrahippocampal infusions

of NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists (Day et al. 2003). Infusions of the NMDA antagonist D-AP5 prior to sample encoding block later memory, whereas infusions given before memory retrieval are without effect. Conversely, the AMPA antagonist CNQX blocks both encoding and retrieval. A spatial memory control task has also been developed with similar pharmacological sensitivity (Bast et al. 2005).

A potential weakness of the single-trial paired-associate encoding task is that, like VPC tasks, performance is never very good. We suspect this is typical of much automatic encoding, yet we can clearly remember some single events for long periods. These may occur in circumstances of surprise or emotional significance, as in "flashbulb" memories (Brown & Kulick 1977) or, more commonly, when new information is directly relevant to a person's existing knowledge base. In a new protocol, aimed at producing long-term reference memories lasting over days (Tse et al. 2007), six paired associates were trained concurrently (one trial/day for each pair), with repeated training across days (**Figure 2*A***, see color insert). After 15 sessions, the animals develop an associative schema denoting the locations of these six foods (inset in **Figure 2*B***) such that the rats could be cued with any of the foods to revisit the correct location and so secure more of the same food. It turns out that once the schema is learned, new paired-associates could then be trained in a single trial (session 21 in **Figure 2*B***), and the level of memory retrieval was very high (**Figure 2*C***).

Implications

Part of the difficulty of discussing incidental and intentional encoding in animals is that the distinction involves a feature of information processing by humans that is not easily captured by specific protocols. The differential effects of HF lesions on incidental tasks, such as visual paired comparison, and deliberate tasks, such as delayed nonmatching to sample (Nemanic et al. 2004), have been noted before (Eichenbaum et al. 2007). The idea that episodic-like memory can be subdivided into automatic and controlled aspects is not new, but the supposition that the automatic component is captured by local synaptic learning mechanisms, such as hippocampal LTP, brings a neurobiological dimension to the debate. And with this comes the possibility of using regionally specific genetically modified animals (Nakazawa et al. 2003) to attribute the relative contribution of NMDA and other receptor mechanisms in different circuits of the hippocampus and cortex to automatic versus controlled processing.

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

D-AP5: amino-phosphono-pentanoic acid

Single-unit recording techniques, coupled to tasks that distinguish retrospective and prospective memory encoding (Ferbinteanu & Shapiro 2003), are also likely to be helpful because they will provide a neural signature, over and beyond place or reward-related information, of the content of information processing on any trial (Kametani & Kesner 1989). Additionally, the mere absence of reward in a task is no grounds on which to classify it as incidental—what matters is the relevance or novelty of the information in relation to the task in which an animal is engaged. Moreover, incidental encoding can still occur during a deliberate task. Given these complexities, it seems clear that there is still a huge task before us of designing appropriate behavioral protocols for animals to study the ever more subtle aspects of memory processing that are revealed by taking a neurobiological perspective.

During the course of a day, it is to be expected that a great deal of information that is automatically encoded should be forgotten rapidly, with only a subset retained—an insight about memory originally proposed by Marr (1971). This raises the possibility of there being a window of time in which separate processes intervene to determine information retention. That is, there is no need for all the neurobiological events that determine persistence to occur or be set in train when an event occurs. This is not to deny that on-line cognitive processes will influence the electrophysiological or hemodynamic signature of a stimulus and so contribute to its eventual memorability (Brewer et al. 1998,

Wagner et al. 1998). Rather, it is to recognize that various memory-related neural events take time—such as signal-transduction, gene transcription, and the transport of molecules to synaptic targets. A key novel feature of our neurobiological framework of memory persistence builds upon the neural concept of synaptic tagging and capture (see below).

SYNAPTIC TAGGING AND CAPTURE: COGNITIVE AND BEHAVIORAL IMPLICATIONS

Memory Consolidation and the Concept of Synaptic Tagging and Capture

The idea that memory traces might gradually stabilize over time is an old one. That a time period is required for a memory to be maintained for any length of time was first proposed by Müller and Pilzecker (see Lechner et al. 1999 for a summary in English). They called this the consolidation period—a time during which interfering material could impair the recall of the target memory at a later time. Retroactive inhibition paradigms have since provided evidence that new traces are subject to consolidation (Heinemann et al. 1981, McGeoch 1932).

The understanding of how the brain contributes to consolidation in humans drew upon seminal reports of amnesic patients. One of the earliest reports of memory loss came from the study of Korsakoff syndrome, first described in 1887, which characterizes the memory loss associated with chronic alcoholism (Shimamura et al. 1988). However, this syndrome involves a wide range of abnormalities in the brain, offering less precision about the link between a specific brain area and a particular memory function. One well-characterized amnesic patient, H.M., was reported by Scoville & Milner (1957). H.M. had selective surgical damage to the medial temporal lobe for the relief of epilepsy and is reported to have had a remote memory gradient of around 3+ years (Corkin 1984). This temporal graded retrograde amnesia was later demonstrated in animal models using experimental lesions (Kim & Fanselow 1992, Zola-Morgan & Squire 1990).

Parallel to human studies, early animal studies offered different evidence for causal links between brain and memory consolidation. Duncan (1949) applied electroconvulsive shock (ECS) to rodents after training to induce experimental amnesia, a procedure that was later shown not to be dependent on the punishment effect of ECS (Gold et al. 1973). Experimental amnesia was also demonstrated by using protein synthesis inhibition, validating the role of protein synthesis in memory consolidation (Squire & Barondes 1972). This was an important advance because it suggested that cerebral protein synthesis was more than mere housekeeping—rather, it was a vital biological process necessary for new memories to be stabilized. The idea that such manipulations, when applied within a certain time window after training, impair the long-term maintenance of the memory was theorized within a consolidation framework (Matthies 1989, McGaugh 2000). A distinction between systems consolidation (suggested by the human studies) and cellular consolidation (suggested by the ECS and protein synthesis-inhibition work with animals) is now widely used (Dudai & Morris 2000). Cellular consolidation reflects processes happening at the single-cell level involving signal-transduction pathways and gene activation, whereas systems consolidation involves an interaction between distinct brain areas.

The theoretical framework developed by Morris (2006) capitalizes on these earlier ideas by relating mechanisms of cellular consolidation to the physiological phenomenon of LTP. Specifically, it was proposed that memory traces in the mammalian brain are encoded as distributed patterns of synaptic weights that persist over time. LTP is a physiological model of such changes, but lasting for variable durations of time (Bliss & Lømo 1973). A protein synthesis–independent form of LTP, often called early LTP (E-LTP), is perhaps akin to the rapidly decaying memories seen in the event arena (**Figure 1**). Protein synthesis–dependent late LTP (L-LTP) lasts longer, both in vivo

(Krug et al. 1984) and in vitro (Frey et al. 1988). The difference between E-LTP and L-LTP also reflects a key difference between STM and LTM—that de novo protein synthesis is required for a short-lasting trace to be converted into a long-lasting one. It draws upon experimental work in *Drosophila* (Belvin & Yin 1997), *Aplysia* (Montarolo et al. 1986), early learning in birds (Rose 1995), and mammalian memory (Davis & Squire 1984, Dudai & Morris 2000, Goelet et al. 1986, Kelleher et al. 2004).

The new perspective, now embedded within the hippocampal-neocortical interactions theory, is the synaptic tagging and capture (STC) hypothesis of memory trace formation (Frey & Morris 1997). This hypothesis accepts that plasticity related proteins (PRPs) are critical for the persistence of synaptic memory traces, but argues against the standard model that their de novo synthesis is necessarily triggered by neural activity associated with the actual events to be remembered. New PRPs are still required, but their synthesis may be regulated in other ways and over a longer time window. According to this idea, the creation of long-term memory traces is a dual process. In one step, the potential for a long-term memory is established locally at synapses in the form of rapidly decaying E-LTP accompanied by the setting of a synaptic tag and triggered by glutamatergic activation of NMDA and AMPA receptors. In the other step, a series of biochemical interactions, including activation of various signal transduction pathways and protein-protein interactions, converts this synaptic potentiation into a stabilized trace at those synapses at which tags have been set. The events that lead to these interactions can be set in motion shortly before the event to be remembered, at the same time, or shortly afterward. This leads to the interesting psychological idea that the persistence of memory does not have to be determined at the exact moment of initial memory trace formation.

