The Restless Engram: Consolidations Never End

Yadin Dudai

Department of Neurobiology, Weizmann Institute of Science, Rehovot 76100, Israel; email: yadin.dudai@weizmann.ac.il

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Abstract

Memory consolidation is the hypothetical process in which an item in memory is transformed into a long-term form. It is commonly addressed at two complementary levels of description and analysis: the cellular/synaptic level (synaptic consolidation) and the brain systems level (systems consolidation). This article focuses on selected recent advances in consolidation research, including the reconsolidation of long-term memory items, the brain mechanisms of transformation of the content and of cue-dependency of memory items over time, as well as the role of rest and sleep in consolidating and shaping memories. Taken together, the picture that emerges is of dynamic engrams that are formed, modified, and remodified over time at the systems level by using synaptic consolidation mechanisms as subroutines. This implies that, contrary to interpretations that have dominated neuroscience for a while, but similar to long-standing cognitive concepts, consolidation of at least some items in long-term memory may never really come to an end.

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INTRODUCTION

Memory consolidation: hypothetical process in which a memory item is transformed into a long-term or remote form

Those who consider *In principio erat verbum* ("in the beginning there was the word") as a biblical aphorism only, philosophical connotations notwithstanding, may be gratified to discover that it applies to scientific research as well. Occasionally, scientific practice is shaped by terms whose original meaning has mutated over time. The study of memory consolidation provides an intriguing example. Since first proposed by Muller & Pilzecker (1900), the term consolidation has acquired multiple usages and meanings. It even budded off new terminology by acquiring a prefix (reconsolidation). Given the recent impressive advance of research on this topic, it seems apt to explore what memory consolidation currently means and the implications concerning our understating of memory at large.

Imaginative and resourceful as they were, Muller and Pilzecker were not the first to identify consolidation. Roman orators already knew about it (Quintillian 1C AD/1921). Though not yet so termed, consolidation entered the clinical discourse as a consequence of observations of amnesic patients (Ribot 1882). This and additional findings that preceded and coincided with the studies by Muller and Pilzecker are not reiterated here (Dudai 2004). Many impressive advances in molecular, cellular, and systems neuroscience that relate to memory mechanisms are also not discussed. Instead, the present discussion focuses on selected recent developments that have changed our view on how memories become long-term and on their subsequent fate.

CONCEPTS AND CRITERIA

Memory consolidation is the hypothetical process in which a memory item is transformed into a long-term form. It is commonly addressed at two levels of description and analysis: the cellular/synaptic level and the brain systems level. Synaptic consolidation refers to the post-encoding transformation of information into a long-term form at local nodes in the neural circuit that encodes the memory. The current central dogma of synaptic consolidation is that it involves stimulus ("teacher")-induced activation of intracellular signaling cascades, resulting in posttranslational modifications, modulation of gene expression, and synthesis of gene products that alter synaptic efficacy. Synaptic consolidation is traditionally assumed

to draw to a close within hours of its initiation. The stimulus that triggers it in the local node may represent perceptually or internally driven information. Synaptic consolidation is found throughout the animal kingdom.

Systems consolidation refers to the postencoding reorganization of long-term memory (LTM) over distributed brain circuits. The process may last days to years, depending on the memory system, task, and author. The conventional taxonomy of LTM systems (Squire 2004) distinguishes between declarative memory, which is memory for facts (semantic) or events (episodic) that requires conscious awareness for retrieval, and nondeclarative memory, a collection of memory faculties that do not require conscious awareness for retrieval. Systems consolidation commonly refers to declarative memory, but may exist in nondeclarative memory as well.

"Reconsolidation" refers to a consolidation process that is initiated by reactivation of LTM. The process is assumed to transiently destabilize LTM.

How Is Consolidation Identified?

Although certain changes detected in the brain may reflect consolidation, none can so far be used as a definitive signature of consolidation. Currently, the only accepted criterion to infer consolidation is the existence of a time window of susceptibility to amnesic agents. An amnesic agent that does not exhibit time-dependent decrease in efficacy is assumed to affect maintenance or expression of memory rather than consolidation (Shema et al. 2007).

RE-CONSOLIDATION, OR IS IT?

The traditional consolidation hypothesis implied that, for any item in LTM, consolidation starts and ends just once. Accordingly, classical discussions of consolidation referred explicitly to the "fixation" of memory (Glickman 1961, McGaugh 1966). Social psychology and introspection favored a shakier engram (Bartlett 1932), but proponents of the consolidation hypothesis drew a distinction between the postulated immutability of consolidated memory items and the dynamic nature of behavior (McGaugh 1966). The view that consolidation occurs just once per item was, however, challenged by the late 1960s. Researchers reported that presentation of a reminder cue (RC) rendered a seemingly consolidated memory item labile to amnesic agents (Misanin et al. 1968). The prototypical experimental protocol goes like this: Training is followed by time to complete the postulated consolidation period. An RC, usually the conditioned stimulus (CS), is then presented to reactivate the memory. An amnesic agent is administered simultaneously or immediately afterward. LTM is then retested. Under these conditions, LTM may be blocked. No such effect is detected if retrieval is not followed by the amnesic agent or the amnesic agent is not preceded by retrieval. This reactivation-induced reopening of a consolidation-like window challenged the unidirectional memory maturation view (Spear 1973) and was termed reconsolidation (Rodriguez et al. 1993, Przybyslawski & Sara 1997).

Reservations concerning interpretations as well as paradigmatic drives diverted the exploration of reconsolidation away from mainstream memory research. Although a few groups pursued the topic (reviewed in Sara 2000), the notion lost favor, as reflected, for example, in the number of publications: Of the 27,061 papers relating to "memory" published in the psychobiology literature from 1993 to 1999, only 6 referred to "reconsolidation" (*Thomson Reuters Science Web of Knowledge*). The notion of reconsolidation was ultimately revitalized by a study that targeted an identified memory circuit in the brain (basolateral amygdala) and blocked reactivated LTM of a well-defined task (fear conditioning) with a widely used amnesic agent (the protein synthesis inhibitor anisomycin) (Nader et al. 2000). This signal paper triggered a surge of interest, data, and insights. Bibliometry

Synaptic consolidation: hypothetical process in which information is transformed into a long-term form at local nodes in the neural circuits that encode the memory

Systems consolidation: hypothetical process in which an experience-dependent internal representation is converted into a long-term form and reorganized over distributed brain circuits

Reconsolidation: postulated consolidation process initiated by reactivation of a long-term memory item in the system that already stores this item

Long-term memory (LTM): item lasting long after it is encoded; in behavioral neuroscience, "long" is conventionally considered more than one day

Declarative memory: requires conscious awareness for retrieval, usually classified into memory for facts (semantic) and memory for events (episodic)

Nondeclarative memory: can be retrieved in the absence of conscious awareness, for example, habit and skill

again illustrates the trend: From 2001 to 2010, of the 61,950 publications on memory, 413 referred to reconsolidation (*Thomson Reuters Science Web of Knowledge*), presenting an almost 50-fold absolute increase per annum in the scientific vox populi.

Phenomena construed as reconsolidation have now been reported in many species and memory protocols. They were demonstrated mostly in synaptic consolidation but shown to occur also in systems consolidation (Debiec et al. 2002, Winocur et al. 2009). The resurrection of reconsolidation was not greeted smoothly. Reservations were raised once again concerning interpretations (McGaugh 2004). Yet, it soon became a widely accepted and stimulating observation (Dudai 2004, Nader & Hardt 2009, Alberini 2011, McKenzie & Eichenbaum 2011). The present discussion refers to only a few key questions that have gained particular attention as the field has progressed.

Engram: the physical record of a memory item in the brain; a memory trace

RC: reminder cue

CS: conditioned stimulus

US: unconditioned stimulus

Boundary Conditions for Reconsolidation

Reconsolidation seems not to occur every time LTM is reactivated. Understanding the conditions under which it takes place is likely to cast light on storage and retrievability of memory in general. Among the boundary conditions for reconsolidation identified so far, two are noted here. The first relates to competition among memories that are elicited by the RC. The second relates to the role of new information upon presentation of the RC.

When multiple associations are elicited by the RC, the one that comes to dominate behavior tends to reconsolidate (Eisenberg et al. 2003). In most reconsolidation studies, the competing associations are the original CS–unconditioned stimulus (US) association and the "inhibitory" CS–US association (i.e., the outcome of experimental extinction). If one could identify exactly when to intervene with an amnesic agent in the course of retrieval/extinction training, it would be possible to favor or block one of the competing traces. This appears to depend on the task and on the kinetics of RC presentation (Eisenberg et al. 2003, Suzuki et al. 2004, Garelick & Storm 2005, Monfils et al. 2009, Perez-Cuesta & Maldonado 2009, de la Fuente et al. 2011). Yet, this approach has already been reported to allow attenuation of fear memories (Monfils et al. 2009, Schiller et al. 2010) (see below).

Another important boundary condition for reconsolidation is the requirement of novel information at the time of the reactivation session. Studying fear conditioning in the crab *Chasmagnathus*, Pedreira et al. (2004) concluded that impairing reactivated LTM by a protein synthesis inhibitor was effective only when there was a mismatch between what the animal expected and what actually occurred. Such mismatch drives learning (Rescorla & Wagner 1972). Indeed, using spatial memory and intrahippocampal infusions of a protein synthesis inhibitor in the rat, Morris et al. (2006) identified reconsolidation only when the protocol involved encoding of new information at the time of retrieval (see also Rodriguez-Ortiz et al. 2008). Similarly, Winters et al. (2009) reported that, in object recognition in the rat, the N-methyl-D-aspartate (NMDA) glutamate receptor inhibitor blocked reactivated LTM so long as salient novel contextual information was present during memory reactivation. Of relevance is also the observation that blockade of the NMDA receptor, which is critical for encoding, blocked reconsolidation, but not expression, of fear memory in the rat (Ben Mamou et al. 2006). Evidence supporting the importance of encoding in triggering reconsolidation could also be inferred from studies of human procedural (Walker et al. 2003) and declarative (Hupbach et al. 2007, Forcato et al. 2009, Kuhl et al. 2010) memory. All in all, this evidence raises the possibility that reconsolidation has to do with updating old with new information (but see Tronel et al. 2005). The possibility should also not be excluded that the two boundary conditions—trace competition and need for new information—reflect a common basic requirement, as the new information may be considered to compete with the old.

Reconsolidation as an Opportunity for Memory Enhancement

If reconsolidation updates memory, one should also be able to exploit it for reinforcing memory. Indeed, this has been demonstrated by several studies. Tronson et al. (2006) reported that, upon retrieval of long-term fear conditioning in the rat, inhibiting the activity of the enzyme protein kinase A in the amygdala impaired memory, whereas stimulating this enzyme enhanced memory. In humans, it is more practical to use sensory and verbal stimuli instead of pharmacological agents. Coccoz et al. (2011) trained volunteers to associate syllables in a distinct audiovisual context. They reactivated LTM by presenting the training context followed by one of the cue syllables, but instead of getting the opportunity to complete the test, the participants were instructed to immerse their arm in ice-cold water. A day later memory was tested, this time without interruption. The exposure to the stressor upon reactivation of the memory enhanced performance on the subsequent day. Similar results, though taxing shorter-term memory, were reported by Finn & Roediger (2011), this time using pairs of Swahili-English vocabulary words as memoranda and presenting negatively arousing pictures immediately after a cued recall test. Performance on the subsequent recall test was best for items whose initial retrieval was followed by the negative pictures.

Luckily, an arm in ice or annoying pictures are not the only ways to exploit reconsolidation for the sake of improving memory. Both schoolchildren and university students can improve their memory by practicing self-testing, because retrieval practice is a powerful mnemonic enhancer (Karpicke & Roediger 2008). This could well be the contribution of reconsolidation to success in the classroom (Roediger & Butler 2011).

Reconsolidation in the Real World

That some types of memory could be enhanced merely by testing was known before reconsolidation was implicated in the process, and the practical benefit of knowing that reconsolidation is involved is still unclear. Similarly, reconsolidation may help in understanding why episodic information becomes distorted over time (Hupbach et al. 2007, Edelson et al. 2011), but it is unlikely that this understanding could be used to remedy false memory. In contrast, in some other real-life phenomena in which reconsolidation may be involved, understanding the mechanisms may culminate in beneficial interventions. The most salient example concerns the attempt to ameliorate posttraumatic stress disorder. Two approaches are used. In one, investigators administer shortly before, during, or immediately after memory reactivation a drug that suppresses physiological manifestation of emotion. A β-blocker is the drug of choice because of its proven safety. Following this administration, patients with chronic posttraumatic stress disorder had attenuated memory for one day in human eyeblink conditioning to noise (Kindt et al. 2009), emotional enhancement of verbal information (Kroes et al. 2010), and a physiological response associated with imagery of trauma (Pitman et al. 2006). Despite these results, the clinical value of this approach is still unclear.

The other approach is nonpharmacological. Schiller et al. (2010) adapted for humans the procedure devised by Monfils et al. (2009) for the rat. Monfils et al. (2009) conditioned rats to associate tone with shock, and after 24 h, they activated the memory by the tonal CS, followed by extinction training within or after the reconsolidation window, which closes within a few hours. When tested for subsequent LTM, the rats that received extinction training within the reconsolidation window, but not afterward, displayed attenuated conditioned fear 24 h later. There was no reversal of fear as judged by spontaneous recovery, renewal (testing in a different context), reinstatement (retraining on the US only), and saving (amount of training needed for reacquisition of the task after extinction).

Schiller et al. (2010) exploited similarly the extinction-reconsolidation boundaries in humans. They trained participants to fear a

visual CS by associating it with a mild shock to the wrist. A day later they presented the CS only. The participants were then trained in an extinction paradigm after 10 min or 6 h. In the 10-min group, LTM, as expressed in skin conductance response to the CS, was blocked even one year later. It now remains to be seen whether these results hold also for real-life complex recollections. It is not expected to be easy: Even in rats, higher-order associations are not blocked by blocking reconsolidation (Debiec et al. 2006), and resilient real-life traumatic memories in humans are expected to be densely associated. Nevertheless, the approach provides hope for treatment.

Can blockade of reconsolidation erase memory, or just block its expression? The tools available to assess memory erasure in reconsolidation are identical to those used in the study of extinction and consolidation. The gold standard is the lack of spontaneous recovery, reinstatement, renewal, and saving. Hence, demonstrating that the defect is a storage rather than a retrieval impairment relies on a negative finding: Memory not found, ergo memory not there. To circumvent the problem, researchers need new methods so they can identify the neuronal signature of the distinct engram (Nader & Hardt 2009).

Are Consolidation and Reconsolidation the Same?