Relevant Data

In the original tagging experiment (hippocampal CA1 brain slices in vitro), Frey & Morris (1997) arranged for one afferent stimulus pathway (S2) to be strongly tetanized in the presence of anisomycin (an antibiotic drug with a number of actions including the inhibition of protein synthesis). Ordinarily, this protocol leads to a short-lasting potentiation lasting 2–3 hr. However, when S2 tetanization occurs 1 hr after equally strong stimulation to an independent S1 pathway to the same population of neurons given in the absence of anisomycin, long-lasting LTP (>8 hr) occurs on both pathways. This is paradoxical, as LTP lasting 8 hr is known to depend on protein synthesis, yet is here induced on S2 during the inhibition of such synthesis. It was argued that synaptic tags on the S2 pathway (that are set by a post-translational mechanism) sequester PRPs induced in response to stimulation of the S1 pathway.

Follow-up studies have included weak-before-strong experiments showing that weak tetanization, which ordinarily results only in STP, can lead to L-LTP after strong stimulation of S1 (Frey & Morris 1998); competitive maintenance under circumstances of competition for PRPs (Fonseca et al. 2004); priming experiments (Young & Nguyen 2005); tag-resetting investigations (Sajikumar & Frey 2004b); and intriguing cross-tagging and capture experiments revealing that E-LTP can be transformed in L-LTP by prior L-LTD on an independent pathway, and vice versa, i.e., E-LTD to L-LTD by L-LTP on the other pathway (Sajikumar & Frey 2004a). The latter finding strongly suggests that the PRPs upregulated by L-LTP and L-LTD are overlapping. Using a transgenic mouse overexpressing a constitutive CREB, Barco et al. (2002) have shown the relatively immediate induction of L-LTP (identified in this case by its insensitivity to depotentiation). These findings are complemented by earlier experiments in *Aplysia* neurons in culture (Bailey et al. 2000, Martin et al. 1997), suggesting the phenomenon might be widespread in diverse neural circuits. In conclusion, STC points to dual regulation of potentiation (strength) and persistence (stability) via interacting synaptic and cytosolic processes and suggests a powerful framework for enriching

the repertoire of long-term memory mechanisms (**Figure 3*A***, see color insert). Further physiological and molecular aspects of STC, beyond the scope of this review, are discussed in Kelleher et al. (2004) and Reymann & Frey (2007).

Cognitive and Behavioral Implications

Various behavioral paradigms have been developed to explore the relevance of these physiological ideas to memory formation. Frey's group has examined the persistence of LTP in vivo as a function of reinforcing behavioral events happening shortly after LTP induction. For example, Seidenbecher et al. (1997) observed that allowing thirsty rats to drink water within a discrete interval after induction of an LTP that normally decayed to baseline could result in this LTP in vivo lasting much longer. They argued and presented evidence that this was due to engaging reward-associated dopaminergic neurons whose activation of the hippocampus triggered signal-transduction mechanisms that upregulate the availability of PRPs. The idea that a dopaminergic input to the hippocampus might modulate the persistence of memory has also been successfully tested using a water-maze paradigm.

In a particularly interesting test of the STC framework, recent experiments have shown that the memory for weakly trained inhibitory avoidance, which is normally forgotten over 24 hr, can persist if the trained animals are given the opportunity to explore a separate novel environment (Moncada & Viola 2007). This exposure has few stimulus attributes in common with the inhibitory avoidance paradigm itself and would not be expected to interfere or enhance performance in a direct stimulus-specific manner. Instead, exploration is known to upregulate plasticity-related mRNAs (such as Arc and zif-268), raising the possibility that they or other similarly upregulated genes synthesize PRPs that are captured at task-relevant synapses in the hippocampal network and so stabilize the learning-associated synaptic changes responsible for inhibitory avoidance memory. Moncada & Viola (2007) established that the ability of exploration to enhance memory for inhibitory avoidance was sensitive to both intrahippocampal infusions of anisomycin and the D1/D5 antagonist SCH23390 given shortly before exploration—indicating a clear compatibility with the STC framework. Parallel and independent work by our own group indicates that novelty exploration can increase appetitive one-trial spatial memory, which is normally rapidly forgotten within 24 hr (S-H Wang, R Redondo, and RGM Morris, manuscript in preparation).

It has also been shown, using a conditioned taste-aversion task, that weak aversive conditioning of a taste can be made more persistent by prior strong conditioning of a different novel taste. The novelty of the facilitating, strong taste is critical; a well-familiarized taste did not enhance the subsequent learning. The facilitating taste conditioning is, however, unable to rescue the learning impairment seen when strong taste conditioning is induced during protein synthesis inhibition (Merhav & Rosenblum 2008). This pattern of results fits aspects of STC. Moncada & Viola's (2007) finding suggests that PRP upregulation by novelty exploration can be used by later learning. This implies that the exploration has a neurobiological impact on a hippocampal cell population that at least partially overlaps with or encompasses the cell population activated by a contiguous learning event. It is possible that box exploration drives a dopamine input from the VTA to HPC, while learning may trigger a specific cell assembly within HPC (Lisman & Grace 2005). Frey & Morris (1998) also predict a substantial overlap of the population of cells affected by both events—something more difficult to achieve in behavioral studies than in in vitro slice work. On the other hand, Merhav & Rosenblum's (2008) finding implies that although the facilitating taste helps with subsequent learning, the upregulation of PRPs either is not sufficient to rescue the impairment induced by protein synthesis inhibition in the insular cortex or is not in the same pool of cells that are recruited to represent the learning event (**Figure 3*B*,*C***).

Implications

There are a number of outstanding issues concerning the possible role of STC in cellular consolidation. First, the phenomenon, widely studied in vitro, has not yet been shown neurophysiologically in vivo. Such experiments are not easy but are underway in several labs. Second, STC is a cellular phenomenon, but activation of PRPs may be triggered by neural events such as novelty detection and consequent upregulation of neuromodulatory transmitters that involve diverse neural circuits. It is therefore a phenomenon that links cellular and systems aspects of consolidation. This is important because, as noted in the Theoretical Overview: Hippocampal-Neocortical Interactions Theory section above, STC acts as a kind of filter that selects a subset of automatically captured events and thus allows only them to be subject to the longer time scale of systems consolidation. The dovetailing of time scales is intriguing and merits further examination. Third, the phenomenon of behavioral tagging, as first shown by Moncada & Viola (2007), deserves more investigation—not least because it forces us to think more about behavior as a stream of events and actions over time, whose underlying neurobiological mediation interacts, than as the discrete events we isolate and study in laboratory experiments.

HIPPOCAMPAL-NEOCORTICAL INTERACTIONS IN SYSTEMS CONSOLIDATION AND THE ROLE OF SCHEMAS

The Concept of Systems Consolidation and Mental Schemas

The question of whether the HF is always required for explicit memory formation or has a time-limited role has long been studied and debated. We have already noted that patients with medial temporal lobe damage can show temporal-graded amnesia, impairing recent but not remote memory (Scoville & Milner 1957, Zola-Morgan et al. 1986). This upward temporal gradient—paradoxically better memory for older information—suggested that the HF is required for consolidating memory over time, with long-term memory traces gradually consolidated in relevant cortical areas (Squire 1992). Systems consolidation theory has been developed, hypothesizing that the HF is required to strengthen the initially weak connections among cortical modules/areas that are encoded in parallel with the potential index sites in the hippocampus (Teyler & DiScenna 1986). Complementary to work on patients, recent functional brain imaging data in humans suggest that during the recall of semantic memories (i.e., facts), hemodynamic activity in the HF is highest for recent news events (3 years) but decreases with the age of the events (over a 30-year span) (Smith & Squire 2009). Takashima et al. (2006) have also shown that for confident memory recall, there is reduced hippocampal activity for 90-day memories compared to 1-day information.

However, flat gradients of remote memory are also seen in amnesic patients, notably in Korsakoff cases (McCarthy & Warrington 1990), leading initially to the idea that amnesia may be a problem of memory retrieval. While Korsakoff cases are complicated by damage and metabolic abnormalities in more widespread brain areas (Kopelman 1995), several studies have shown flat gradients of retrograde amnesia in more focused MTL-damaged patients (e.g., Cipolotti et al. 2001). Some functional brain imagining studies also reveal HF to be equally activated for recent or remote memories in the retrieval of autobiographical memories (Ryan et al. 2001).

Accordingly, proponents of multiple-trace theory have challenged the standard model (Moscovitch et al. 2006, Nadel & Moscovitch 1997). This theory proposes that, upon each occasion of memory retrieval, a new trace may be created by the HPC—regardless of memory age. Although the gist of a memory may be intact after HF damage, the theory asserts that the detail and vividness of memory requires the HPC (Nadel et al. 2000). Specifically, it suggests that HPC is always required for storage and retrieval of allocentric and spatial

memories (Rosenbaum et al. 2001), whereas semantic memory is mediated by neocortex alone, subject to the completion of a systems consolidation process after learning.

Our alternative perspective considers the place of prior knowledge or mental schemas in determining the speed with which systems consolidation takes place. According to the standard model, it is widely thought that it takes a long time before intercortical connections become strong enough to support unaided memory retrieval. From a theoretical perspective, it has sometimes been argued that the HF is a fast learning system, whereas the cortex is a slow learning system (McClelland et al. 1995). Supporting evidence comes from recent immediate early gene (IEG) studies in animals, which show that a dynamic shift in maximal IEG expression after learning—from HF to cortex—takes place over weeks (Frankland & Bontempi 2005). However, the animals in which these observations are made are typically experimentally naïve at the time of initial training. This is not only unlike the situation in human amnesics, who have a lifetime of experience behind them, but is also unnatural in that adult learning by animals in their normal habitat will generally take place against a background of prior knowledge.

The question we considered is whether new information processed by the HF can be consolidated into the cortex more easily, or in a different way, if this new information is relevant to prior knowledge. An extensive body of human literature suggests that it should (Bartlett 1932, Bransford 1979). Associative frameworks of knowledge are stored in the cortex, with growing evidence that the dynamic changes in circuitry required involve activity-dependent synaptic plasticity, with dendritic and synaptic growth mediated by BDNF and other growth-associated signal-transduction pathways (Osada et al. 2008). Like the standard model of consolidation, it is reasonable to suppose that such growth processes take time. However, once a framework or schema is created, it may then be possible to assimilate relevant new information relatively easily. We therefore created a paradigm in which animals first learned multiple paired-associates involving spatial locations over several weeks—and so became task experienced—and were then required to learn two new paired-associates, each in a single trial. As described in the Automatic Aspects of Episodic Memory-Like Encoding in Animals section above, a single trial of training proved sufficient to create a memory of the new paired-associates lasting at least 24 hr (Tse et al. 2007). We turn below to the issue of what happens when lesions of the HF are made shortly after such training.

Relevant Data

Because the site and extent of brain damage varies across human amnesic patients, complicating comparisons across studies (Rosenbaum et al. 2001), we focus here on animal studies. These offer greater precision of lesion size and location and the opportunity of using other techniques, such as IEG expression, to study consolidation (Frankland et al. 2007).

Several animal studies suggest that the HF plays a time-limited role in the stabilization of certain memories, such as contextual fear conditioning (Kim & Fanselow 1992; see review in Morris 2007). Brain imaging approaches, using immediate early-gene activation, also support similar ideas that recent, contextual fear memory triggers more IEG expression in the hippocampus and less expression in the neocortex (e.g., anterior cingulate cortex, infralimbic and prelimbic cortex), whereas the opposite pattern is observed for remote memory (Frankland et al. 2004). A similar finding was reported using a spatial radial-maze task (Maviel et al. 2004).

However, whereas a temporal gradient of amnesia or IEG expression is seen for context fear conditioning and certain radial-maze paradigms, such a gradient does not occur with spatial learning in the water maze. Several studies have now shown that HF lesions made remotely after training still impair memory that might have been expected to have been consolidated in neocortex over such an interval (Broadbent et al. 2006, Clark et al. 2005, Martin et al. 2005). On the face of it, these data support

multiple trace theory. Moreover, using both causal and correlational approaches, Teixeira et al. (2006) showed that hippocampus inactivation by lidocaine at retrieval disrupted both 1-day and 30-day spatial memory in the water maze. In addition, memory recall at 1 day or 30 days after training was equally good at triggering IEG expression in subfields of HF. These studies suggest the HF plays a special lasting role in supporting spatial navigation that relies on the use of allocentric information.

Thus, the debate between standard systems consolidation theory (Squire & Bayley 2007) and multiple trace theory (Moscovitch et al. 2006) also exists for animal work and is unresolved for several reasons. Each theory has abundant supporting evidence. In addition, multiple trace theory can accommodate negative findings that do not seem to fit the theory (e.g., the lack of remote memory impairment could be because the level of detail of the memory is not tested); likewise, standard systems consolidation theory can also explain findings that appear at first to be in conflict. Although new findings will continue to inform this debate, new issues are also emerging: (*a*) whether the qualitative nature of memory traces changes over time; and (*b*) whether systems consolidation can occur in a much shorter time scale, challenging the concept of "fast" and "slow" learning systems.

Regarding the first issue, recent studies using context fear conditioning suggest remote memory can generalize across contexts, whereas recent memory tends to be more discriminative. For example, Winocur et al. (2007) showed that, when tested a few days after learning, animals discriminated a dangerous context that was previously paired with footshock and a safe context that had never been paired with footshock. In contrast, their remote memory tested weeks later of the dangerous context remained generalized to the safe context. When HF lesions were made one day after training, the generalization remained, although the overall performance was also reduced. Wiltgen & Silva (2007) made similar findings and indicated that a deficit in retrieval may contribute to poor performance of an old context memory because brief re-exposure to the training context was sufficient to enhance discrimination on the next day. Biedenkapp & Rudy (2007) also found that context memory can become less precise with time. Interestingly, pre-exposure to the to-be-reinforced context, but not to an irrelevant context, helped to maintain the discrimination for longer.

These changes in the performance of normal animals when memories are tested at varying intervals after training must be born in mind when making comparisons between control and lesioned animals. For example, when remote memories generalize across contexts in normal animals and if generalization is also observed in lesioned animals, it cannot be unambiguously claimed that the brain area targeted plays an equally important role in recent and remote memory. To address this, a paradigm that allows for similarly precise recent and remote memory becomes crucial. Wang et al. (2009b) showed that context discrimination can remain as good when tested 42 days later as when tested after 1 day later when a training protocol is used that encourages discrimination between reinforced context and nonreinforced context. Control experiments showed that this is not an effect of memory strength, as equivalent training compressed into one session did not encourage discrimination over time (**Figure 4*A***, see color insert). Critically, HF lesioned mice discriminated similarly to sham-lesion controls when lesions were made 42 days but not 1 day after training (**Figure 4*B***). The 42-day lesioned animals also discriminated well in reinforced versus novel contexts or versus hybrid contexts that contained some elements of reinforced and nonreinforced context. This study suggests that the ability to differentiate between contexts can be preserved without the hippocampus, provided sufficient time has been allowed for systems consolidation.

Training protocols not only influence whether memory retains its precision over time; training can also determine if the HF is persistently required for representing memory. For example, extensive familiarity with the

environment where the memory is going to be built can enable the memory to become hippocampus independent. Winocur et al. (2005) showed that if rats were substantially habituated to a complex training village containing multiple pathways for accessing water and food in various compartments, post-training hippocampus lesions did not impair performance in searching around the village—suggesting that extensive experience of an enriched environment can enable animals to maintain at least some aspects of spatial memory without the hippocampus. However, it is unclear whether rearing in an enriched environment promotes hippocampal-independent spatial memory, or whether the extensive experience of the training and testing environment is critical for the observation of a lack of effect of the lesions.

Rapid Systems Consolidation

Our new schema idea about consolidation has emerged from our work with the concurrent paired-associate task following an astonishing but predicted observation—cortical consolidation can occur very rapidly. Having previously learned six paired-associates and developed a schema, rats trained for a single trial on each of two new paired-associates 48 hr prior to being given bilateral HF lesions could successfully recall the correct location at which to dig for more food when given a recall trial two weeks later (Tse et al. 2007; **Figure 5*A***). Moreover, upon returning the control and HF lesioned animals to the old test environment many weeks later, the HF animals were immediately (trial 1) above chance in remembering the correct locations to visit in the cued-recall paradigm that they had learned prior to being given the lesions (**Figure 5*C***). A within-subjects design was used in which one testing environment made sense with associations between flavors and locations remaining stable over days and weeks. In the other environment, they remained stable for only two days before being changed, such that a given flavor now had no stable spatial paired-associate. When the animals were given the opportunity to learn two new paired-associates in two trials in each environment (one trial per associate), without re-exposure to the old flavors, learning was successful in the stable environment but unsuccessful in the inconsistent environment, when memory was tested 24 hr later (**Figure 5*D***). Thus, prior knowledge plays a causal role in encoding and/or consolidation. Last, and most critical, an investigation of the time interval after learning new paired-associates before hippocampal lesions were made revealed that lesions made 3 hr after training blocked consolidation completely, whereas those made 48 hr after training did not (**Figure 5*E***). This finding confirmed the observation of rapid systems consolidation and set a boundary condition, requiring further investigation, of the time over which it may take place. This short interval also points to the potential importance of sleep in consolidation, in keeping with much current theorizing in humans (Stickgold & Walker 2007) and in animals (Buzsaki 1989, Sutherland & McNaughton 2000).