The types of neuronal mechanisms that subserve reconsolidation are basically similar to those that subserve consolidation. First and foremost, inhibitors of macromolecular synthesis block both processes (Nader et al. 2000). Differential contributions of a spectrum of receptors, intracellular signaling, and transcription factors to reconsolidation versus consolidation have, however, been described. Examples of these differences include the obligatory involvement of brain-derived neurotrophic factor, but not the transcription factor Zif268, in consolidation and vice versa in reconsolidation of contextual fear memory in the rat hippocampus (Lee et al. 2004); the recruitment in reconsolidation of only a subset of immediate-early genes that are induced in consolidation (von Hertzen & Giese 2005); and the requirement for the interaction between specific initiation factors in the lateral amygdala in consolidation but not reconsolidation of elemental fear conditioning in the rat (Hoeffer et al. 2011). It remains to be determined whether a differential contribution to reconsolidation could be identified in mechanisms that have recently gained increased attention in consolidation research, such as additional growth factors (Chen et al. 2011), protein degradation (Lee et al. 2008), and epigenesis (Day & Sweatt 2011).

The question arises, however, whether the molecular dissociations, once found, reflect a fundamental dissociation between consolidation and reconsolidation. Differences in the contribution of specific molecular components to encoding, extinction, or reconsolidation can stem from differences in cue valence, context, or test demands (Berman & Dudai 2001, Tronson & Taylor 2007). This probably accounts for the lack in generalization of molecular signatures across reconsolidation tasks (Tronson & Taylor 2007). Hence, even if some differences are identified in the molecular signatures of consolidation and reconsolidation, the question remains whether they reflect genuine mechanistic differences that warrant proclaiming these as distinct natural kinds. The suggestion was, therefore, made that reconsolidation is use-dependent lingering consolidation, whose function is to update learned information (Dudai & Eisenberg 2004, Alberini 2005, McKenzie & Eichenbaum 2011). In that case, it might pay off to stop updating information about events that do not significantly change or such that lose their relevance. This might happen in some cases as memory ages (Milekic & Alberini 2002, Eisenberg & Dudai 2004, Inda et al. 2011).

THE ENGRAM TRANSFORMED

If reconsolidation is lingering consolidation, it brings us already into the time domain of

systems consolidation. Evidence for systems consolidation stems from both human (clinical and neuropsychological) and animal research (Dudai 2004, Squire 2004, Frankland & Bontempi 2005, Wang & Morris 2010, Winocur et al. 2010, McKenzie & Eichenbaum 2011). In line with the early clinical observations that contributed to the emergence of the consolidation hypothesis (Ribot 1882, Burnham 1903), a substantial number of studies report that "global" amnesics, i.e., patients with damage in their medial temporal lobe (MTL), displayed temporally graded retrograde amnesia on declarative memory tasks. The type of memory tested, whether episodic or semantic, is highly relevant, as explained below. In addition, a substantial number of studies using animal models of amnesia confirm that the hippocampus is required for LTM for only a limited time after encoding (Squire et al. 2001; for studies with differing conclusions, see Winocur et al. 2010, Sutherland & Lehmann 2011). In addition, a substantial number of functional brain imaging studies in healthy human participants show reduced recollection-correlated activity over time in mediotemporal structures but increased activity in the neocortex (e.g., Smith & Squire 2009; see also Smith et al. 2010). Similar conclusions emerge from metabolic mapping in laboratory animals (Bontempi et al. 1999, Ross & Eichenbaum 2006).

The Standard Model of Systems Consolidation

A dominant model that attempted to explain graded retrograde amnesia was the standard consolidation theory (SCT) (McClelland et al. 1995, Squire 2004; for an influential harbinger, see Marr 1971). This model posits that the hippocampus is only a temporary repository for memory and that the neocortex stores the memory thereafter. Specifically, the model postulates that encoding, storage, and retrieval of declarative information is initially dependent on the hippocampal complex (HPC) and related MTL structures as well as neocortical areas relevant to the encoded stimuli. The hippocampal trace is probably a compressed version of the representation. Over time, the information reorganizes by replaying (see below) the hippocampal representation to the neocortex. This reinstates the corresponding neocortical memory, resulting in incremental adjustments of neocortical connections and establishment of a long-lasting, reorganized representation, while the hippocampal memory decays.

SCT: standard consolidation theory

HPC: hippocampal complex

MTT: multiple-trace theory

The Multiple-Trace and the Trace-Transformation Models

Over time, some evidence that seems incompatible with SCT has accumulated. Most significant, the effect of MTL lesions on subtypes of declarative memory is not consistent: Autobiographical episodes are the most severely affected, and the retrograde temporal gradient for this type of memory is either absent or very shallow, sparing only memories acquired several decades earlier. Driven by these observations and corresponding findings in animal models of amnesia, Nadel & Moscovitch (1997) proposed an alternative, the multiple-trace theory (MTT). MTT posits that the HPC rapidly and obligatorily encodes all episodic information. This information is sparsely encoded in distributed ensembles of HPC neurons, acts as an index for neurocortical neurons that attend the information, and binds them into a coherent representation. The resulting hippocampal-neocortical ensemble constitutes the memory trace for the episode. Because reactivation of the trace commonly occurs in an altered context, it results in newly encoded hippocampal traces, which, in turn, bind new traces in the neocortex. This results in multiple traces that share some or all the information about the initial episode. Over time, having multiple related traces facilitates the extraction of factual information into a semantic representation of the gist of the episode. This information integrates into a larger body of semantic knowledge and becomes independent of the specific episode. Contextual information about the episode, which is required for bona fide episodic recollection, continues,

Remote memory: lasts longer than a few months (in animals) to many years (in humans)

TTT: trace-transformation theory

SAM: schema assimilation model

however, to depend on the HPC as long as the memory exists. Opponents to MTT claimed that patients with well-characterized MTL lesions show intact remote, including autobiographical, memory, unless the damage exceeds the MTL (Squire & Bayley 2007). This argument has been challenged (Rosenbaum et al. 2008, Race et al. 2011). It also does not explain why functional neuroimaging identifies in healthy individuals HPC activation in retrieval of remote autobiographical memory (Gilboa et al. 2004, Viard et al. 2010). Among the open questions concerning the functional imaging data are the following: To what extent do cue-induced imagining processes (Hassabis et al. 2007), as opposed to genuine recollection, contribute to HPC activation? Does this activation reflect processes essential for, or just correlative to, retrieval?

An update of MTT, the trace-transformation theory (TTT), focuses on the proposed abstraction and transformation of HPC-neocortical episodic information into neocortical semantic representations (Winocur et al. 2010, Winocur & Moscovitch 2011). The resulting gist memories are posited to coexist and interact with those representations in which the context/episodicity is retained and that remain HPC dependent. Winocur et al. (2007) tested a TTT prediction in the rat by using context-dependent versions of two hippocampal-dependent tasks—peer-induced food preference and contextual fear conditioning. They tested the rats at short and long intervals in the training context or in a different context. According to TTT, but not according to a conservative reading of SCT (which predicts that HPC memories are reorganized in a similar form in the neocortex), the change in context is expected to affect performance at the short but not the long interval when the contextless schematic version of the memory is supposed to take over. This indeed was the case.

The Schema Assimilation Model

SCT and MTT consider systems consolidation as a gradual, lengthy process. The schema assimilation model (SAM) (Tse et al. 2007) posits that systems consolidation could be accomplished quickly if a previously established body of related knowledge, i.e., a mental schema (Bartlett 1932), is available into which the new knowledge may be assimilated. Tse et al. (2007) trained rats using hippocampal-dependent flavor-location associations. After the rats learned a set of different associations over a few weeks, a single trial learning was sufficient to consolidate rapidly the memory of a new association: Although hippocampal lesion 3 h after training disrupted subsequent LTM, a similar lesion at 48 h was ineffective, demonstrating that LTM was no longer hippocampal dependent. No such effect was seen when the rats were trained with inconsistent flavor-location-paired associates, indicating that formation of a postulated schema is a prerequisite for rapid systems consolidation. The rapid schema–dependent learning was associated with upregulation of immediate-early genes in the medial prefrontal cortex (Tse et al. 2011), whereas pharmacological intervention targeted at that area prevented the new learning as well as the recall of consolidated information. These findings are in agreement with the assertion of earlier models that initial memory is in both the HPC and the neocortex (see also Lesburgueres et al. 2011), but they are in disagreement with the assumption that the neocortex is a slow learner (on additional evidence for fast cortical learning, see Takashima et al. 2009; on sleep and consolidation, see below).

That different systems consolidation models coexist is a stimulating situation, as they provide opportunities for new hypothesis-driven experiments, which are likely to generate not only new data but also new models.

WORKING AT REST

Synaptic consolidation processes take place immediately after encoding and re-encoding. But when does systems consolidation happen? Apparently some of the action takes place when we rest and while we sleep. The contribution of rest and sleep to consolidation is one of the

most fascinating frontiers in current consolidation research.

The idea that sleep enhances memory predates scientific investigation. Quintillian (1C AD/1921) turns his readers' attention to the "curious fact. . .that the interval of a single night will greatly increase the strength of the memory." It took some time for scientific research to reconfirm that this is the case (Jenkins & Dallenbach 1924). Systematic analyses of sleep and brain mechanisms followed with the development of functional brain-imaging techniques (Smith & Butler 1982, Karni et al. 1994). Ample evidence now supports the claim that memory consolidation benefits from sleep (Stickgold & Walker 2007, Diekelmann & Born 2010a; for a dissident view, see Vertes & Siegel 2005). However, questions arise regarding which (type of) memory, which (process of) consolidation, and which (mechanism of) sleep are involved.

A Reminder Concerning Sleep

Sleep is a natural, reversible physiological and mental state characterized by reduced consciousness, suspended volitional sensorimotor activity, and altered metabolism (Steriade & McCarley 2005). It involves the cyclic occurrence of phases, each conventionally defined by characteristic differences in brain activity, coordinated eye movements, and tonic muscle activity. The standard classification of sleep in primates and felines is into rapid eye movement (REM) and non-REM (NREM) stages. In humans, they alternate roughly every 90 min. NREM is further divided into substages, corresponding to the depth of sleep. NREM stage N3 (formerly stages 3 and 4), in which the deepest sleep occurs, is referred to as electroencephalogram (EEG) slow-wave sleep (SWS) based on the prevalence of EEG slow waves (below 4Hz). Other types of field-potential oscillations that characterize SWS include "spindles" (0.5–2 s, 10–15 Hz) and transient, sharp-wave "ripples" (SWR) (50–120 ms, 100–250 HZ). SWR probably reflect a transient relief of inhibition, permitting windows of opportunity for the expression of selective representations (Csicsvari et al. 1999). REM sleep is characterized by ponto-geniculo-occiptal waves and theta activity (approximately 4–7 Hz). REM and NREM also differ markedly in the level of activity of neuromodulatory systems in the brain during each of the phases (Pace-Schott & Hobosn 2002). SWS appears mostly in early sleep, whereas REM sleep occurs mostly at late sleep. Dreams, the succession of sensorimotor and affective hallucinatory experiences that occur involuntarily during sleep, are prevalent during REM but not confined to it (Nielsen 2000, Nir & Tononi 2010).

SWS: slow-wave sleep

SWR: sharp-wave "ripples"

REM: rapid eye movement

NREM: non-REM

Which Memory Systems Benefit from Consolidation in Sleep?

The evidence for the role of sleep in consolidation of acquired sensory and motor skills was initially considered more robust than that for other types of memory (Walker & Stickgold 2004). A wide spectrum of skills have been studied in this respect (Karni et al. 1994, Walker et al. 2005, Ferrara et al. 2008, Mednick et al. 2009, Wamsley et al. 2010a). It is now well established, however, that declarative memory benefits from sleep as well, though the involvement and contribution of distinct sleep stages and the underlying brain mechanisms to declarative and nondeclarative memory may differ (Diekelmann & Born 2010a,b; Walker & Stickgold 2010; also see below). A broad spectrum of tasks that involve declarative components or are considered "classical" declarative tasks have been investigated (Fenn et al. 2003, Wagner et al. 2004, Sterpenich et al. 2009, Diekelmann et al. 2011, Rauchs et al. 2011, Wilhelm et al. 2011).

Which Properties of Memory Increase the Benefit from Consolidation in Sleep?

Sleep may promote the preferential strengthening of emotional memoranda (Sterpenich et al. 2009) and of items that are expected to be subsequently retrieved (Rauchs et al. 2011, Wilhelm et al. 2011). The possibility that

consolidation in sleep favors selected items gains support from multiple lines of evidence. Rudoy et al. (2009) trained awake participants to associate object locations with sound and found that only those associations that were cued during sleep with their relevant sound were strengthened. This was taken to indicate that specific associations are preferentially reactivated and strengthened during sleep. At the brain physiology level, Huber et al. (2004) reported that activity in SWS has a local component that can be triggered by a sensorimotor adaptation task that involves specific brain regions. Additional electrophysiological evidence shows that most sleep slow waves and their underlying neuronal states occur locally in the brain and, hence, are fit to process information selectively (Nir et al. 2011).

When and How in Sleep

An early report on the role of sleep in consolidation of perceptual skill suggested that REM sleep is critical (Karni et al. 1994). Furthermore, a brief nap was reported to be effective in off-line improvement of skill performance only when the nap contained both REM and SWS but not when it involved only SWS (Mednick et al. 2003). The role of REM and NREM in the effect of napping on other types of tasks that involve skill components is task dependent (Korman et al. 2007, Wamsley et al. 2010b). The possibility was also raised that, at least in some motor skills, siesta-induced improvement is not due to napping but to resting (Rieth et al. 2010). Additional studies proposed a role in skill consolidation for both REM and NREM stages (Stickgold et al. 2000). Two types of processes have been proposed: stabilization against interference and gain in performance. The suggestion was further made that stabilization benefits from the SWS stage, whereas enhancement benefits from the REM stage (Sagi 2011). However, whether skill consolidation in sleep involves enhancement in addition to stabilization remains unclear (Brawn et al. 2010).

A signal set of findings that paved the way to the exploration of the neuronal and circuit mechanisms involved in memory consolidation at large was that hippocampal place cells (Pavlides & Winson 1989) and place-cell ensembles (Wilson & McNaughton 1994), postulated to encode place representations, "replay" during sleep periods that follow performance on spatial behavioral tasks. The order of firing in the task is largely preserved in the replay (Skaggs & McNaughton 1996). Most studies reported that the replay occurred during SWS, particularly during SWR (Nadasdy et al. 1999, Lee & Wilson 2002, Diba & Buzsaki 2007, Ji & Wilson 2007). The reactivation of hippocampal maps during post-training rest/sleep periods was further reported to predict performance on hippocampal-dependent matching-to-place reward tasks (Dupret et al. 2010). SWR are associated with increased cortico-hippocampal communication (Siapas & Wilson 1998). Indeed replay in SWS was found in the neocortex (Ji & Wilson 2007, Euston et al. 2007, Payrache et al. 2009), but also in the ventral striatum (Lansink et al. 2009). The presumed "reading out" in the SWR is accompanied by compression of the replay (Nadasdy et al. 1999, Euston et al. 2007, Ji & Wilson 2007); in other words, the postulated representation is played in "fast forward" (and, as noted below, under certain circumstances in "fast backward"). The virtual speed is 15–20 times faster than in the real world (Davidson et al. 2009). Replay in REM was also reported during periods of theta modulation with a "read-out" rate close to real time (Louie & Wilson 2001).