Implications and Related Issues

Since the idea was first proposed that hippocampus processes information for memory automatically and rapidly (Marr 1971), computational models have been developed to account for how memory traces may or may not become hippocampus independent (McClelland et al. 1995, Meeter & Murre 2004). At the neuronal level, one early suggestion is that a replay of neuron assembly activity that represents a memory can be the mechanism for strengthening intercortical connections that may eventually become strong enough to support memory without the hippocampus—possibly via sharp waves (Buzsaki 1989). During sleep, replay of a neural firing pattern that was previously recorded during training in the awake period is observed in the rat hippocampus (Skaggs & McNaughton 1996) and prefrontal cortex (Euston et al. 2007). Takehara-Nishiuchi & McNaughton (2008) further showed that prefrontal cortical neurons maintain increased activity for up to six weeks

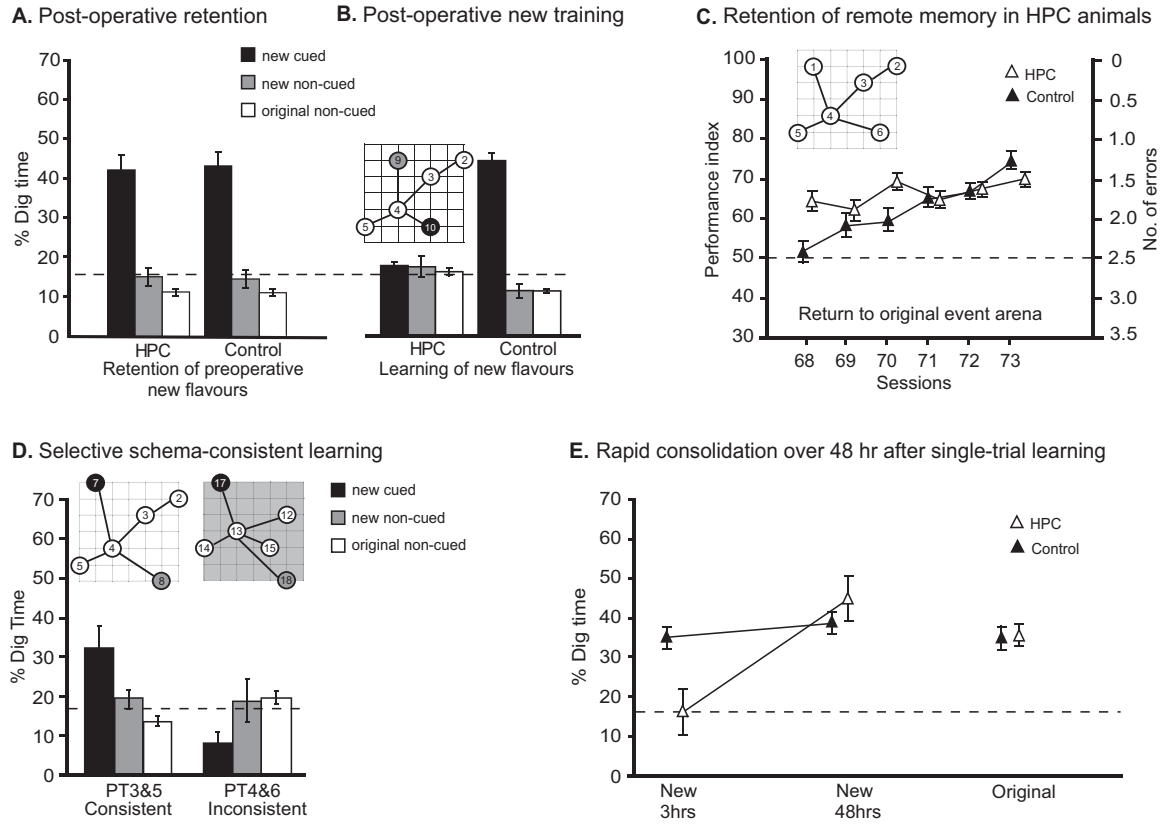

Figure 5

Rapid consolidation in association with schemas. (*A*) Normal retention by HPC-lesioned rats when a retention test was given two weeks after lesions made 48 hr after a single trial of training to each of two new paired-associates, after extensive training on a schema of six paired-associates. (*B*) The same HPC-lesioned rats are unable to learn new paired-associates in the event arena. (*C*) After extensive training in a new context over many weeks, return of the control and lesioned animals to the original training context reveals effective memory by the HPC-lesioned animals on the first trial of training. Poorer memory by controls, which rapidly catch up, probably reflects interference that they, but not the HPC-lesioned rats, have from the other context of learning. (*d*) Extensive training with a consistent schema or an inconsistent schema in separate contexts enables new paired-associate learning and retention over 24 hr only in the consistent environment. (*E*) Varying the time when HPC lesions are made after introducing two new paired-associates against the background of a prior schema reveals a rapid upward gradient of systems memory consolidation.

after training. Evidence for hippocampus-neocortical interaction comes from a study showing that signatures of neural activity in the hippocampus coincide with neocortical activity (Battaglia et al. 2004), suggesting an orchestration of activity between hippocampus and neocortex. A recent study showed that at the time of memory recall, neuronal activation that resembles firing patterns that occurred during encoding may be replayed (Gelbard-Sagiv et al. 2008). Although these observations point to a correlational biological mechanism, the causal role of this mechanism in supporting systems consolidation needs future studies.

What is the distinction between a memory that permanently requires the hippocampus and a memory that can become hippocampus independent? A temporal gradient of retrograde amnesia is observed in context fear conditioning (Kim & Fanselow 1992) but not water-maze learning (Martin et al. 2005); thus, it has been proposed that the HPC is necessary for

the latter, as it plays a critical role in spatial navigation in which the constant use of allocentric information is required to guide the animals' sense of location, direction, and destination. However, the HPC may also play a role in other components of spatial learning, such as distance estimation by using visible beacons (Clark et al. 2007). Of note here is Teixeira et al.'s (2006) observation that HPC inactivation can trigger more thigmotaxic behavior (i.e., swimming near the walls) whether given under recent or remote conditions. It is unclear whether HPC inactivation encourages animals to use different swimming strategies (swimming near the wall) compared to control animals (preferentially swimming in the center zone).

One discrepancy between the schema version of the event arena and reference memory in the water maze is that performance can be eventually independent of HPC in the event arena but always requires it in the water maze. One possibility is that in the event arena, the cued-recall nature of the memory test (where a particular flavor is given to cue the corresponding location), and that only a limited number of target locations are used (e.g., six open sandwells), is easier or does not require recollection. For the water maze, on the other hand, the free-recall nature of the memory test is harder and may require recollection.

RECONSOLIDATION AND THE UPDATING OF MEMORY

The Concept of Reconsolidation

One outstanding question about consolidation theory is whether memory traces are permanently stabilized once they are consolidated. Some early studies suggest this may not always be the case. For example, the loss of an apparently consolidated fear memory was demonstrated when ECS was applied immediately after memory recall (Misanin et al. 1968, Schneider & Sherman 1968). This cue-induced amnesia suggested that a once-consolidated memory could still be plastic, leading to the concept of a reconsolidation process. Lewis (1979) proposed the idea of active and inactive states of memory to describe the lability of the memory. Two decades later, interest in this concept has been reawakened (Nader et al. 2000, Sara 2000).

At first sight, reconsolidation appears paradoxical. The framework we have discussed so far supposes that when an animal is confronted by unexpected new events, it engages an automatic encoding process, which may then trigger the successive steps of cellular and systems consolidation. As time goes by, a stable long-term memory trace is established that would be accessed at the time of memory retrieval. Why and when might it be appropriate for that access to reinstate lability' of the trace? We suggest below that the "why" component of reconsolidation differs across distinct types of memory (particularly in amygdala versus hippocampus). However, for hippocampus-dependent memory, we concur with others in proposing that reconsolidation occurs when there is new information at the time of memory retrieval—information that might potentially require an established long-term memory trace to be altered. Hence, the function of re-engaging lability is to change or strengthen the ostensibly consolidated trace. These ways of thinking about reconsolidation have been called memory updating (Dudai 2004), as the new information at reactivation updates information acquired during earlier experiences. There are two major sources of updating: training-induced updating, and updating induced by a discrepancy between training and reactivation.

Memory updating, as a particular form of reconsolidation, may be involved in the recall-triggered modification of existing long-term memories. Memory updating during retrieval mirrors the novelty detection proposed in Morris (2006) and bears the automaticity property of Proposition #1. Novelty detection is evident in studies showing increased exploration of objects in new contexts (Good et al. 2007, Save et al. 1992), in studies showing increased immediate early-gene expression in the hippocampus after exploration in a novel environment

(Guzowski et al. 2006), and in studies exploiting exploration in a novel place with respect to its impact on other learning (Moncada & Viola 2007). In the context of memory reconsolidation, novelty is likely derived from mismatch between consolidated and current information, which then re-engages the encoding process.

Relevant Data

The past decade has seen the publication of new evidence for the memory reconsolidation phenomenon. For example, Nader et al. (2000) showed that auditory fear memory can be weakened by protein synthesis inhibition in the amygdala after memory reactivation. In this study, several important control conditions were performed: No memory impairment was observed when protein synthesis inhibition was given without memory reactivation; a time window was identified, as no memory impairment was seen when the protein synthesis inhibition was long delayed after reactivation; and an intact post-reactivation short-term memory test was used to rule out nonspecific side effects of the drug. Diverse studies have shown memory reconsolidation in a wide spectrum of animals and various types of memory (Nader & Hardt 2009).

In an examination of reconsolidation in context-related learning using systemic drug application, it has been shown that context-associated memory, such as contextual fear conditioning (Eisenberg et al. 2003) and inhibitory avoidance (Przybyslawski et al. 1999), undergoes reconsolidation. Despite the ubiquitous nature of the phenomenon, reconsolidation does not always occur after memory reactivation. Several factors have been described to determine when memory reconsolidation happens.

The first of these factors is memory strength. For a stronger training protocol, a longer reactivation session is required to trigger reactivation and a reconsolidation process that is susceptible to protein synthesis inhibition (Suzuki et al. 2004). A second factor is memory age. Inhibitory avoidance memory undergoes reconsolidation if reactivation occurs within seven days but not when scheduled two to four weeks after training (Milekic & Alberini 2002). Similar data, but over a different time scale, have been reported for context fear memory in mice (Suzuki et al. 2004). Third, there is evidence that reactivation should be nonrewarded. This was first suggested many years ago in the era of cue-induced amnesia (DeVietti & Holliday 1972), and was recently shown in context-visual danger-association learning in crabs (Pedreira et al. 2004). Paradoxically, although a nonreinforced trial at reactivation may be necessary for observing reconsolidation, multiple nonreinforced trials may give rise to extinction—and with it, new learning. Thus, fourth, when reactivation is a prolonged nonreinforced session that triggers extinction, the extinction process can dominate, and reconsolidation will fail to occur (Suzuki et al. 2004). On the other hand, if the training is so weak that a nonreinforced trial is sufficient to trigger extinction, then the impairment of extinction, instead of a reconsolidation impairment, is observed (Eisenberg et al. 2003).

Although these factors have been discussed and called boundary conditions (Nader & Hardt 2009, Tronson & Taylor 2007), the same set of conditions, based on studies with systemic treatments that affect the entire brain, may not apply to reconsolidation in specific brain areas. For example, memory age may not be a boundary condition in hippocampal reconsolidation based on current studies. It was shown in rats that old (45 days after training) context fear memory still undergoes reconsolidation in the hippocampus (Debiec et al. 2002). Although in mice it might not be the case (Frankland et al. 2006), the discrepancy could be due to the differential potency of intervention (i.e., impairment of recent memory is only partial in the mice studies but more substantial in rat studies (Debiec et al. 2002, Lee 2008). On the other hand, memory strength (Mamiya et al. 2009) and reactivation procedures (Fischer et al. 2004) are critical in the hippocampus reconsolidation.

Memory Updating and Spatial Memory

We now focus on an aspect of reconsolidation most relevant to a theme of this review—the circumstances in which it occurs in association with spatial memory. Morris et al. (2006) trained animals in a reference memory water-maze task in which the submerged escape platform remained at a fixed location across days. When the memory of the platform location was reactivated by one nonreinforced probe trial, post-reactivation protein synthesis inhibition in the dorsal hippocampus did not impair the memory. A positive control for the effectiveness of the anisomycin established separately that overnight consolidation of this reference memory task requires protein synthesis. However, when the animals were trained to search for new platform locations on each day, in the episodic-like delayed-matching-to-place task (Steele & Morris 1999), protein synthesis inhibition immediately after a nonreinforced probe trial was sufficient to impair memory tested on the following day. A control with the omission of memory reactivation showed that this impairment was seen only if anisomycin was contingent on memory reactivation. Taken together, the findings from this study suggest that reconsolidation is only observed when the reactivation involves new memory encoding.

On the other hand, other studies have suggested that spatial reference memory in a water maze can undergo reconsolidation. For example, Rossato et al. (2006) showed that reactivation with one nonreinforced probe trial rendered memory labile if coupled to anisomycin infusion into area CA1 of the dorsal hippocampus. Further experiments indicated that this spatial memory did not undergo protein synthesis-dependent reconsolidation when memory reactivation was omitted, anisomycin infusion delayed, and most importantly, when reactivation was a reinforced, relearning trial. The same lab later used a similar paradigm to confirm the same conclusions by using intra-CA1 PKC inhibition (Bonini et al. 2007) and intra-CA1 mRNA inhibition (Da Silva et al. 2008).

The idea that the reference memory in the water maze can undergo reconsolidation was also demonstrated in mice. Artinian et al. (2007) used intra-CA3 anisomycin infusion and different reactivation protocols and found impaired reconsolidation when the reactivation involved (*a*) a swimming/relearning trial, (*b*) a placement on the submerged platform without swimming, or (*c*) a placement on the emerged platform without swimming. Thus, mere exposure to the platform in the water maze may be sufficient to reactivate spatial reference memory, which then becomes labile and sensitive to protein synthesis inhibition (Artinian et al. 2008).

It might seem puzzling that water-maze spatial memory sometimes undergoes reconsolidation, but sometimes does not. Its occurrence could reflect when the hippocampus engages memory updating during reactivation. One occasion is when updating occurs in the course of training of the delayed-matching-to-place task. In this task, animals are explicitly trained to find a new platform location on each day. Hence, at every first trial on a training day, the animals encode new information and retain it to guide later swimming trials on the same day. In this case, the reactivation trial of a memory reconsolidation experiment would trigger the retrieval of the previous day's platform location at the same time as an updating process is engaged for the expected new learning of the day. This may render the memory trace of the retrieved memory labile such that, when protein synthesis in the hippocampus is inhibited, information about this platform location is lost (Morris et al. 2006; **Figure 6**, see color insert).

Another scenario is that updating is triggered by some feature of testing that is different from the usual events of training. Most reconsolidation studies use a short, nonreinforced trial to reactivate the memory that had previously been acquired through consistent reinforcement. This procedural difference may itself trigger hippocampal protein synthesis to register the new nonreinforced experience

along with the memory. In other words, the short, nonreinforced reactivation may be insufficient to cause behavior change or induce extinction, but the experience is nonetheless linked to the memory by the hippocampus. The hippocampal protein synthesis then acts to restabilize the memory network with links to the new nonreinforced experience. It is possible that the negative finding in reference memory by Morris et al. (2006) was due to familiarization with the nonreinforced probe trials that were used daily throughout the course of training. This frequent use of probe trials during training may have greatly reduced the necessity of registering the lack of reinforcement with memory reactivation and/or may have introduced a partial-reinforcement condition (Prados et al. 2008) that resulted in persistent nonlabile memory traces. Memory trace strength may then reach an asymptote that greatly reduces the possibility of observing an updating process in the HPC at reactivation (**Figure 6**).