However, most importantly, structured replay of hippocampal place cells preserving information on the distinct behavioral experience was found to also occur in the awake state. Such replay is observed time locked either to an immediate experience (Foster & Wilson 2006, Csicsvari et al. 2007, Diba & Buzsaki 2007) or to a spatially and temporally remote one (Davidson et al. 2009, Karlsson & Frank 2009). What happens in sleep may, thus, cast light on the processes and mechanisms that relate

to consolidation in the awake state as well. The replay in the awake state is either forward or backward. For example, Foster & Wilson (2006) reported sequential reverse replay during awake periods immediately after a run on a track, when the rat pauses, with the reverse replay declining with familiarity, whereas Diba & Buzsaki (2007) reported forward replay at the beginning of such a run, as if in anticipation of the run, but reverse replay at the end of the run. Moreover, Dragoi & Tonegawa (2011) reported that some of the replays in aware-rest states are "preplays," i.e., sequences that match those subsequently recorded when the rats were running in a new place. The potential implications of this finding are discussed below.

A single SWR is brief, allowing replay of only a limited distance (approximately 1–2-m run), which fits routine laboratory mazes but not the real life of a wild rat. How does the brain replay realistic distances? It appears that firing sequences corresponding to long runs through a large environment are replayed in chains of shorter subsequences, with each segment corresponding to a single SWR (Davidson et al. 2009).

All in all, it has been proposed that: (*a*) Forward replay during "gaps" in the behavioral performance subserves the retrieval of path information to aid memory-guided decision making; (*b*) postexperience forward replay in both awake and sleep states is likely to subserve consolidation of acquired representations; and (*c*) reverse replay in the awake state may subserve episodic binding (Carr et al. 2011). Thus, once the episode is bound and familiar, additional fast-backward replay may not be needed (see above). Interestingly, echoing the latter proposal, human functional brain imaging in a realistic episodic task revealed immediate (within seconds) poststimulus activity in the hippocampus and in the dorsal striatum that predicted subsequent memory performance. This off-line activity may reflect episodic binding and initiation of consolidation (Ben-Yakov & Dudai 2011). Tambini et al. (2010) reported memory-related enhanced corticohippocampal functional connectivity in rest periods spanning minutes after associative encoding sessions. It is also noteworthy that reactivation of memory during waking and sleep may have different roles and outcomes concerning long-term trace stability. Hence, Diekelmann et al. (2011) reported that reactivation of object-location associations by odor cues during waking resulted in destabilization of the trace, but in SWS it resulted in fast stabilization.

The aforementioned studies potentially implicate replay in memory consolidation by way of correlation (though admittedly, only some of these studies actually correlated replay with subsequent memory). Yet interventional methods suggest a causal link as well. Girardeau et al. (2009) and Ego-Stengel & Wilson (2010) stimulated the hippocampus to selectively disrupt SWR activity in maze-trained rats. They found that disruption during post-training rest periods that included sleep impaired improvement of performance over days of training. This was taken to imply that ripple-related activity could be required for uninterrupted memory consolidation. Of further relevance, disruption of sleep continuity in the mouse by optogenetic stimulation of hypocertin/orexin neurons in the lateral hypothalamus, thereby promoting arousal, impaired later performance on novel object recognition. This was correlated with fragmentation of NREM sleep; the minimal time for uninterrupted sleep critical for consolidation on the task was estimated to be 60–120 s (Rolls et al. 2011). Although no effect on distinct representations or firing patterns was determined, these findings indicate a novel approach to the dissection of consolidation processes at large. They also strengthen the notion that sleep may be not only a correlate, but also a necessary mechanism for proper consolidation.

A few cautionary remarks are necessary. First, because replay is not unique to sleep, any unique contribution sleep provides to consolidation cannot be accounted for solely by replay. If replay in sleep has any specific contribution, it must be considered in combination with other features of sleep, such as the unique metabolic

ACSH: active consolidation in sleep hypothesis

and neuromodulatory milieu and their relevant signaling cascades (e.g., Aton et al. 2009). Thus, whatever we learn from replay in sleep could inform us about consolidation in the awake state as well.

Second, the relevance of the laboratory protocols to real life raises some issues. Many of the aforementioned protocols use task repetition and, hence, heavily tax procedures and learning sets. By contrast, realistic episodic memory is a single trial involving novelty. In this context it is worthy to reiterate that encounter with novel memoranda seems to modify the pattern of replay (Foster & Wilson 2006, Dragoi & Tonegawa 2011).

Third, and probably the most relevant question at this point in time, is whether replay is indeed specifically instrumental in consolidation. Replay may be a signature of a more global information-processing mechanism, in which case, it may be permissive but not sufficient for consolidation.

As noted above, replay is not a simple function of experience (Gupta et al. 2010, Dragoi & Tonegawa 2011). Given this, it is tempting to raise the possibility that what is played, replayed, or preplayed are combinatorial internal representations that could serve as raw material for perceiving, anticipating, reacting, recollecting, and planning. Such representations are likely to gain more visibility in sleep because of the decrease in volitional activity. Linked to a broader conceptual level, this points to the potential role of cue-invoked selection of "prerepresentations" as a Darwinian mechanism in the operation of the mind (Young 1979, Heidmann et al. 1984, Dudai 2002). Seen that way, consolidation, similar to development, perception, and retrieval, involves pruning and selecting information about the world.

How It Might Work

With the above in mind, we now consider models of how consolidation could occur in sleep. To do so, it is useful to note the postulated goals of sleep. An influential overall idea is that sleep evolved to maintain homeostasis (Crick & Mitchison 1983, Borbely & Achermann 1999, Tononi & Cirelli 2006). A specific version of this idea was developed by Tononi & Cirelli (2006). They suggest that plastic processes during wakefulness result in a net widespread increase in synaptic strength in the brain and the role of sleep is to downscale synaptic strength to a baseline level that is energetically sustainable and possibly also more useful for new learning the next day. They further propose that this function is achieved during SWS. This means that sleep plays a necessary role in sustaining memory systems, and is at least permissive yet not necessarily instrumental, let alone sufficient, for consolidation. However, as research proceeds, instrumentality may be unveiled. For example, increasing the signal-to-noise ratio of privileged representations may drive them to consolidate effectively.

A different idea is that sleep involves active processes that consolidate memory, and is hence necessary and instrumental, and possibly also sufficient, in implementing steps in consolidation. This is the "active consolidation in sleep hypothesis" (ACSH) (Diekelmann & Born 2010a). ACSH could be considered an extension of the SCT that posits that declarative memory involves initial storage in the cortico-hippocampal system (step 1), but over time, via representational replay, gets reinstated in the neocortex (step 2). ACSH adds that step 2 benefits from sleep (Diekelmann & Born 2010a). ACSH gains support from additional developments in computational models (Kali & Dayan 2004), though these models do not specify sleep per se as obligatory in implementing the stages proposed.

Diekelmann & Born (2010a) suggest how ACSH may be implemented in the brain. They draw on the sequential hypothesis of sleep proposed by Giuditta et al. (1995), among others. The sequential hypothesis proposes that information acquired during the waking period is processed first in the early sleep stages, NREM and particularly SWS. Subsequent processing occurs in the later sleep stage, REM, and information eventually emerges in a new form upon awakening. Diekelmann & Born (2010a)

propose specifically that, during SWS, slow oscillations, spindles, SWR, and low cholinergic activity all coordinate to promote the reactivation and redistribution of hippocampal-dependent memories to the neocortex, thereby instantiating system consolidation. Subsequently, during REM sleep, high cholinergic and theta activity promote synaptic consolidation of the newly redistributed representations in the neocortex. Ultimately, the individual wakes up with a consolidated memory. Similar systems-synaptic sequences may take place in certain nondeclarative memories as well (Dudai 2004). This type of model is agnostic to the specific systems consolidation models discussed above.

Despite their differences, the aforementioned "homeostatic" and "active" accounts of sleep are not mutually exclusive. Whereas the former emphasizes the function of sleep in general, the latter focuses on its role in consolidation. The evolution of sleep may have been initially driven by homeostatic pressure and active consolidation became nested into it over time. Furthermore, consolidation may have evolved to comply with homeostatic needs (Fischer et al. 2005). In addition, when discussing these models, the possibility should not be neglected that we may be entrapped by an adaptationist philosophy. The mechanisms discussed may have evolved as a by-product of inherent structural and functional constraints of biological systems and not under the selective pressures we contemplate (Gould & Lewontin 1979). Analysis of this possibility, which applies to many models in biology, exceeds the scope of this discussion.

CONSOLIDATIONS INTEGRATED

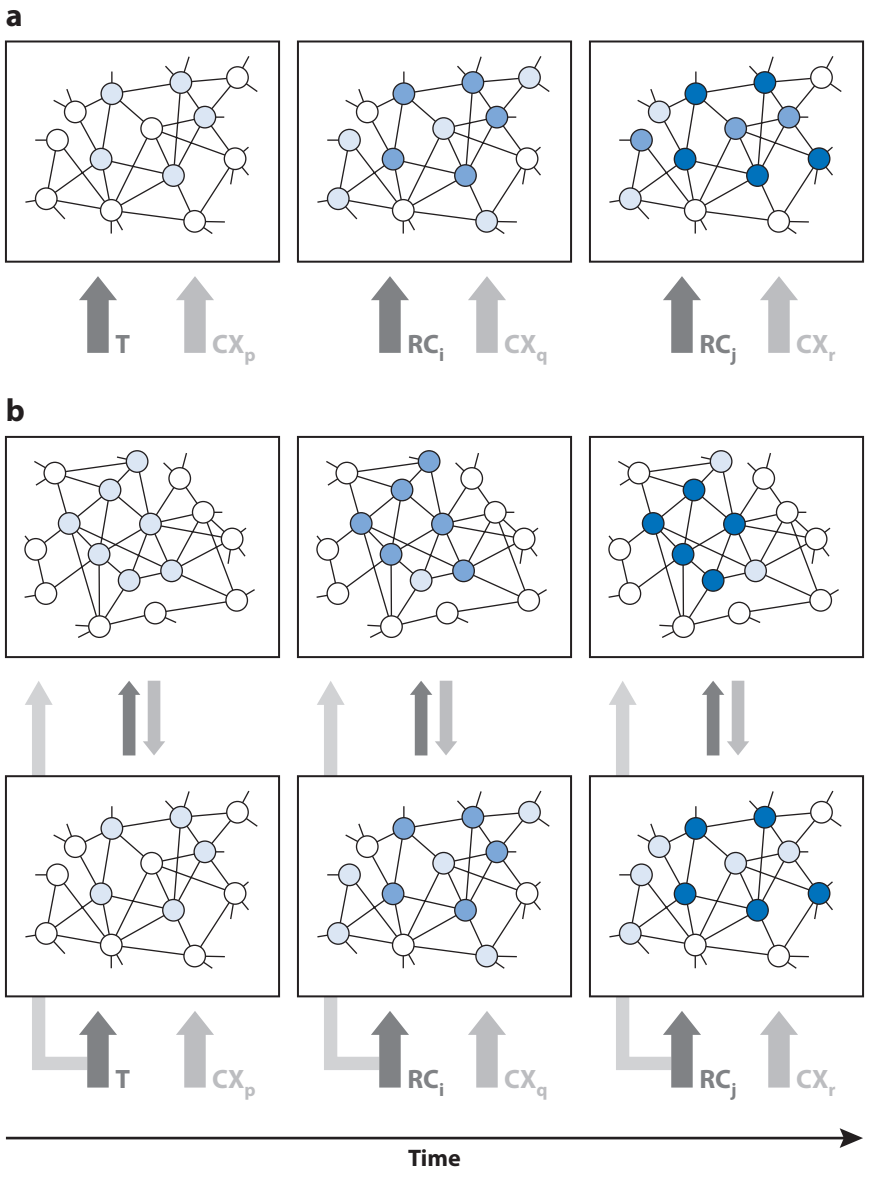
Memory is the retention over time of experience-dependent internal representations or of the informational capacity to reactivate or reconstruct such representations (Dudai 2002). Consolidation is the mechanism that shifts these representations into a long-term form. In considering how this is achieved, three questions are particularly relevant. First, which level of organization of the neural system is critical for encoding the content of the distinct representation? Second, is the circuit that initially encodes the representation also the one that maintains it over time? Third, how does the system ensure that the acquired representation is updated when the world changes?

The assumption that the content of a memory item is encoded at the circuit level is not a secured given, yet is highly reasonable (Dudai 2002). Furthermore, at least in complex memory systems in the mammalian brain, the neural system that encodes the information in the first place may not be identical to the system that stores the information later on, therefore trace migration occurs (McClelland et al. 1995). Given that, an integrative broad-brush depiction of consolidation considers synaptic consolidation as the elementary mechanistic process that converts experience-dependent synaptic change into a longer-term representation. If a mismatch develops between this representation and reality, new information will modify either new or old synapses in the circuit, again by triggering synaptic consolidation. The latter, thus, functions as a subroutine activated once the external and internal cues favor off-line persistence of the change. When this change applies to information already encoded as LTM, we dub it reconsolidation.

In reality, relevant information probably pre-exists in the brain; therefore, even what we deem in the laboratory as consolidation may involve reconsolidation. In memory systems in which information migrates to other distributed brain circuits to free neuronal space and/or distill information into new forms, synaptic consolidation remains the elementary subroutine that executes the process, modifying synapses as they receive new information from other circuits that previously encoded or processed relevant information (**Figure 1**). Seen this way, synaptic consolidation is a local process indifferent to the representational semantics and activated in a similar way regardless of whether the information originated

in the perceptual apparatus or in mnemonic circuits.

Consolidations all have the same computational goal—to allow the adequate level of persistence in the face of expected change (Dudai 2009). Synaptic consolidation is the term we assign to the manifestation of the process at the cellular, elementary "syntactic" level, whereas systems consolidation refers to the circuit, representational "semantic" level. Synaptic consolidation is the basic building block of systems consolidation. In simple systems, the goal of systems consolidation is achieved within the same circuit that first encoded the memory; therefore, we do not see the waves of change in which information redistributes among



circuits. However, local migrations may still occur within the original circuit. It is all a matter of resolution.

ON THE RECONSOLIDATION OF TERMS AND IDEAS

Overall, the evidence discussed in this article suggests that consolidation of information in the behaving brain rarely stops unless one or possibly two conditions occur. Either the behavior and the context in which it is executed remain constant, there is no new information, and therefore no need to learn and update; this probably never happens even in simple systems living in boring environments, but even then, the capacity to update must remain viable. Or, alternatively, the internal representations become highly irrelevant to behavior and therefore not reactivated.

Because knowledge is always based on previous knowledge, and echoing the preamble to this chapter, it might be proper at this point to reactivate the methodology of the Vico (1710), the Italian philosopher who trusted that much can be learned about a culture from the etymology of words used. "Consolidation" is from the Latin *consolidare*, *con-* "together", *solidare* "make firm." The process that we term consolidation in memory research indeed subserves the binding together of acquired information into useful representations, but that information is evidently far from becoming solid. Shortly after the term was first introduced into memory research, emphasis was placed on the *solidare*, and as the term consolidated into the language of the science of memory, that connotation became widespread and guided research to look for stabilization mechanisms. Research in recent years has reconsolidated the connotation of the term to emphasize the inherent malleability of memories. In doing so, the neuroscience of memory reconciles with the intuitive, dynamic view of memory that dominates the cognitive sciences.

Figure 1

Schematic variants of memory consolidation. (*a*) Long-term memory (LTM) is stored in the same circuit, or in parts of the circuit, that initially encoded the memory. The "teacher" stimulus (T) triggers a set of intracellular signaling mechanisms that culminate in long-term alterations (depicted as changes in color) in the efficacy of a set of synapses that subserve encoding of the internal representation. This time-limited process, which is assumed to mature within hours, is termed synaptic consolidation and is an obligatory step in the neural registration of any type of LTM. Reactivation of the LTM by a reminder cue ($RC_{i,j}$) that is associated with new information (e.g., change in context, $CX_{q,r}$) re-triggers synaptic consolidation mechanisms in the same and in additional nodes in the circuit, resulting in synaptic alteration. This is termed reconsolidation and involves some transient destabilization of the original trace. In real life, even the initial consolidation may involve reconsolidation of previous knowledge; in which case, the differentiation between T and RC is not absolute. (*b*) LTM redistributes into new brain territories. The information is encoded first in one location (*lower panel*) and/or in parallel in both locations (*lower and upper panels*). Over time, it migrates, at least in part, from one location to another while probably undergoing metamorphosis in content and cue dependency. The potential direct input of $CX_{p,q}$ to the upstream location has been omitted for simplicity. In each of the locations, the process is executed by synaptic consolidation, whereas T/RC/CX each encodes either sensory and modulatory input (as shown in panel *a*) or information about the item already processed in LTM, manipulated in the absence or in the presence of overt retrieval. This overall process is termed systems consolidation. Hence systems consolidation recurrently recruits synaptic consolidation processes as subroutines. Systems consolidation, which matures within days (or nights) to months or even longer, traditionally deals with the transformation over time of declarative memory in the corticohippocampal system. Processes similar in nature may, however, operate in other memory and brain systems, including in distributed local circuits within the same brain region. For further details, see text. The time arrow is indicated only for the slower, horizontal axis for simplicity.

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Neuron
Perspective

Memorable Trends

Yadin Dudai[1,*] and Richard G.M. Morris[2,*]
[1]Department of Neurobiology, Weizmann Institute of Science, Rehovot 76100, Israel
[2]Centre for Cognitive and Neural Systems, Edinburgh Neuroscience, The University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ, UK
*Correspondence: yadin.dudai@weizmann.ac.il (Y.D.), r.g.m.morris@ed.ac.uk (R.G.M.M.)
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The current neuroscience of memory takes on board the remarkable achievements of molecular neurobiology and merges them with findings from systems neuroscience and cognitive psychology. This results in a highly dynamic depiction of the memory trace, appreciating its restlessness and incessant assimilation into accumulating knowledge. With an armamentarium of amazing methodologies at hand, and more around the corner, we still lack dictionaries of neuronal codes, able to translate spatiotemporal patterns of brain activity into behavioral tokens. But the path to getting there continues to fascinate, to be accompanied by fresh challenges and new approaches.

The past is a foreign country: they do things differently there. L.P. Hartley's poetic ode to nostalgia (*The Go-Between*) shrinks to a bare factual statement upon comparing memory research reported in *Neuron* in its first days and now. The first experimental paper to explicitly target putative memory-related research in *Neuron* used acute single microelectrode recording in hippocampal slice (Kauer et al., 1988). Twenty-five years and 8,000 articles later (over 400 of which are research papers with learning or memory in their title, with many more on neuronal plasticity at large), a study of memory in the mammalian brain reported in *Neuron* may already combine chronic tetrode recording arrays and precise optogenetic perturbation in the freely behaving rat (Smith and Graybiel, 2013).

That the contemporary tools of the trade are first and foremost options that creative scientific minds use in new ways is evident from the fact that both of these papers can be considered groundbreaking at their time. Expanding the toolbox available to the discipline, which has perhaps happened most strikingly in the last decade, enables neuroscience to take new steps forward. Imagine, for example, human memory research now in the absence of noninvasive functional imaging; the advances in our understanding of our own brain machinery is even more impressive given that this popular capability was unavailable only a rather short scientific-while ago (the first positron emission tomography [PET] study of human memory to appear in *Neuron* was in 1996 [Schacter et al., 1996], with the first fMRI paper following shortly thereafter). When *Neuron* started almost a decade earlier, cognitive neuroscientists really did do things differently.

The technology has changed and with it some of the questions that can be tackled more successfully. But has the evolution of methods, concepts, and data blended with creativity to advance the character of memory research in the past 25 years? Our view is that they are doing so, and we now reflect on the future implications of the current state of the art. We attempt to chart patches of the changed terrain of the science of memory and how it has changed and propose a few idiosyncratic conclusions on where it might be going.

Time Present and Time Past

The Trace Goes Dynamic

Psychological conceptions of learning and memory have long distinguished the acquisition or "encoding" process, from that of "trace storage" and the subsequent processes of "consolidation" that somehow enable storage to be lasting. Efforts to translate these concepts into the neurobiological domain distinguish the very rapid events associated with memory encoding in one-shot learning, such as activation of the glutamate NMDA receptor in neurons of the hippocampus, with those associated with the subsequent creation of biophysical, biochemical, or structural changes thought to mediate lasting trace storage. A memory "trace" or "engram" is a hypothetical entity that refers to physical changes in the nervous system that outlast the stimulus. However, while the trace may be created and sustained for a while, that is no guarantee that it will last. All too often, as in long-term potentiation decaying back to "baseline" levels, experience-induced perturbations of structure and function are short lasting. However, a key idea was that a consolidation process can be engaged to enable these physical changes to be sustained and then to last indefinitely (McGaugh, 1966).

Specifically, much of the research in the neuroscience of memory in the past century was embedded in the conceptual framework of a "dual-trace" model (Hebb, 1949): a short-term trace, which dissipates rapidly unless converted by consolidation into a long-term trace. It was generally thought that consolidation occurs just once per item and that the long-term trace would be stable and essentially permanent unless the areas of the brain that store the memory were damaged or the ability to retrieve the information somehow impaired. This conceptual framework was strongly influenced by the view that the neurobiological mechanisms of consolidation and maintenance of long-term memory are similar or even identical to those operating in tissue development, in which the cells become committed to their fate for the rest of their life unless struck by an injury or pathology. Indeed, much in the models and terminology of the highly successful molecular neurobiology of memory (Kandel, 2001) resonates with the reductionist world of the molecular biology of development. The influence and the interest of developmental neurobiologists in memory mechanisms continues to

this day, although with a corresponding sense that things may be less fixed than they once seemed (Hübener and Bonhoeffer, 2010).

The initial reductionist approach to neurobiology (Benzer, 1967; Kandel and Spencer, 1968) resulted in portrayal of a dynamic microcosmos within synapses and neurons. This was in regard to the encoding of the memory and its possible transition from a short-term to a long-term trace. The proposed molecular and cellular mechanisms of encoding and consolidation in even the simplest forms of learning, such as habituation, sensitization, and classical conditioning, were depicted as interacting signal-transduction cascades of synapse-to-nucleus-to-synapse communication, each shaped by state-dependent checks and balances of facilitation and repression. Particularly influential has been the research program of reflex modification in *Aplysia* (Castellucci et al., 1970; Kandel and Schwartz, 1982; Bartsch et al., 1995; Byrne and Kandel, 1996; Martin et al., 1997; Bailey and Chen, 1988; Shobe et al., 2009). A complementary picture emerged from the neurogenetic analysis of memory in *Drosophila* (Dudai et al., 1976; Dubnau and Tully, 1998; Waddell and Quinn, 2001; Keleman et al., 2007), in which lines such as *amnesiac* remain memorable for their failure to make this short-to-long transition coupled to some missing aspects of these cascades. These and studies in other organisms and model systems (e.g., Etcheberrigaray et al., 1992; Malenka and Bear, 2004; Gao et al., 2012) unveiled a rich molecular toolbox of neuronal plasticity that has been conserved and elaborated in evolution to permit memory traces to be formed (Kandel, 2001; Glanzman, 2010).

Yet the outcome—the "stored" long-term trace—was still conveniently considered by many as "fixed." The flexibility of behavior was appreciated, even championed, but a conceptual distinction was nonetheless made between the postulated permanence of the memory trace and its flexible use in providing the organism with capacity to vary its response to the world (McGaugh, 1966). This dissonance between the assumed engramatic stability and the observed behavioral mutability was even insightfully considered embarrassing (McGaugh, 1966) and hence in need of resolution.

On this point, some views in early cognitive and social psychology were arguably rather different. Here, the reconstructive but frail nature of real-life memory was an engine of excitement rather than of embarrassment (Bartlett, 1932) and served as a basis for influential experiments (Deese, 1959) that decades later found their way into brain research (Schacter et al., 1996). A major trend in the evolving science of human memory is bridging the gap between cognitive psychology concepts and the molecular and cognitive neuroscience views of memory. Whereas the cognitive psychology of memory opens out to biological interpretations of behavioral phenomena (e.g., retroactive memory interference interpreted as memory consolidation; Wixted, 2004), molecular and cognitive neuroscience is at last beginning to appreciate the restless, ever changing, and reconstructive nature of memory cherished by cognitive psychology (Dudai, 2012). In this respect, neuroscience is coming of age; we have moved away from the silos of thinking that permeated separate departments of psychology, physiology, and molecular biology to recognition that different levels of analysis have things to say to each other (Roediger et al., 2007).

Four examples illustrate this trend toward a more dynamic conception of the trace and of memory processing in general. The first refers to the ostensible and now questionable *permanence of the consolidated trace*; another to the *veracity* of memory; a third to the nature of the representations formed and the *assimilation* of new information into previously stored representations; and a fourth to the supposition that retrieval may represent a *transient alliance* of representations.

The Trace Reboots

The view that consolidation occurs just once per item was challenged in the late 1960s by reports that presentation of a "reminder cue" rendered a seemingly consolidated long-term memory item again labile to amnesic agents (Misanin et al., 1968). This reactivation-induced reopening of a consolidation-like window called into question the supposition that consolidation produced immutable stability and so came later to be termed "reconsolidation" (Sara, 2000). Some methodological concerns combined with the capricious nature of the history and sociology of science pushed reconsolidation under the radar for many years. A major step forward came with a study that replicated Misanin's observation of reconsolidation but did so by applying an amnesic agent directly into the identified amygdalar circuit that mediates long-term fear conditioning (Nader et al., 2000). This single paper had an unprecedented influence on the popularity of reconsolidation as a process to study, with the annual number of papers that describe and analyze the phenomenon soaring 50-fold within a few years. Besides providing new insights into the molecular and brain mechanisms of memory, the initially subversive concept of reconsolidation was rapidly subsumed into mainstream neuroscience. There has been extensive work on specifying the boundary conditions of reconsolidation, on pharmacological and molecular dissociations between consolidation and reconsolidation, and on the possible relevance of reconsolidation to cognitive and behavioral therapies for diverse conditions (Alberini, 2005; Nader and Hardt, 2009; Dudai, 2012).

The Trace Errs

In the classical neurobiological sequence of memory processes, operating in a healthy nervous system, there is seemingly little room for error. What will later be retrieved from the passive attic of stored traces must, of necessity, be what was put there in the first place. It took decades for the normal imperfections of memory to be considered by brain scientists as natural and research-worthy phenomena (Schacter, 2001). This may sound surprising to the biological ear, even if only because modern biology rests on the shoulders of molecular genetics, which uses imperfections (mutations) as its most effective and successful research tool. In early cognitive neuroscience as well, brain damage that caused abnormalities of function was the gateway to understanding the key attributes of memory systems that should ordinarily work as they evolved to do, but the supposition was that subjects without such damage would display memory processes that behaved in a well-brought-up manner.

Again, bibliometrics illuminates the trend. Between 1985 and 1999, only 63 papers in the Science Citation Index (*Thomson Reuters*) had "[brain AND memory AND false]" in their title,

compared to 575 in the period 2000–2012; correcting for the doubling of the number of papers having brain as their topic between these periods, this still yields a 5-fold increase in the interest of the neuroscience community in the inaccuracies inherent in our memory.

A particular contribution to this trend was provided by the introduction of noninvasive functional imaging methods, mainly fMRI, that collectively permit convenient investigation of the brain of healthy participants. Coupled to adaptation of classic protocols used in cognitive psychology to the scanner environment, imaging has confirmed that the brain does indeed deserve its renewed reputation as an occasionally mischievous mnemonic device. All in all, the emerging picture is that recollection is a reconstructive process that is naturally prone to various types of intrusions, modifications, and even illusions (Schacter and Addis, 2007). This apparent sloppiness includes, among others, mistakes in identifying the source of the information ("misattribution"), incorporation of misleading and superfluous external or internal information, and bias by previous knowledge and belief (Schacter, 2001)—all indicating that either the trace is far from being a static replica of the original experience or that the recollective process acts on a veridical trace to produce a memory of questionable veracity. That these "sins of memory," as Schacter aptly describes them, may have a selective advantage should not be forgotten; for example, one could suggest that retaining the gist without remaining bound for too long to the full details of an experienced episode may facilitate anticipation of future different scenarios and promote creative imagination (Bar, 2009; Moulton and Kosslyn, 2009).

Studies involving multiple techniques have identified a number of potential mechanisms by which memory might have the opportunity to drift from the ostensibly exact coordinates of real events. One might envisage that this could happen, for example, in the immediate offline fast compressed replay of an episode (Davidson et al., 2009), during reactivation and consolidation of episodes in sleep during the night after (Diekelmann and Born, 2010), in slow systems consolidation that trims representations and converts episodic into semantic knowledge (Winocur et al., 2010; Furman et al., 2012), in fast systems consolidation in which new information is assimilated into existing mental schemas (Tse et al., 2007; see below), and, finally, in updating during reconsolidation (Wang and Morris, 2010).

Assimilation of the New with the Old

The classic approach to laboratory experimentation on learning and memory, certainly in animal laboratories, is the conduct of the study with subjects that are considered to have either no previous experience with the specific task or, at least, equivalent but well-controlled experience. This simplicity has long been thought to be the best way to identify the quintessential mechanisms of encoding, storage, consolidation, and retrieval. The problem is that this is artificial, because adult organisms will typically have a great deal of prior knowledge, and its possession may change the manner in which these processes occur.