A variation of memory reactivation in the water-maze task is to provide reinforcement without the swimming (Artinian et al. 2007). In this case, the updating process could be associated with incremental learning. Although learning curves can be very sharp in some cases (e.g., context fear conditioning), it can be more gradual in others (e.g., spatial learning in the radial-arm maze). The build-up of learning strength can be a more incremental process (Rescorla & Wagner 1972). During each additional learning trial, the previous learning experience is reactivated with more information added from the subsequent trial. It is possible that when incremental learning occurs during memory reactivation, hippocampal protein synthesis is also engaged (e.g., in Artinian et al. 2007, but not in Bonini et al. 2007). Lee (2008) showed that a second learning trial followed by a previously consolidated weak learning trial can strengthen context fear memory, supporting the idea of updating through incremental learning. Because the incremental part and the original part of the memory were both impaired by interference of reconsolidation, it suggests that additional learning indeed triggers the representation of the previous learning.

Extinction Differs from Memory Updating

After animals have acquired a learned task, the omission of reinforcement generally causes a decline in performance, which is called extinction (Pavlov 1927). Extinction is not a simple process of erasing the previously acquired memory, but rather is a form of new learning that inhibits the expression of a still present long-term memory (Bouton 2004). Evidence supporting this comes from the observation that once a memory is extinguished, it can reappear if the animal is provided with appropriate cues (Miller & Kraus 1977). The relevance of this to reconsolidation is that a memory reactivation trial in the absence of further reinforcement is—operationally speaking—an extinction trial. Accordingly, the question arises of when memory reactivation triggers reconsolidation and when it contributes to extinction.

Studies of taste aversion show that inhibition of protein synthesis in the insular cortex disrupts the extinction memory trace when nonreinforced reactivation extinguishes performance after a weak training, but it interrupts reconsolidation if reactivation is not sufficient to cause extinction after a strong training (Eisenberg et al. 2003). It is proposed that the dominant trace during reactivation requires protein synthesis for stabilization (new learning during extinction) or restabilization (old memory subject to reconsolidation). The concept of trace dominance is also supported by experiments using systemic anisomycin treatment in context fear conditioning and reference water-maze learning in mice (Suzuki et al. 2004).

Does trace dominance also occur in the hippocampus? That is, can one see differential effects of intrahippocampal anisomycin as a function of whether memory retrieval is or is not activating an extinction process? Morris et al. (2006) showed that reactivation with eight nonreinforced probe trials caused extinction of

spatial memory that persisted for one week. Immediate postextinction infusion of anisomycin in the hippocampus did not disrupt extinction, suggesting that the extinction memory trace associated with removal of the escape platform over several trials is not consolidated in the hippocampus in a protein-synthesis manner. New data by Mamiya et al. (2009) point to a role for the medial prefrontal cortex in this process. One exception showing extinction in the water maze requiring the hippocampus is likely due to side effects of altered performance by prereactivation drug treatment (Rodriguez-Ortiz et al. 2008).

Rossato et al. (2006) also supported the idea that extinction of spatial learning is not consolidated in the hippocampus when extinction involved as many as 16 nonreinforced probe trials. Interestingly, when extinction involved fewer trials (4 or 8), spatial memory showed spontaneous recovery on the next day. This recovery was blocked by intrahippocampus anisomycin infusion immediately after the extinction trials. The authors suggest that the role of reconsolidation here is to recover or update retrieval-weakened memory from incomplete extinction. When inhibitory learning in other brain areas (potentially in frontal cortex; Quirk & Beer 2006) is not fully established and decays overnight, the interference in water-maze performance seen after a small number of extinction trials will dissipate and so lead to spontaneous recovery.

Implications and Related Issues

Current literature so far points to a set of factors that create an automatic updating process that requires the hippocampus. To summarize, these include updating driven by training protocols, updating triggered by mismatch between training and reactivation, and updating triggered by incremental learning. Future studies are needed to determine whether this model, mainly based on spatial water-maze and context fear learning, extends to other type of memories.

Importantly, the same set of factors does not apply to amygdala-based learning. Evidence from auditory fear conditioning suggests that reconsolidation always occurs in the amygdala, whether the reactivation is a brief nonreinforced session (Duvarci & Nader 2004, Nader et al. 2000), a reinforcer (Wang & Nader 2003), an extinction session (Duvarci et al. 2006), or even a relearning session (Duvarci & Nader 2004). Other factors such as direct or indirect memory reconsolidation in second-order conditioning (Debiec et al. 2006, using auditory fear conditioning; but see Tronel et al. 2005, using inhibitory avoidance) and overtraining (Wang et al. 2009a) seem to be critical to influence reconsolidation in the amygdala.

The distinction between hippocampus-based reconsolidation and amygdala-based reconsolidation may reflect very different psychological functions. This brings us back to the "why" of reconsolidation that was touched on earlier. First, hippocampus is hypothesized to process associations and to serve as an index to access memory traces represented in the cortex (Teyler & DiScenna 1986, Teyler & Rudy 2007). In the other hand, the tone-fear traces of emotional conditioning are believed to be stored within the intrinsic circuitry of amygdala (Fanselow & LeDoux 1999, Han et al. 2009, LeDoux 2007). Second, in the hippocampus-neocortical system, the associations are arbitrary—e.g., factual associations. It is not beneficial to change the content of knowledge about such facts, or personal events, each time we retrieve them unless there is conflicting or new information that requires updating. In contrast, in amygdala, the associations learned are about the value (e.g., fearfulness) of initially neutral stimuli. Having learned that a stimulus is fearful, there may be good reasons to re-evaluate whether it continues to be fearful every time we experience it. The amygdala might have it both ways—be very slow about extinction and yet always open to change. Slow because having learned that a stimulus is fearful, it would be in the survival interests of the animal to be conservative about changing its appraisal of the stimulus. At the same time, it would not be in the interests of an animal to retain unaltered the memory that every

stimulus that had been associated with a negative outcome in the past would remain fearful forever. So, in the case of value learning, it could be that retrieval constitutes an opportunity for changing prior learned association—a change is distinct from the new learning associated with extinction.

Recent studies also suggest that reconsolidation in cortex is different from reconsolidation in hippocampus or the amygdala. For example, Mamiya et al. (2009) used both a brain-imaging approach and local protein synthesis inhibition to show that in context fear memory, reconsolidation requires the hippocampus as well as amygdala, whereas extinction requires the prefrontal cortex and amygdala. It therefore seems that different brain areas are performing different functions during memory reconsolidation.

Finally, memory reactivation is critical to trigger reconsolidation, as many studies show normal memory after the application of amnesic agents when reactivation is omitted (Tronson & Taylor 2007). What mechanism in the hippocampus is responsible for the retrieval of the memory and hence the requirement of protein synthesis for reconsolidation? Several recent studies have been trying to approach this by looking at the molecular mechanisms needed to destabilize memory traces (Alberini et al. 2006). Lee (2008) suggests that some existing proteins associated with memory retrieval need to be degraded to allow for the new protein synthesis to restabilize the trace. If protein degradation is subject to interference, memory traces may stay in a locked state. Similar ideas have emerged in relation to NMDA receptor activation during the retrieval of auditory fear memory in the amygdala (Ben Mamou et al. 2006) and voltage-gated calcium channels (Suzuki et al. 2008).

CONCLUSION

This review updates a neurobiological theory of hippocampus function in memory (Morris 2006) with reference to recent findings related to automatic encoding and to synaptic and behavior tagging/capture. It also discusses hippocampal-neocortical interactions at the systems level, particularly in relation to schemas and reconsolidation.

First, we reassert that hippocampus has the property of automatic encoding of relational events (Eichenbaum 2004), objects-in-places (Eacott & Easton 2007), and goals-in-places (Day et al. 2003), and hence leads to rapid associative memory. Linking this rapid learning to synaptic plasticity, studies have shown that hippocampal NMDA receptors are required for the encoding of one-trial place information, and AMPA receptor activation is required for memory retrieval both in the event arena (Bast et al. 2005, Day et al. 2003) and in the water maze (Steele & Morris 1999).