The impact of prior knowledge is greater or lesser for certain forms of representation. In cases in which the emotional or affective value of a stimulus is strongly changed by a conditioning experience, prior knowledge will generally have little influence. An innocuous stimulus may have a long history of being innocuous, but the sound of the weekly fire alarm coupled to visible flames and the smell of smoke changes things forever. However, in cases in which learning involves forming an association, whereby one stimulus can evoke the memory of another, or where one is a label or even the meaning of another, prior knowledge is likely to have a critical impact.

Contrast two cases. Certain forms of associative learning studied in the standard way are quite well understood with, for example, the specific role of the amygdala in cued fear conditioning now worked out at the level of the neural circuits, receptors, and molecules involved. Conveniently, the amygdala is positioned such that the changed activity of its neuronal output pathways has a direct effect on heart rate and numerous other sympathetic and parasympathetic expression systems. Thus, behavioral (freezing) and other changes (heart rate) are readily observed. From a representational perspective, this form of associative conditioning may only require a change in the value of the predicting conditioned stimulus (CS) such that it now has access to output pathways useful in circumstances of danger. The past history of CS neutrality may result in some degree of "latent inhibition" but does not otherwise affect this capacity for learning.

In contrast, the parallel-distributed associative machinery of the neocortex is able to store "associations" of the representational form that CS1 evokes a memory of CS2 (Holland, 1990; for an earlier discussion of such type of associations, see Konorski, 1950). This form of learning is likely different from cued fear conditioning in that CS1 now does not change value to be quantitatively like that of CS2 but, rather, enters into a network of associations that will ultimately come together as a system of knowledge. Paired-associative learning of this form has long been recognized, both within the animal learning community in studies of intentional actions (Dickinson, 1980) and in neuroscience starting with the seminal studies of Miyashita on the electrophysiological signature of fractal pairings (Miyashita et al., 1993). Research on "systems consolidation" at the memory circuits level, which is distinct from research on "cellular consolidation" at the single-cell level (Dudai and Morris, 2000), has led to the idea that the distributed circuitry of the hippocampus performs a variety of encoding-related operations to stimuli such as pattern separation and pattern completion before subsequently creating event-event or event-context associations that may then be subject to consolidation in neocortex (McClelland and Goddard, 1996). The hippocampus and neocortex are hence considered as complementary learning systems (CLSs; McClelland and Goddard, 1996). Whereas the hippocampus is good at putting anything together with anything, and particularly with spatial information in the case of rodents, the neocortex readily forms representations of individual stimuli but is more restricted functionally in its capacity to link disparate information (e.g., information in distinct sensory processing systems). The neuroanatomical connectivity required may be present, but the strength of connections is initially weak, with experience being the guide as to what gets functionally connected to what. The combined forces of flexible hippocampal-dependent learning, systems consolidation, and the vast storage capacities of the neocortex collectively realize the "binding" task of understanding and representing the world around us and not just changing behavior adaptively to deal with specific types of association.

However, this systems consolidation process is now revealed as one that is influenced by what has gone before. One recent example that combines thinking about prior knowledge with representational associations is the idea of forming ''schemas'' around related paired associates that then alter the rate at which new paired associates can be learned and consolidated (Tse et al., 2007). Specifically, animals are trained to enable one of several flavors of food to be associated with and thus predict the location where more of that foodstuff is available. In this case, neither the different flavors of food nor the locations change ''value'' in the manner that a context does in context fear conditioning; what changes is the ability of one set of cues (flavors) to evoke a memory of the other (places). The use of places also enables the animals to gradually build up a representation of the testing space, over several weeks of training, such that they may be thought to have a mental schema that connects these otherwise independent associations into some kind of framework. Interestingly, once this had been achieved, the encoding, storage, and consolidation of new paired associates can become very rapid—even though it was shown to entail consolidation in the neocortex that had previously been thought to require weeks to accomplish (Tse et al., 2011).

This work was originally suggested as a challenge to the CLS approach, but new work by McClelland (2013) indicates that these findings can be readily accommodated by this framework. Whereas catastrophic interference can occur when new information conflicts with prior associations, necessitating two separate but interdependent learning systems, the new analysis suggests that synergistic effects are seen when the new information to be assimilated is concordant with past associations. This animal and computational work on paired-associate learning is also being considered in elegant human fMRI studies of schema-associated assimilation that point to critical interactions between the medial temporal lobe, prefrontal cortex, and other neocortical regions (van Kesteren et al., 2010) and new models of processing that suggest a differential role for the hippocampus and prefrontal cortex as a function of prior knowledge (van Kesteren et al., 2012).

Trace Alliances

Data from both animal and human studies support the notion that the expression of memory involves a transient alliance of representations (Buzsáki, 2010; Watrous et al., 2013). The notion of highly distributed representations, raised over the years by both theoretical and experimental programs (Hebb, 1949; Lashley, 1950; Rumelhart and McClelland, 1986), hence gains an invigorating new twist. In it, the embodiment of memory items is portrayed as dynamic, ad hoc global network interactions, perhaps mediated by frequency-specific connectivity.

A recent example on how this may happen in episodic memory in the human brain is provided by Watrous et al. (2013). They employed simultaneous electrocorticographical (ECoG) recordings in patients undergoing seizure monitoring and recorded from areas in the medial temporal lobe (MTL), prefrontal cortex (PFC), and parietal cortex, which are the main components of the brain network that is activated in retrieval. The patients were engaged in retrieving spatial and temporal contexts associated with an episode. Phase synchronization was used as a measure of network connectivity. Watrous et al. (2013) found that successful retrieval was associated with greater global connectivity among the sites in the 1–10 Hz band, with the MTL acting as a hub for the interactions. Notably, spatial versus temporal context retrieval resulted in differences in the spectral and temporal patterns of the network interactions: while correct spatial retrieval was characterized by lower-frequency interactions across the network along with early and prolonged increases in connectivity, temporal order retrieval was characterized by faster-frequency interactions, a more delayed increase in network connectivity, and a lower temporal coherence across the network compared with the spatial retrieval. Thus, an alliance of brain regions, with frequency-specific connectivity between them, rather than regionally mediated activity alone, could be central to many instances of retrieval and probably to the formation, maintenance, and updating of episodic memory. Furthermore, it appears that frequency-specific patterns of interregional phase synchronization in large-scale networks can provide insight into how multiple contexts underlying a single episode can be recreated in the same network.

Candidate coalitions of memory-related representations are also unveiled by methodologies tapping into longer temporal intervals. Methods for assessing functional connectivity in human fMRI data unveil sets of coactivations of regions subserving episodic recollection (e.g., Greenberg et al., 2005; Maguire et al., 2000; Burianová et al., 2012). Within the animal domain, immediate early gene (IEG) mapping offers another opportunity to examine the coactivation and possible coordination of neurons in multiple brain areas during memory retrieval—as reported by Wheeler et al. (2013) for context fear conditioning. Whereas we used to think of plasticity-related gene activation as triggered solely by encoding and necessary for storage, research on reconsolidation (see ''trace rebooting'' above) has alerted us to the phenomena of gene activation during and after a retrieval session. While the timescale of IEG expression is at least three orders of magnitude slower than that studied in ECoG, obscuring whether gene activation is triggered by, required for, or is some epiphenomenon of memory retrieval, it nonetheless offers an opportunity to examine the dynamics of trace activation across the brain. Wheeler et al. (2013) establish that the network interactions that are seen in IEG expression change as a representation consolidates over time.

Time Present and Time Future

T.S. Eliot, whose insights into memory infiltrate our subtitles, saw that life had its retrospective, immediate, and prospective elements. The last of these applies even to memory itself, with a growing number of investigators considering planning from the perspective of memory (Schacter and Addis, 2007; Thom et al., 2013). The prospective aspect of memory research is also intriguing. Given our argument that contemporary conceptions of memory processing are diverting from our dual-trace and fixed storage heritage, we can usefully ask, ''Where are we going''?

In Search of the Engramatic Code

Memory is traditionally measured in terms of the change in an individual's behavior that results from their behavioral experience. This change reflects the encoding and retention over time of experience-dependent internal representations in the brain or

of the capacity to reactivate or reconstruct such representations (Dudai, 2002). Representations, unless possibly of very elementary reflexes, are commonly postulated to be encoded in the spatiotemporal activity of neural circuits, ensembles, or Hebbian ''cell assemblies'' (Buzsáki, 2010). The number of neurons required for a physiologically meaningful representation need not be big (Shadlen and Newsome, 1998), but it is important to recognize that it is commonly assumed to be more than one neuron, even though mechanisms are often discussed as if change happens at a small subset of synapses in a single neuron. The influential reductionist revolution in memory research (Kandel, 2001) focused initially on the molecular mechanisms of synaptic plasticity that are hypothesized to allow memory to take place in the first place (Martin et al., 2000). Hence, the search for the engram in major parts of the discipline tilted for a while more toward the search for the identity and function of the molecular and cellular ''nuts and bolts'' of engramatic machinery rather than the issue of how circuit activity represents the cognitive and behavioral content encoded in the trace. But the ever swinging pendulum of science is now reverting to a more active consideration of the place of circuits, including microcircuits, and how they may mediate diverse aspects of cognitive function. Already we see growing interest in inhibitory neurons as well as excitatory neurons and regulation of the balance of their influence on processing via homeostatic regulation (Turrigiano, 2008), in the selective role of synapses at specific parts of a dendritic tree, on the soma, or on axons (Somogyi and Klausberger, 2005), and the contribution that synaptic integration and clustered plasticity may make to representations (Govindarajan et al., 2006; Branco and Häusser, 2011). This circuit revolution takes on board the earlier understanding of activity-dependent synaptic plasticity (Bliss and Collingridge, 1993; Kandel, 2001) and deploys some of the same neurobiological tools as in the past, but there is a growing sense that the mechanisms of memory will not be satisfactorily understood in the absence of elucidation of the circuit code(s) of internal representations for which some of the new tools available will be invaluable.

Progress continues to be made through novel theoretical ideas and via incremental refinements to long-established techniques coupled to elegant behavioral paradigms and fresh analysis methods. Notable, though definitely not exhaustive, examples include the development of multivoxel pattern analysis techniques in cases in which a qualitative rather than a quantitative change in the blood oxygen level-dependent (BOLD) signal is expected as in episodic memory encoding and retrieval (Chadwick et al., 2012; Kuhl et al., 2012); the use of long-established tetrode recording techniques to discover yet more about place cells, head direction, and grid cells and their role in providing a spatial framework for navigation and the anchoring of event memory (Burgess et al., 2002; Taube, 2007; Moser et al., 2008); new twists to the hippocampal tale such as ''time cells'' in the rat hippocampus (Kraus et al., 2013); the combination of tetrode recording in the macaque with fMRI in humans to unveil conserved patterns of neural activity across the medial temporal lobe during associative learning (Hargreaves et al., 2012); and the exploitation of advanced molecular biology to unveil the role of epigenesis in plasticity and memory (Day and Sweatt, 2011), for example, the involvement of small RNAs in epigenetic control of persistent synaptic facilitation in *Aplysia* (Rajasethupathy et al., 2012).

However, recent outstanding technical developments add significant power to the reductionist approach to memory but also permit more effective approaches to the identification of the representational content and dynamics of memory items in the behaving organism at the circuit level. The technological advances augment and feed the realization that circuit research will move us to the next stage of understanding perceptual, attentional, and mnemonic codes. An emerging assumption is that understanding the patterns of firing of identified neurons in specific macro- and microcircuits will constitute the level of detail to which we must turn. But how? It is now becoming possible, using combinations of advanced electrical recording, miniaturized in vivo chronic microscopy, conditional genetic switches, and optogenetics, both to monitor the activity of such neurons and circuits and also to perturb selected elements of this activity with a view to making causal inferences about mechanisms. Activating and inhibiting these elements will play an increasingly critical role in establishing sufficiency with respect to expressing the elements of memory.

Much of this type of work is conducted on the hippocampus, long implicated in multiple aspects of mammalian memory (Buzsáki and Moser, 2013), although the amygdala, subserving fear conditioning, is also a favorable target (Zhou et al., 2009; Johansen et al., 2010). The neocortex, commandingly positioned above the fray, is gaining the renewed interest it deserves (Gilmartin et al., 2013). Selected examples in animal models include: (1) identification in the behaving mouse of neuronal traces of specific fear-context associations and the generation of synthetic memory traces of such associations by selective activation of neurons engineered to carry receptors exclusively activated by designer drugs (Garner et al., 2012); (2) labeling of specific ensembles contributing to the fear-context engram with channelrhodopsin and subsequent optogenetic reactivation of the ensemble (Liu et al., 2012); and (3) identification by hippocampal recording with chronic tetrode arrays of compressed activity signatures during sharp-wave ripples that may represent specific spatial memory information (Pfeiffer and Foster, 2013). Whether the activity signatures unveiled in these and other studies are or are part of the neural code of active memory representations still awaits further investigation, e.g., on how these messages are read and construed by downstream brain circuits (Buzsáki, 2010). But these findings represent a significant step forward on the road to decipher the neuronal language of memory.

In humans, still limited at the time of writing by the lower temporal and/or spatial resolution of current noninvasive functional imaging and the relatively crude methods of ''noninvasive'' intervention (e.g., transcranial magnetic stimulation and direct current stimulation), the pace of advance is a bit slower but still highly noticeable. Classifier multivoxel pattern analysis, noted above, already permits identification of BOLD signatures of some types of visual categories (though not tokens within these types) in candidate memory representations (Rissman and Wagner, 2012). Intracranial electrophysiology in human patients is inherently limited in terms of scope and experimental design, but the expanding use of this approach, ranging from ECoG

(see above), single-unit recording, and microstimulation, is likely to provide further information on the correlation, and ultimately necessity and sufficiency, of neuronal memory representations (Suthana and Fried, 2012).

The trend, made possible by the fast development of advanced techniques, is to tap further into the network alliances, global circuits, and microcircuit processes and cellular mechanisms that process information for effective encoding, create suitable representations, and maintain information over time. This trend is likely to gain further momentum in the forthcoming decade, driven by research questions in basic science but also by potential clinical applications involving brain-machine interface (BMI) and the development of neuromorphic technology (see below).

Increasing Realism

The scientific era in human memory research began with an intentional and systematic disregard to the meaning of the information to be remembered by selecting nonsense syllables as memoranda (Ebbinghaus, 1885). In animal learning also, there had been a supposition early on that an abstract and mathematical account of all there was to know about learning could be realized from studying the behavior of a rat at the choice point of a maze—culminating in the formalisms of Hull (1951) that are now, perhaps fortunately, lost to time. The dominance of simple, quantifiable, yet artificial and often meaningless, memoranda provoked Neisser (1978), almost a century later, to question whether psychologists were studying interesting or socially significant aspects of memory. Part of the Ebbinghausian tradition was carried into the human fMRI protocols, e.g., strings of paired associates composed of normally unrelated words or arbitrary still pictures to model episodic encoding. This was highly productive, but in recent years, more realistic learning and memory paradigms are encountered in the scanner environment, including the use of movies as episodic memoranda (Hasson et al., 2008), of navigation by knowledgeable taxi drivers (Hartley et al., 2003), recollections modified by social interactions (Edelson et al., 2011), and the use of that universal engine of memory, fear, under strikingly realistic conditions (Sharot et al., 2007). In parallel, it is noteworthy that the outcome of research on brain and cognitive mechanisms of memory spills into key aspects of daily life and society (Schacter and Loftus, 2013). The growth of "social neuroscience" portends growing interest in social aspects of memory in both human and animal-based neuroscience.

Similarly, it seems that more attention is devoted to the effectiveness of realistic milieu in animal models used in memory research, with renewed emphasis on the real-life cognitive universe of rodents (particularly space, odors, somatosensory stimuli, and their interactions, e.g., Morris et al., 2006; Sauvage et al., 2008; Buzsáki and Moser, 2013). The general understanding, itself rooted in several older animal psychology schools and now resurrected, is that animals learn better when the memoranda make sense in their world. Hints of a similar trend seem to emerge in the primate literature as well (Paxton et al., 2010). It is likely that widespread use of novel consumer technology (such as Google-type glasses or personal activity monitors), miniaturization of noninvasive functional imaging devices for humans, and facilitated real-time web communication will render more realistic memory experiments easier and more popular.

Memory Systems Updated?

The dominant taxonomy of memory systems, echoing earlier philosophical notions (Ryle, 1949), was shaped by studies of "global amnesics" like H.M. and other patients (Scoville and Milner, 1957; Rosenbaum et al., 2005; Squire and Wixted, 2011), supported by lesion studies in animal models (Mishkin, 1982; Olton et al., 1979; Fanselow, 2010). It has long portrayed the brain as possessing two major types of memory systems—declarative (explicit) memory for facts and events, for people, places, and objects ("knowing that") and nondeclarative (implicit) memory, the memory for perceptual and motor skills ("knowing how"). Whereas declarative memory is held to involve particular types of representation and conscious awareness for recollection, it also requires an intact hippocampus—at least at the time that a memory is acquired. In contrast, nondeclarative memory is thought to be a heterogeneous collection of experience-dependent changes shown in behavior and not to rely on the hippocampus but on a number of other brain systems: the cerebellum, the striatum, the amygdala, and, particularly in invertebrates, simple reflex pathways themselves. This taxonomy was immensely useful as a conceptual framework for both human and animal studies, in teaching where it is little short of a blessing, and as an engine for new experimental programs.

Recent ideas and data, however, have raised questions about this taxonomy. One issue relates to what can be concluded from brain damage/lesion studies, which identify *necessity*, compared to physiological approaches, which measure *correlates* of a presumed process—be it in neural firing, BOLD, IEG activation, or in other ways. Specifically, the demonstration in double-dissociation lesion studies that the integrity of the hippocampus is not necessary for declarative memory retrieval after a long consolidation period (e.g., retrieval of semantic memory) need not imply, as perhaps it was taken to do so in the past, that it cannot or does not participate when functioning normally. Functional imaging data suggest, in contrast, that brain circuits traditionally considered to be the hallmark of declarative memory (hippocampus) or of procedural memory (basal ganglia) take part, in the healthy brain, in tasks in which they may not previously have been expected to play a role (Reber et al., 2012; Scimeca and Badre, 2012; see also Voss et al., 2012). There is also a growing realization that the classic temporal gradient of retrograde amnesia, challenged in the development of the multiple-trace theory of Nadel and Moscovitch (1997), may not be reliably secured in animal models. Related to growing uncertainty about the taxonomy is the question whether "conscious awareness" is indeed a natural type of classifier for memory systems (Henke, 2010).

This also raises the more general question of what memory systems are (Roediger et al., 2007). Are such systems rigidly interconnected sets of brain areas dedicated to specific types of mnemonic tasks? Or should they be considered as ad hoc coalitions of computational modules that are recruited per task (Cabeza and Moscovitch, 2013)? The latter view resonates nicely with the dynamic view of memory expression, discussed above. It is likely that in the forthcoming years our view of memory systems will become updated, not unlike memory itself.

Prepare for the Bionic Future

Coinciding with the 25th anniversary of *Neuron* is a new revolution in neuroscience. Not only have concepts of memory-in-brain changed over the past 25 years, partly in response to the astounding new methodologies that are altering the way brain research is done, but also the style of work is changing. The discipline itself is experimenting, not without intense debates, in "big science" projects that reflect the colossal demands imposed by the sheer complexity of the brain and the technological and cognitive resources required to tackle them effectively (Kandel et al., 2013). Whatever path this revolution takes, it is highly likely that some of the achievements of the multipronged new sciences of the brain will culminate in understandings and capabilities that not long ago were confined to fictional universes only, and some of these will be directly related to human memory.

One possibility is that the science of biological memory will make the leap from the vintage point of the curious observer to that of the active player. Some harbingers are already with us: new attempts to enhance memory, which have a long history (for a recent basic science example, see Alberini and Chen, 2012), or attempts to erase memory to ameliorate posttraumatic stress disorder (PTSD) in humans guided by research on reconsolidation (Schiller et al., 2010). But one should consider also the potential capabilities of brain-machine interfaces (BMIs, e.g., Hatsopoulos and Donoghue, 2009) not only to compensate for the deficits and retrain lesioned brain and bodies, but also, once noninvasive techniques are further developed, to augment the capability of intact brains. The potential ethical and social implications of such capabilities should not escape our notice.

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Leading Edge
Review
Cell

The Molecular and Systems Biology of Memory

Eric R. Kandel,[1,2,3,4,*] Yadin Dudai,[5] and Mark R. Mayford[6]
[1]Kavli Institute for Brain Science
[2]Zuckerman Mind Brain Behavior Institute
[3]Howard Hughes Medical Institute
[4]Departments of Neuroscience, Biochemistry and Molecular Biophysics, and Psychiatry
College of Physicians and Surgeons of Columbia University, New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, USA
[5]Department of Neurobiology, Weizmann Institute of Science, Rehovot 76100, Israel
[6]Department of Molecular and Cellular Neuroscience, The Scripps Research Institute, La Jolla, CA, USA
*Correspondence: erk5@columbia.edu
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Learning and memory are two of the most magical capabilities of our mind. Learning is the biological process of acquiring new knowledge about the world, and memory is the process of retaining and reconstructing that knowledge over time. Most of our knowledge of the world and most of our skills are not innate but learned. Thus, we are who we are in large part because of what we have learned and what we remember and forget. In this Review, we examine the molecular, cellular, and circuit mechanisms that underlie how memories are made, stored, retrieved, and lost.

Introduction

Memory is the glue that holds our mental life together. Without its unifying power, both our conscious and unconscious life would be broken into as many fragments as there are seconds in the day. Our life would be empty and meaningless.

Moreover, disturbances of memory can affect our cognitive capabilities and thus our quality of life at all stages of life. Early disorders of learning and memory hinder the development of children, the normal weakening of memory with time irritates and frustrates the aging, and the specter of Alzheimer disease haunts the elderly and their families. During the last four decades, neuroscience, the biological study of the brain, has succeeded in establishing a common conceptual framework that extends from cell and molecular biology, on the one hand, to brain system biology and psychology, on the other. Within this new, interdisciplinary structure, the scope of memory research ranges from genes to cognition, from molecules to mind.

Where Is Memory Stored?

Forty years ago, we learned from the pioneering work of Milner and her colleagues that certain forms of long-term memory rely on the hippocampus and the medial temporal lobe for their acquisition and early retention. It soon emerged (Scoville and Milner, 1957; Penfield and Milner, 1958; Milner, 1962; Milner et al., 1968; Warrington and Weiskrantz, 1968; Squire, 1992; Schacter and Tulving, 1994) that the brain has two major types of memory: explicit (declarative) memory, for facts and events, people, places, and objects; and implicit (nondeclarative) memory, for perceptual and motor skills. Whereas major aspects of explicit memory require the hippocampus and adjacent cortex —and in humans involve conscious awareness—implicit memory does not require conscious awareness and relies mostly on other brain systems: namely, the cerebellum, the striatum, the amygdala, and, in invertebrate animals, simple reflex pathways themselves.

In this review we will first focus on how simple implicit memory is acquired and maintained in invertebrates and discuss the molecular biology and structural mechanisms of short-, intermediate- and long-term memory. We will then consider briefly the mechanisms of implicit memory in the mammalian brain. From there, we will focus on explicit memory in rodents and nonhuman primates, examining the complex cellular mechanisms and neural circuitry needed to acquire, maintain, and express this learned information. Finally, we will examine distinctive features of human memory storage.

To give the general reader of *Cell* a sense of the major issues emerging in the field of memory, we have been selective rather than exhaustive. A selective approach is bound to involve idiosyncratic choices from the large body of excellent work on memory. While we try to discuss most of the major contributions to the field, we focus initially on studies of *Aplysia* in order to provide a coherent narrative of how molecular biology revolutionized our understanding of simple forms of neuronal plasticity and implicit memory. In the second part of our review, we focus on connecting our molecular insights into implicit memory to the more complex systems of explicit memory, highlighting specific aspects of the vast literature on genetically modified mice. Finally, we focus on the mechanisms recruited by the human brain to encode, consolidate, reactivate, and update explicit memory, areas in which memory studies have made a particularly significant contribution.

Throughout this review we will emphasize that memory storage is not the result of a linear sequence of events that culminates in an indelible, long-term memory. Rather, it is the dynamic

outcome of several interactive processes: encoding or acquisition of new information, short-term memory, intermediate-term memory, consolidation of long-term memory, maintenance of long-term memory, and destabilization and restabilization of memory in the course of retrieving, updating, and integrating a given memory with other memories. We can see these dynamics at work in multiple levels of analysis and brain organization and in varying degrees, from simple to complex memory systems. These dynamics are initiated by molecular and cellular modifications at the level of individual synaptic connections and extend to more distributed changes throughout multiple synaptic connections of many neurons embedded in larger neuronal networks whose interactions are expressed at the behavioral level.

Part I: The Cell and Molecular Biology of Implicit Memory Storage

How Is Implicit Memory Stored?

Although it was clear by the early 1970s that there are two major types of memory, little was known about how either type is formed or stored. In fact, we did not even have a frame of reference for studying the biological bases of memory (Kandel and Spencer, 1968). We could not distinguish, experimentally, between the two leading—and conflicting—approaches: the aggregate field approach advocated by Lashley in the 1950s and by Adey in the 1960s, which assumed that information is stored in the bioelectric field generated by the aggregate activity of many neurons; and the cellular connectionist approach, which derived from Cajal's idea that memory is stored as an anatomical change in the strength of synaptic connections (Cajal, 1894). (In 1948 Konorski renamed Cajal's idea synaptic plasticity [the ability of neurons to modulate the strength of their synapses as a result of use (Konorski, 1948)].)

To distinguish between these disparate approaches to memory storage, it soon became clear that one needed to develop tractable behavioral systems. Such systems would make it more likely to see how specific changes in the neuronal components of a behavior cause modifications of that behavior during learning and memory storage. From 1964 to 1979, several simple model systems of implicit memory emerged: the flexion reflex of cats, the eye-blink response of rabbits, and a variety of simple forms of reflex learning in invertebrates: namely, the defensive gill-withdrawal reflex of *Aplysia*, olfactory learning in *Drosophila*, the escape reflex of *Tritonia*, and various behavioral modifications in *Hermissenda*, *Pleurobranchaea*, *Limax*, crayfish, and honeybees (Alkon, 1974; Dudai et al., 1976; Krasne, 1969; Kupfermann and Kandel, 1969; Menzel and Erber, 1978; Quinn et al., 1974; Spencer et al., 1966; Thompson et al., 1983).

In short order, a number of insights emerged from this reductionist approach. The first was purely behavioral and revealed that even animals with relatively few nerve cells—from approximately 20,000 in the central nervous system of *Aplysia* to 100,000 in *Drosophila*—have remarkable learning capabilities. These simple nervous systems can give rise to a variety of elementary forms of learning: habituation, dishabituation, sensitization, classical conditioning, and operant conditioning. Each form of learning, in turn, gives rise to short- or long-term memory (Carew and Sahley, 1986).

The first studies focused on short-term changes, those lasting from a few minutes to an hour. They found that single-trial learning and the formation of short-term memory, evident in both the gill-withdrawal reflex of *Aplysia* and the tail-flick response of crayfish, result from changes in the strength of certain critical synapses. Subsequent studies revealed that these short-term changes in synaptic strength result from the modulation of the release of chemical transmitters from presynaptic neurons. A decrease in the amount of transmitter released was found to be associated with short-term habituation, whereas an increase was associated with short-term dishabituation and sensitization (Castellucci et al., 1980; Castellucci and Kandel, 1976; Cohen et al., 1997; Zucker et al., 1971).

Studies of memory in invertebrates also uncovered a family of psychological concepts paralleling those described in vertebrates by the classical behaviorists Pavlov (1927) and Thorndike (1911) and by their modern counterparts Kamin (1969) and Rescorla and Wagner (1972). These concepts (Hawkins and Kandel, 1984; Sahley et al., 1981; Zhang et al., 2012) include the distinction between various forms of associative and nonassociative learning as well as a critical insight about associative learning: the conditioned stimulus (CS) plays an important role in learning not simply because it precedes the unconditioned stimulus (US), but because it predicts the unconditioned stimulus, making it no longer surprising (Rescorla and Wagner, 1972).

Thus, for the first time, psychological concepts that had been inferred from purely behavioral studies could be explained in cellular and molecular terms. For example, the finding that the same sensory neuron-to-motor neuron synapses that mediate the gill-withdrawal reflex also underlie learning and memory showed us that the storage of implicit memory in simple systems does not depend on specialized neurons that store information. Rather, the capability for storing implicit memory is built into the neural architecture of the reflex pathway itself and depends on its capability for synaptic plasticity.

The study of simple forms of learning in simple systems paved the way to the investigation of the molecular underpinning and the potential role of these identified elementary building blocks of neural plasticity in learning and memory in more complex brains and more complex types of memory. It also stimulated the search for additional cellular, and especially circuit, mechanisms that have evolved advanced mnemonic capabilities. Accordingly, in our review, we will begin with a discussion of molecular and cellular investigation of short-, intermediate- and long-term forms of simple implicit memory and then progress to a discussion of these phases in both implicit and explicit memory in the mammal and then the human brain.

Encoding and Storing Short-Term Memory

Studies of the synaptic connections between the sensory and motor neurons that control the gill-withdrawal reflex in *Aplysia* revealed that a single sensitizing stimulus to the tail increases the strength of the synaptic connections between the sensory and motor neurons. The stimulus leads to the activation of modulatory neurons that release serotonin onto the sensory neuron (Marinesco and Carew, 2002; Glanzman et al., 1989; Mackey et al., 1989). Serotonin, in turn, increases the concentration of cyclic adenosine monophosphate (cAMP) in the sensory cell. The cAMP molecules signal the sensory neuron to release

more of the transmitter glutamate into the synaptic cleft, thus temporarily strengthening the connection between the sensory and motor neuron. In fact, simply injecting cAMP directly into the sensory neuron produces temporary strengthening of the sensory-motor connection (Brunelli et al., 1976).