Second, the encoding of events in HPC engages signal transduction cascades that contribute to cellular consolidation, enabling the memory of selected events to persist. The idea of synaptic tagging and capture has been widely demonstrated in brain-slice recoding and recently in behavior learning (Moncada & Viola 2007). This offers a biological mechanism by which distinct prior experiences that are temporally (and anatomically) close to subsequent learning can influence the persistence of memory of other events. One potential advantage of this is to allow for the modulation of memory through events that are contiguous to each other. One potential drawback of this might be interference between events. This disadvantage may be avoided by distinct representations at the anatomical level.

Third, the memory of events may persist (Wang et al. 2009b) or change (Winocur et al. 2007) with time. Memory traces can reorganize in the brain in a time-dependent manner. Complimentary to the role of HPC in automatic encoding, selective systems consolidation occurs in cortical areas. One benefit from this is to reduce information processing load on the HPC when facing new information flooding in. This systems consolidation process typically takes days to weeks but can be facilitated when new information is assimilated into a prebuilt mental framework (Tse et al. 2007). We suggest that once the knowledge of the environmental

context, or a mental schema of paired-associates, is represented in cortical areas, the HPC is only required for rapidly updating any new event in relation to these frameworks. To associate the updating component within these frameworks takes fewer links or biological modifications (and hence less time) relative to their initial acquisition.

Finally, reactivation and reconsolidation of an encoded event is functionally related to information updating, whereas automatic encoding is triggered by novelty detection (Lisman & Grace 2005, Nyberg 2005). This issue, extensively studied in animals, recently received attention in human work (Kumaran & Maguire 2009). To study learning and memory, novel tasks are typically used to allow for comparisons between control and experimental conditions and so avoid confounding interference from previous experiences. In this case, the activation of the HPC is likely to correlate with how novel an event may be and to follow a repetition-suppression rule (Grill-Spector et al. 2006). However, during memory retrieval or reactivation, subjects may refer to previous learning experiences to compare with a current situation, and the hippocampus will follow an updating/mismatch rule as suggested by both animal studies (Fyhn et al. 2002) and human literature (Kumaran & Maguire 2007).

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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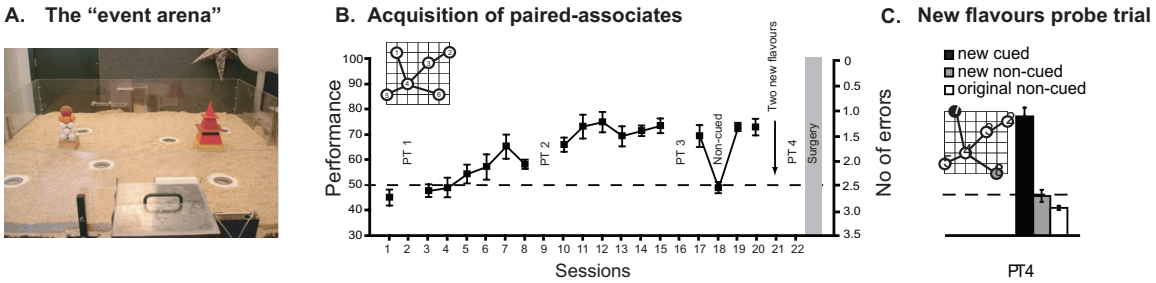

Figure 2

Paired-associate learning in rats. (*A*) Arena with the multiple sandwells for the concurrent task of Tse et al. (2007). (*B*) Gradual acquisition of a schema (*inset*) over 15 sessions, a noncued control task (S17–S19), and the learning of two new associates (S21). (*C*) Effective cued recall of new flavors in a probe test (S22) after only one training trial (S21).

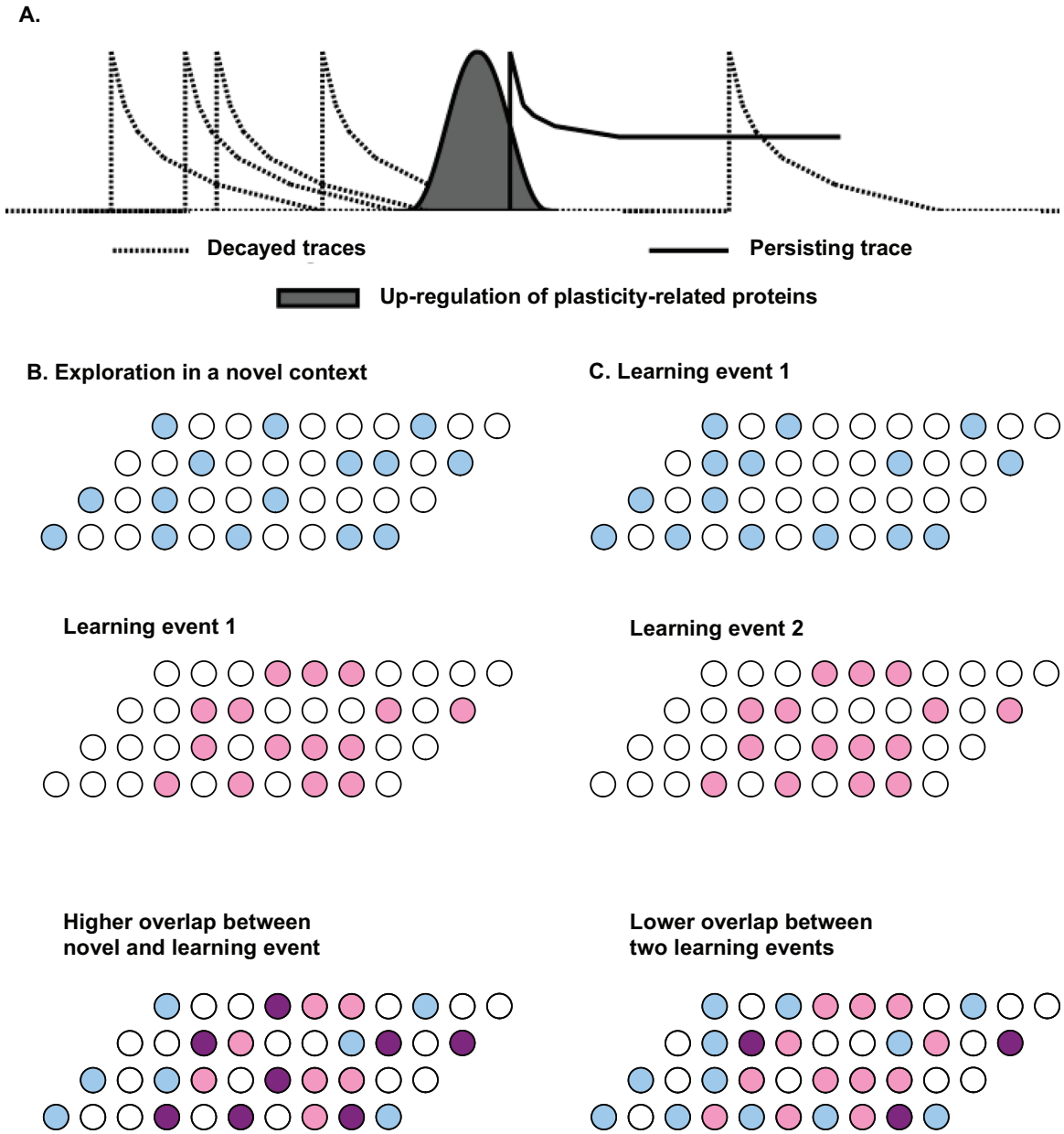

Figure 3

Synaptic tagging and capture. (*A*) The LTP traces that are induced by a weak tetanus and the memory traces that are formed after weak training normally decay with time (*dashed curves*). However, if there is a temporary upregulation of plasticity-related proteins (PRPs) that can be captured by neurons encoding these events (either tetanus or training), LTP or memory occurring around the same time can persist longer (*solid curve*). (*B*) A hypothetical example shows when the event that upregulates PRP (e.g., exploration in a novel context) has a higher overlap with the learning event (event 1) at the neuronal level. It is likely that event 1 can capture the PRP induced by novelty exploration. (*C*) A hypothetical example shows when two learning events encourage representations by separate neurons. The PRPs upregulated by event 1 are less likely to be captured by the tags associated with event 2.