Classical Conditioning

Next, Hawkins and his colleagues (Hawkins et al., 1983) and Walters and Byrne (1983) succeeded in producing classical conditioning of the *Aplysia* gill-withdrawal reflex and began to analyze the mechanisms underlying this form of learning. Paired training, in which the conditioned stimulus (stimulation of the siphon) is applied just before the unconditioned stimulus (a shock to the tail), produces a greater increase in the gill-withdrawal reflex than either stimulus alone or than unpaired stimuli. This is because the firing of an action potential by the sensory neuron just before the tail shock causes greater facilitation of the synaptic connection between sensory and motor neurons, an action also known as activity-dependent enhancement of synaptic facilitation.

Further experiments indicated that classical conditioning is in part due to activity-dependent enhancement of the same molecular signal, cAMP, used in sensitization (Kandel, 2001; Hawkins et al., 1983; Antonov et al., 2001) and in part due to the recruitment of a postsynaptic contribution (Murphy and Glanzman, 1997). Abrams analyzed the presynaptic component and found that an influx of calcium ions into the sensory neuron, which occurs during paired firing, enhances the activity of Ca^{2+}-sensitive adenylyl cyclase, the enzyme that synthesizes cAMP (Kandel, 2001; Abrams et al., 1991). Thus, if serotonin, which increases the concentration of cAMP in the sensory neuron, arrives at the synapse just after the influx of calcium ions, the synthesis of cAMP and the strengthening of the sensory-motor synapses are further enhanced.

In addition to classical conditioning, gill withdrawal, as well as biting, in *Aplysia* can be modified by operant conditioning (Brembs et al., 2002; Hawkins et al., 2006).

Long-Term Memory Consolidation

Beginning in 1980, the insights and methods of molecular biology were brought to bear on the nervous system, making it possible to identify molecular mechanisms of short-term memory that are common to different animals and to explore how short-term memory and long-term memory are stored.

Benzer and his students discovered that *Drosophila* can learn fear and that mutations in single genes interfere with short-term memory (Dudai et al., 1976; Quinn et al., 1974). Byers, Davis, Dudai, Quinn, and Livingstone found that in several lines of *Drosophila*, the mutant genes represent one or another component of the cAMP pathway (Byers et al., 1981; Dudai et al., 1983; Livingstone et al., 1984), the same pathway that underlies sensitization and classical conditioning in *Aplysia*.

These elementary forms of learning produce distinct differences in the duration of memory storage (Carew et al., 1972; Pinsker et al., 1973; Quinn and Dudai, 1976). Moreover, the behavioral changes that accompany learning were soon found to have biological parallels in synaptic plasticity. Short-term and intermediate-term memory parallels synaptic strengthening that lasts from minutes to hours, and long-term memory parallels synaptic strengthening that lasts from days to weeks (Castellucci et al., 1978; Carew et al., 1979).

This glutamatergic synaptic connection (Dale and Kandel, 1993; Trudeau and Castellucci, 1993) can be reconstituted in dissociated cell culture. Montarolo et al. (1986) reproduced the changes in synaptic strengthening produced by behavioral learning simply by replacing the sensitizing stimuli to the tail with brief applications of serotonin (Marinesco and Carew, 2002; Glanzman et al., 1989). Thus, a single brief application of serotonin produces a short-term increase in synaptic strength (short-term facilitation), whereas repeated, spaced applications produce increases in synaptic strength that can last for more than a week (long-term facilitation) (Montarolo et al., 1986). Here, as in classical conditioning, the facilitation is greater if the sensory neuron fires action potentials just before serotonin is released (Eliot et al., 1994; Bao et al., 1998; Schacher et al., 1997). This culture system provides insights into the molecular mechanisms whereby short-term memory is converted to long-term memory, a process termed consolidation (Muller and Pilzecker, 1900; McGaugh, 1966; Dudai, 2012).

The first clue to this conversion came from pharmacological studies in vertebrates. Flexner, followed by Agranoff and his colleagues and Barondes and Squire (Davis and Squire, 1984), observed on the behavioral level that the formation of long-term, but not short-term, behavioral memory requires the synthesis of new proteins. A cellular study of long-term memory in *Aplysia* showed that this protein synthesis reflects new gene expression, which is initiated in long-term sensitization by the repeated release of serotonin. Under these conditions, the serotonin-induced increase in cAMP persists, causing the catalytic subunit of cAMP-dependent protein kinase (PKA) to recruit mitogen-activated protein kinase (MAPK); both then move to the nucleus of the cell, where they phosphorylate transcription factors and thus activate the gene expression required for long-term memory (Bacskai et al., 1993; Martin et al., 1997b).

In 1990, Dash found that during long-term facilitation in *Aplysia* neurons, PKA activates gene expression by means of the cAMP response element binding protein, CREB-1 (Dash et al., 1990). By preventing CREB-1 from binding to its DNA response element, he could eliminate long-term facilitation without any effect on short-term facilitation. Most of the signaling cascade that leads to the activation of CREB appears to be conserved through evolution, and many aspects of the role of CREB in synaptic plasticity described in invertebrates have also been observed in the mammalian brain. That said, the role of CREB in models of explicit memory in vertebrates appears to be more complex than it is in implicit memory in invertebrates (Barco et al., 2002; Lonze and Ginty, 2002; Pittenger et al., 2002).

In *Aplysia* sensory neurons, CREB-1 activity leads to the expression of several immediate-response genes that stabilize and prolong the PKA signaling involved in short-term facilitation (Hegde et al., 1997). CREB-1 also induces the transcription factor CCAAT-enhancer binding protein (C/EBP), which is critical for long-term facilitation (Alberini et al., 1994) and leads to a second wave of gene expression that produces the growth of new synaptic connections (Bartsch et al., 2000; Puthanveettil and Kandel, 2011).

Initial studies of the molecular switch from short-term to long-term memory in *Aplysia* and *Drosophila* focused on positive regulators that promote memory storage, as CREB-1 does.

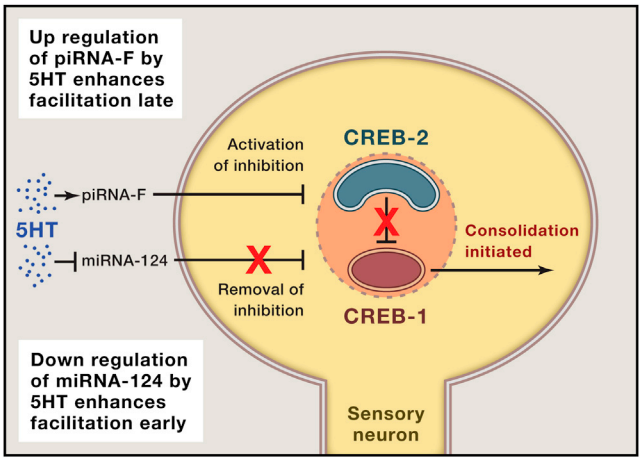

Figure 1. Epigenetic Mechanism in Memory

Epigenetic regulation of the transcriptional switch: 5HT inhibits miRNA-124 and thus facilitates the activation of CREB-1, which begins the process of memory consolidation, while piRNA, also activated by 5HT, but with a delay, leads to the methylation and thus repression of the promoter of CREB-2, allowing CREB-1 to be active for a longer period of time.

Subsequent studies revealed that the switch is also constrained by memory suppressor genes (see Abel et al., 1998). One of these is CREB-2 (Bartsch et al., 1995), which when overexpressed blocks long-term synaptic facilitation in *Aplysia*. When CREB-2 is removed, a single exposure to serotonin, which normally produces an increase in synaptic strength lasting only minutes, will increase synaptic strength for days and induce the robust growth of new synaptic connections, as we shall see (Bartsch et al., 1995).

The CREB-mediated response to external stimuli can be modulated by a number of kinases (PKA, CaMKII, CaMKIV, RSK2, MAPK, and PKC) and phosphatases, which suggests that it integrates signals from these various pathways. The ability to integrate signaling, as well as to mediate activation through CREB-1 or suppression through CREB-2, may explain why CREB transcription factors are central to memory storage and why CREB-dependent gene expression has been conserved through evolution. Other transcription factors also contribute to the regulation of transcription that accompanies long-lasting synaptic change in different forms of learning and in different animal species (Albensi and Mattson, 2000; Izquierdo and Cammarota, 2004; Yin et al., 1994; Waddell and Quinn, 2001).

Chromatin Alteration and Epigenetic Changes in Memory Consolidation

Epigenetic mechanisms, which change gene expression but do not alter the underlying DNA, were widely known to be involved in the formation and long-term storage of cellular information in response to transient environmental stimuli during development, but their possible relevance to adult brain function was discovered only in relatively recent studies (Guan et al., 2002; Levenson and Sweatt, 2005). These studies suggest that epigenetic marking of chromatin may have long-lasting effects on the regulation of transcription at loci that are involved in long-term synaptic changes in both simple and complex animals (Hsieh and Gage, 2005). Guan and his colleagues (Guan et al., 2002) found that both excitatory and inhibitory transmitters can activate signaling pathways that switch transcription on or off via CREB-1 and CREB-2 and subsequently affect the structure of nucleosomes through acetylation and deacetylation of the residues of histone proteins in chromatin.

Another important regulator of transcription are small, noncoding RNA molecules. In *Aplysia*, the most abundant, well-conserved microRNA that is specific to the brain is miR-124. This molecule is found in the sensory neuron, where it binds to and inhibits the messenger RNA of CREB-1 (Rajasethupathy et al., 2012). Serotonin inhibits miR-124, thereby disinhibiting the translation of CREB-1 and making possible long-term memory transcription (Rajasethupathy et al., 2012). The brain of *Aplysia* also contains a class of small, noncoding RNA molecules, piRNA, that had previously been thought to exist only in germ cells (Rajasethupathy et al., 2012). The concentration of one of these molecules, piRNA-F, increases in response to serotonin, leading to the methylation and silencing of CREB-2. Thus, serotonin regulates both piRNA and miRNA molecules: a rise in piRNA-F silences CREB-2, while a drop in miR-124 activates CREB-1 for over 24 hr, establishing stable, long-term changes in the sensory neurons that consolidate memory and put it in long-term storage (Figure 1). These findings reveal a new, epigenetic mechanism for regulating the gene expression underlying long-term memory storage (Landry et al., 2013).

Long-Term Memory and Synaptic Growth

In a seminal study, Bailey and Chen (1988) found that the storage of long-term memory is accompanied by structural changes with both habituation and sensitization of the *Aplysia* gill-withdrawal reflex. The sensory neurons from habituated animals retract some of their presynaptic terminals, thus making fewer synaptic connections with motor neurons and interneurons. In contrast, the sensory neurons from animals exposed to long-term sensitization more than double the number of their presynaptic terminals. This learning-induced synaptic growth is not limited to sensory neurons. The dendrites of the motor neurons, which receive the signals from the sensory neurons, grow and remodel to accommodate the additional sensory input.

These results demonstrate that structural changes in both the presynaptic sensory cell and the postsynaptic motor cell accompany even elementary forms of learning and memory in *Aplysia*. Together, these early cellular studies of simple behaviors provided direct evidence supporting Cajal's suggestion that synaptic connections between neurons are not immutable, but can be modified by learning and that anatomical modifications are likely to subserve memory storage. Finally, the finding that both post- and presynaptic neurons participate in growth implies that a signaling system presumably exist that leads to the activation of the postsynaptic cell by a process that, in the short-term, starts in the presynaptic neuron (Glanzman, 2010).

Intermediate-Term Memory and the Propagation of Information for Growth

In 1995, Ghirardi and her colleagues (Ghirardi et al., 1995; Sutton and Carew, 2000) identified an intermediate phase in the transition between short- and long-term facilitation and behavioral sensitization in *Aplysia*. This phase requires protein synthesis but not gene transcription. Subsequent studies by Antonov et al. (2010) found that whereas short-term sensitization

and short-term synaptic facilitation are presynaptic and involve covalent modifications of existing proteins mediated by PKA, intermediate-term facilitation and behavioral sensitization involve both presynaptic (PKA and CaMKII) and postsynaptic (Ca^{2+}, CaMKII) covalent modifications, as well as both presynaptic and postsynaptic protein synthesis (Sutton and Carew, 2000).

Jin et al. (2012a, 2012b) explored the question of how the presynaptic neuron recruits the activity of the postsynaptic neuron. They found that the intermediate phase begins with PKA in the presynaptic neuron mediating a three-fold increase in spontaneous release of glutamate, which acts as an anterograde *trans*-synaptic messenger to the molecular machinery of the postsynaptic cell and induces the initial steps of new synaptic growth. It does so by activating metabotropic glutamate receptors (mGluR5), which increase the production of inositol triphosphate (IP-3), thus causing the release of calcium stored within the postsynaptic cell. Calcium, in turn, leads to the insertion of new copies of the amino-methyl-propionic acid (AMPA) type of glutamate receptor in the postsynaptic cell and to the first phase of postsynaptic remodeling that leads to synaptic growth.

Maintenance of Long-Term Memory

A single neuron can have up to a thousand synapses. These synapses, as we have seen, are the units of information storage for short-term memory. Given the fact that long-term memory storage requires gene expression, which takes place in the nucleus, one might expect long-term synaptic facilitation to be cell wide.

To explore whether the synapse is also the unit for long-term memory, Martin and her colleagues carried out experiments in which serotonin was applied locally to one of the two branches of the bifurcating sensory neurons in *Aplysia* that innervate two separate motor neurons (Casadio et al., 1999; Martin et al., 1997a). These experiments, as well as parallel experiments by Frey and Morris in the hippocampus (Frey and Morris, 1997), demonstrate that individual synapses can be modified independently and that the change persists for more than 24 hr. This means that long-term facilitation and its associated synaptic changes are synapse specific. Moreover, this synapse specificity requires CREB-1. These findings imply that signals are sent not only from the synapse back to the nucleus (Martin et al., 1997a; Lee et al., 2007) but also from the nucleus to specific synapses.

Once transcription has begun, newly synthesized gene products, both mRNA molecules and proteins, have to be delivered to the specific synapses whose activation originally triggered the gene expression. To explain how this specificity can be achieved efficiently, despite the massive number of synapses in a single neuron, several research groups (Frey and Morris, 1997; Martin et al., 1997a; Michael et al., 1998) proposed the synaptic capture, or tagging, hypothesis. This hypothesis states that the products of gene expression are delivered throughout the cell but are only used at synapses that have been tagged by their previous activity (Barco et al., 2002; Casadio et al., 1999; Dudek and Fields, 2002; Frey and Morris, 1997; Martin et al., 1997a, 1997b).