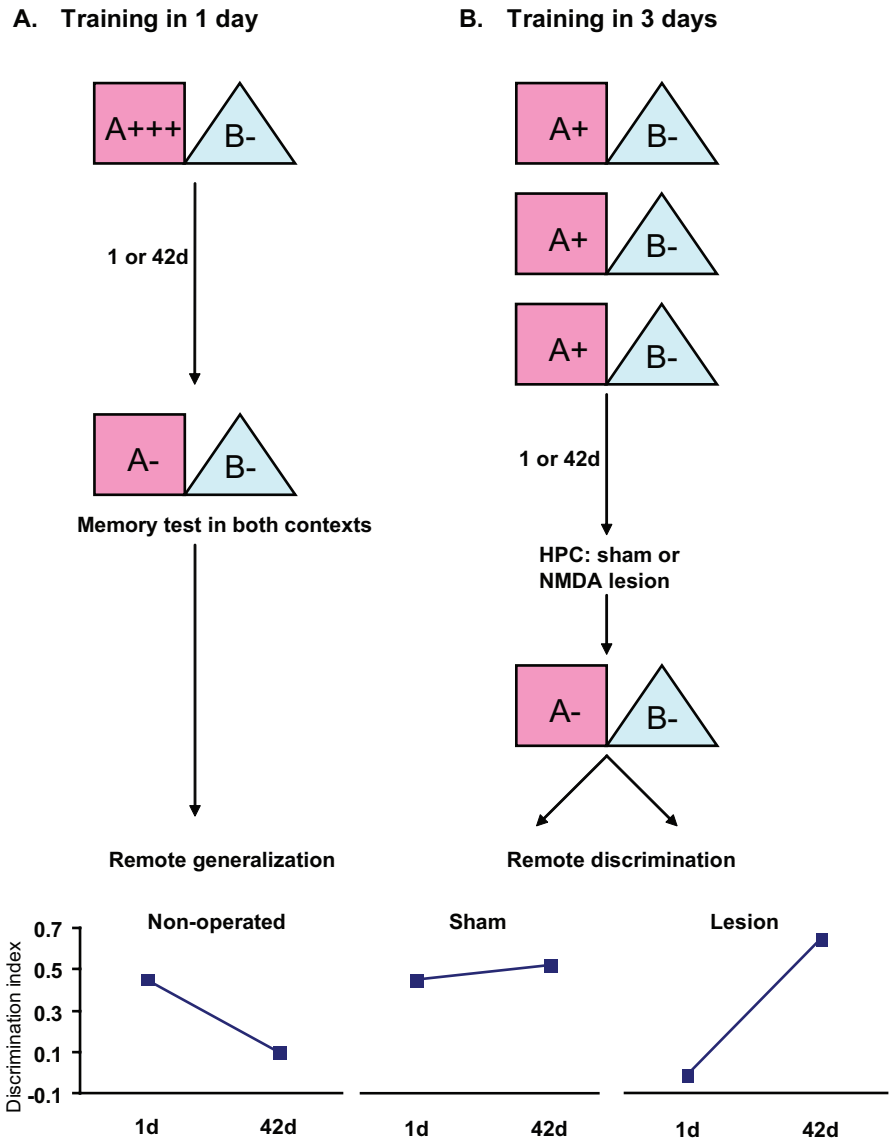

Figure 4

Memory persists or changes with time. (*A*) A training protocol of contextual fear conditioning that encourages memory generalization between contexts at a remote time point. Context A was paired with three footshocks; context B was never paired with footshocks. When tested one day after training, animals showed more freezing in context A than context B, hence better discrimination. When tested 42 days after training, animals froze similarly in context A and B, hence near zero discrimination. (*B*) A contextual fear-conditioning protocol that encourages memory discrimination between contexts across time. Training was spread out over three days; within each day, context A was paired with one footshock while context B was never paired with footshocks. Animals that received sham lesions showed good discrimination at both recent and remote time points (contrasting the poor discrimination at remote time points in **Figure 4*A***). Hippocampus (HPC)-damaged animals showed poor discrimination at recent time points, suggesting a critical role of HPC in consolidating this learning. However, animals could discriminate between contexts when the lesion was made much later, suggesting a time-limited role of HPC.

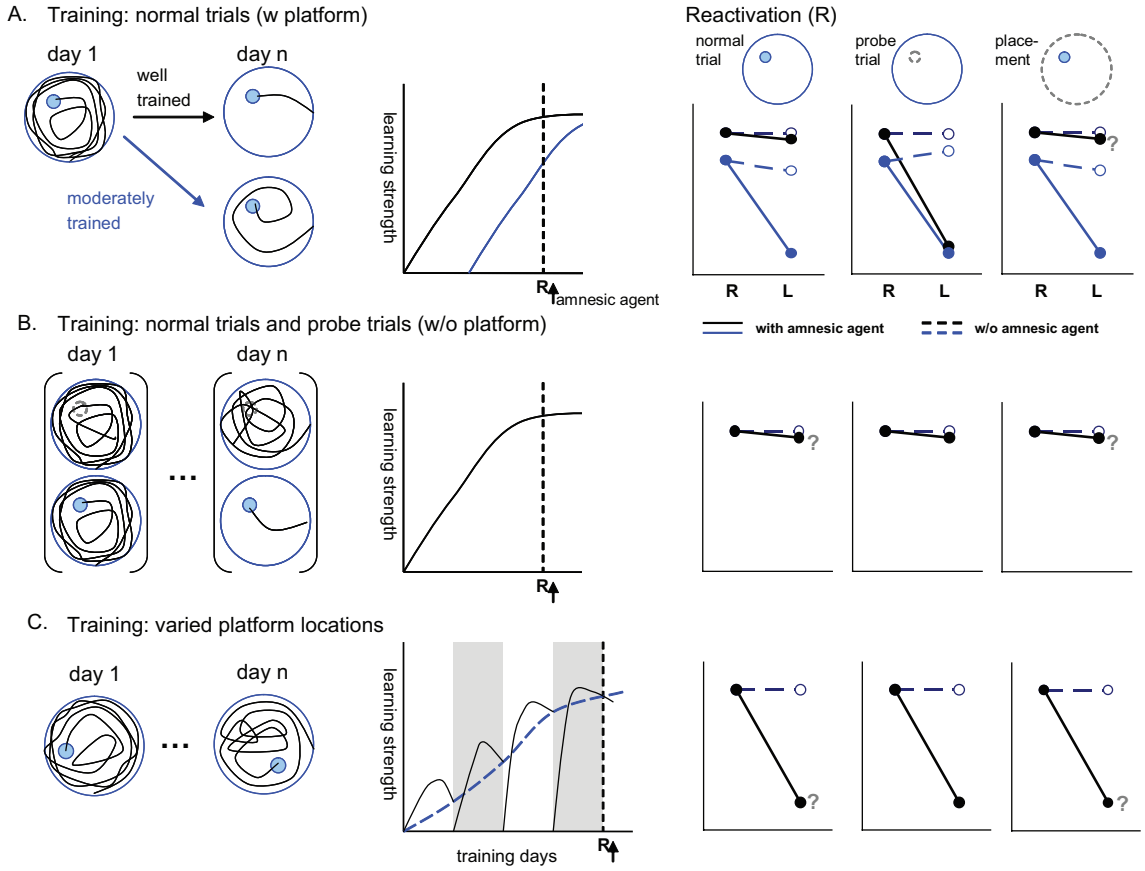

Figure 6

Reconsolidation of spatial memory in the water maze. (*A*) In a standard reference memory task, the escape platform is fixed at one location in the water maze. After moderate training (*middle panel*, *blue curve*), reactivation (R) with another training trial, a probe trial [i.e., omission of platform (*small dashed gray circle*)], or simple placement on the platform without (w/o) precedent swimming in the water maze (*large dashed gray circle*) is likely to trigger memory updating and subsequent reconsolidation in the hippocampus (HPC) (*right panel*). This is revealed by post-reactivation long-tem memory (L) impairment by amnesia agents applied after reactivation (*middle panel*, *short arrow*). However, after performance reaches a plateau (*middle panel*, *black curve*), memoryupdating/reconsolidation in the HPC is unlikely to occur after a training trial. (*B*) If the training mixes nonreinforced probe trials with normal reinforced trials, another trial with or without reinforcement or simple placement is unlikely to trigger memory updating and reconsolidation in the HPC. (*C*) If the training involves changing platform locations across days (e.g. delayed-matching-to-place task), the animals are encouraged to update this information every day. Hence, reactivation with any one of the three scenarios is likely to induce reconsolidation. The symbol "?" refers to the lack of empirical data. *Black irregular curves* in the *large blue circle* (water maze) represent the swimming traces.