How is an active synapse marked? Martin and her colleagues (Martin et al., 1997a) found two components of marking in *Aplysia*: one that requires PKA and initiates long-term synaptic plasticity and growth and one that stabilizes and maintains long-term functional and structural changes at the synapse and requires local protein synthesis. One way of activating protein synthesis at the synapse would be to recruit a regulator of gene translation that is capable of activating dormant mRNA. In *Xenopus* oocytes, for example, maternal RNA is silent until activated by the cytoplasmic polyadenylation element binding protein (CPEB) (Richter, 1999).

Si searched for a homolog in *Aplysia* and found, in addition to the developmental form of CPEB, a new form that had novel properties (Si et al., 2003a, 2003b). Blocking this form of CPEB at a marked (active) synapse prevents the maintenance, but not the initiation, of long-term synaptic facilitation for a day or more after the memory is formed. A remarkable feature of the *Aplysia* form of CPEB is that its N terminus resembles the prion domain of yeast prion proteins, which endows the *Aplysia* CPEB with similar self-sustaining properties. But unlike other prions found to date, which are pathogenic, the *Aplysia* CPEB appears to be functional: the active, self-perpetuating form of the protein does not kill cells, but rather is the active form of the protein that controls synapse-specific translation. Notably, the persistence of long-term memory in *Drosophila* and in mice was also found to involve CPEB (Keleman et al., 2007; Majumdar et al., 2012; Rajasethupathy et al., 2012).

Prion-like proteins are self-replicating structures that were first hypothesized to contribute to persistent memory storage by Tompa and Friedrich (1998). Si et al. (2010) proposed a model of such storage based on the prion-like properties of CPEB in *Aplysia* neurons. There, CPEB can activate the translation of dormant mRNA molecules by elongating their poly-A tail. *Aplysia* CPEB has two states: one is inactive and acts as a repressor, while the other is active. In an unmarked synapse, the basal level of CPEB expression is low and the protein is inactive or repressive. According to the model, serotonin induces an increase in CPEB. If a given threshold is reached, CPEB is converted to the prion-like state, which is more active and lacks the inhibitory function of the basal state. Once the prion state is established at an activated synapse, dormant mRNA molecules, made in the cell body and distributed throughout the cell, are translated—but only at that activated synapse. Because the activated CPEB is self-perpetuating, it could contribute to synapse-specific, long-term molecular change, thus providing a mechanism for the stabilization of learning-related synaptic growth and the persistence of memory storage in stable periods of normal growth, when very low levels of protein synthesis are required (Figures 2A–2C).

Destabilization and Restabilization of Long-Term Memory

Ample data now indicate that in many types of memory, the reactivation of the long-term trace upon its retrieval can result in transient destabilization of the trace that may lead to its change. This is commonly construed in terms of a process of "reconsolidation" (Sara, 2000; Nader et al., 2000), which shares mechanisms with consolidation, and will be discussed later in this review. Reconsolidation has been demonstrated also in *Aplysia* (Lee et al., 2012; Cai et al., 2012). This allows dissection of its mechanisms in identified neurons and synapses. In particular, the question can be investigated whether the same synapses that are involved in encoding and storing the memory trace are

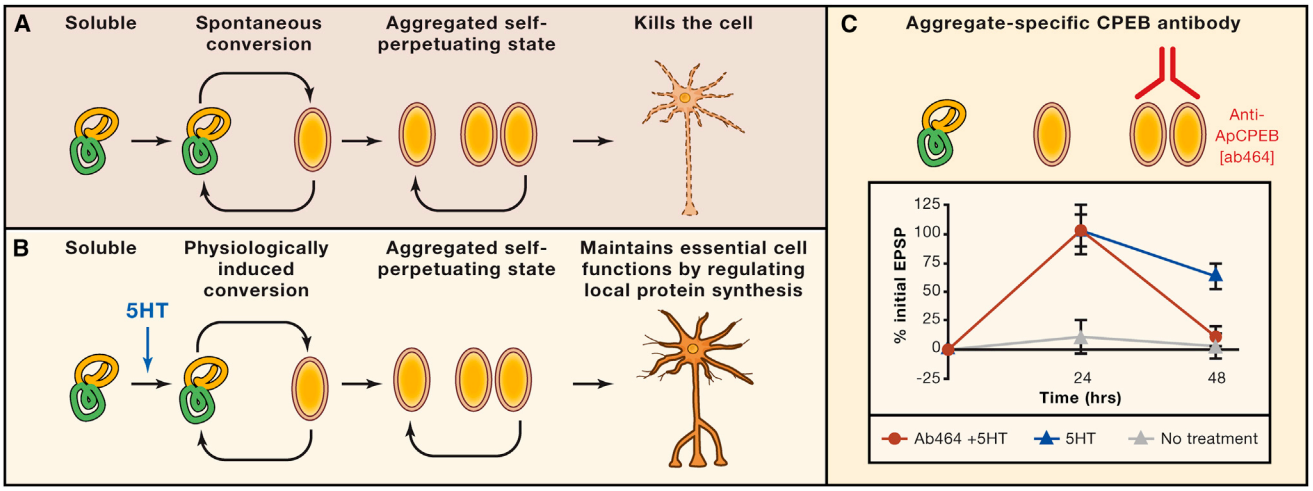

Figure 2. Prions in Memory

(A and B) Schematic models of pathogenic (A) and functional (B) prions.

(C) Antibody that is specific for the aggregated (functional prionic) form of ApCPEB selectively blocks the maintenance of long-term facilitation produced by 5HT. Data are represented as mean ± SEM.

also those that are destabilized and restabilized after synaptic reactivation that accompanies memory retrieval, or whether new and different synapses are recruited.

Lee and his colleagues (Lee et al., 2012) have addressed this issue in the gill-withdrawal reflex in *Aplysia* and found that indeed, the same sensory motor synapses that store long-term facilitation are destabilized by protein degradation during reactivation and restabilized by protein synthesis afterward. This cellular change parallels the behavioral performance on memory retrieval. This finding indicates that the long-term memory trace, once formed, remains potentially dynamic even in simple reflexes at the level of the individual neurons and synapses that have encoded the memory in the first place.

All in all, the reductionist analysis of neuronal plasticity and simple memory in *Aplysia* and *Drosophila* presents us with some molecular and cellular building blocks and operational rules that can serve as a basis for the exploration of more complex memory systems. We will now review selected studies that indicate that these building blocks and rules were exploited and further elaborated and developed by evolution to subserve memory in the mammalian brain.

Implicit, Nondeclarative, Memory in Mammals

Some of the strongest evidence linking learning to synaptic plasticity in the mammalian brain comes from experiments focused on implicitly learned fear (Davis et al., 1994; LeDoux, 2003, 1995). When an animal is presented with a tone that is followed by a shock to the foot—a classical conditioning paradigm—the animal exhibits a learned fear response that can be gauged by freezing in response to the tone alone. This form of learning involves the amygdala, a region of the brain that receives direct auditory information from the thalamus and processed information from neocortex, and which provides an output to areas of the hypothalamus that regulate autonomic fear responses. In isolated brain slices, neurons of the amygdala can undergo increases in synaptic strength in response to repeated stimulation. Importantly, behavioral pairing of a tone and shock, which induces fear learning, also potentiates responses in the amygdala to auditory stimuli in vivo (Rogan et al., 1997) and synaptic responses to electrical stimulation of auditory inputs in vitro (McKernan and Shinnick-Gallagher, 1997).

Both the synaptic changes and the persistence of the memory for learned fear require PKA, MAPKs, and the activation of CREB (Won and Silva, 2008). Moreover, similar to mechanisms of N-methyl-D-aspartate (NMDA) receptor-dependent synaptic plasticity, which we will consider below, learned fear requires the enhanced trafficking of AMPA receptors to the synapses of amygdala neurons (Rumpel et al., 2005). In contrast to learned fear, if a tone predicts a period of safety when an animal is protected from the foot shock, there is a long-term depression of the auditory inputs to the amygdala (Rogan et al., 2005). Thus, learned fear and learned safety involve opposing changes in synaptic strength. Moreover, as with learned fear in *Aplysia*, the synaptic plasticity is modulated heterosynaptically, in this case by dopamine as the heterosynaptic modulatory transmitter (Bissière et al., 2003).

Another form of implicit memory in the mammalian brain is eye-blink conditioning. This is produced by pairing a tone (the CS) with an aversive air puff to the eye (the US), resulting in a learned eye blink that is appropriately timed to the paired US (Thompson et al., 1983). Theoretical and experimental studies suggest prior to learning, activation of cerebellar Purkinje neurons in response to the CS leads to an inhibition of neurons in the interpositus nucleus (one of the deep nuclei of the cerebellum), thereby inhibiting motor output. With conditioning there is a decrease in the activity of the Purkinje cell in response to the CS, resulting in disinhibition of the neurons of the interpositus nucleus, leading to eye blink. This model is consistent with findings that Purkinje cell activity can be reduced as a result of a long-term depression at the excitatory parallel fiber synaptic input onto the Purkinje neurons (Ito, 2001). This decrease in the

strength of the parallel fibers occurs when the climbing fiber inputs to the cerebellum are activated in appropriate temporal proximity to parallel fiber activity. The Purkinje cells become less responsive to input, as a result of a downregulation of AMPA receptors at the parallel fiber to Purkinje cell synapse (Ito et al., 1982; Jörntell and Hansel, 2006).

It is noteworthy that studies of fear learning, eye-blink conditioning, modifications of the vestibular-ocular reflex (Lisberger et al., 1987; Boyden et al., 2006; Gao et al., 2012), as well as experience-dependent modification of reflexes in *Aplysia* and crayfish, all provide support for the role of both synaptic facilitation and synaptic depression as parallel mechanisms for memory encoding and maintenance.

Part II: Explicit, Declarative, Memory in the Mammalian Brain

That explicit memory involves a hippocampal-based memory system for facts (semantic) and events (episodic), which requires conscious participation for recall, first emerged with the detailed studies of the patient Henry Molaison (H.M.) by Milner and her colleagues (Scoville and Milner, 1957; Penfield and Milner, 1958; reviewed by Squire and Wixted, 2011).

A difficulty that emerged immediately in studying hippocampal-dependent explicit forms of memory is the complexity of the component stimuli involved and their learning-induced associations. No longer are the learning cues simple and unimodal sensory stimuli like tone, touch, or shock, which converge on common neurons that undergo the plasticity necessary for learning. With a typical explicit memory, cues to be associated are complex, and finding the neurons within the networks that are altered to form new associations is a daunting task, as is determining which circuit output encodes the representation. We will briefly discuss some of the animal and human studies on explicit memory by examining brain patterns of neuron activation at the gross and single-cell level, which are beginning to reveal how this information is structured with learning and memory retrieval. We will proceed to discuss the still ongoing attempts to explore the role of various forms of long-term potentiation (LTP) as a synaptic plasticity mechanism of explicit memory encoding in the hippocampus. We will also discuss new techniques that allow the behavioral role of the distributed neural networks of explicit memory to be probed directly.

The Emergence of a Systems Approach to Memory Storage

Place Cells. Since the hippocampus was identified as critical for explicit memory based on studies of human amnesic patients, animal studies of the hippocampus focused on the nature of the sensory information with which the hippocampus is concerned. Electrophysiological recording of hippocampal activity in freely behaving rats first demonstrated that the most striking feature of hippocampal neurons is their spatially specific firing (O'Keefe and Dostrovsky, 1971; O'Keefe, 1976; O'Keefe and Conway, 1978; Moser et al., 2008; Griffin and Hallock, 2013). When animals are allowed to move freely in an open space or on more restrictive tracks, individual hippocampal pyramidal neurons are "place cells"; they are active only when the animal passes through a limited region of the environment, their place field, suggesting that the hippocampal neurons encode a map of the animal's spatial location (O'Keefe and Dostrovsky, 1971). Moreover, unlike the topographical organization that characterizes the primary sensory and motor cortex, the hippocampus has a random organization of its place cells. Neighboring place cells do not represent neighboring regions of the environment. Thus the same spatial environment can recruit a different population of cells in different individuals and the same individual can represent different environments with different subpopulations of cells (Redish et al., 2001; Dombeck et al., 2010).

A defining feature of explicit memory, such as the hippocampal-dependent memory for space, is that it requires attention. The recruitment of attention is important not only for optimal encoding of memory but also for subsequent retrieval. Since the hippocampus receives multimodal sensory information, the encoding of this information probably engages several brain structures, each of which might be the target of independent attentional modulation. To explore the relationship between place cells, spatial memory and attention, Kentros et al. (2004) recorded from mice in several behavioral contexts differing in the degree to which they required attention. They found that the long-term stability of place cell firing correlates with the degree of attentional demands. Successful performance of a spatial task was associated with stable place fields in the neurons. Furthermore, conditions that maximize place field stability greatly increased orientation to novel cues. This suggests that storage and retrieval of place cells is modulated by a top-down cognitive process, resembling attention, and that place cells are neural correlates of spatial memory. This place field stability required heterosynaptic modulatory input mediated by dopaminergic modulation through dopamine D1/D5 receptors.

Muzzio et al. (2009a, 2009b) next asked the question "can this attention process be a form of general arousal or need it be specific to space?" They recorded from single cells in the CA1 region of the dorsal hippocampus over a period of 5 days while mice acquired one of two goal-oriented tasks. One task required that the animal find a hidden food reward by attending to the visuospatial cues. The other task required that the animal attend to a particular odor presented in a shifting spatial location. Attention to the visuospatial environment increased both the stability of visuospatial representation and the phase locking to gamma oscillations—a form of neuronal synchronization thought to underlie the attentional mechanism necessary for processing task-relevant information. Attention to a spatially shifting olfactory cue compromised the stability of place fields and increased the stability of reward-associated odor representations. Together, these results suggest that attention selectively modulates the encoding and retrieval of hippocampal representations by enhancing physiological responses to task-relevant information, and that the spatial map requires specifically attention to spatial cues. Also pointing to the importance of attention are studies showing that place cell sequences tend to "point" to goal location during behavior, as if the animal was shifting its attention there (Frank et al., 2000; Wood et al., 2000).

The ensemble of place cells recruited is specific to the environment the animal is exploring but this specificity can take some time to develop, suggesting a learning-based modification of the ensemble (Wilson and McNaughton, 1993; Lever et al.,

2002; Kentros et al., 2004). As we have seen while spatial codes are prominent in the rodent hippocampus, when the task demands are adjusted to require nonspatial information, the response of the rodent hippocampal ensemble is sensitive to this information as well (Wood et al., 1999).

Grid Cells. In his earlier work on place cells, O'Keefe had only explored the CA1 region. It was not known whether the various subregions of the hippocampus represent space. The accepted view was that sensory information is conveyed from the entorhinal cortex through the trisynaptic pathway to the CA3 and CA1 regions of the hippocampus where it is put together as a spatial map. In 2005, Edvard and May-Britt Moser extended this idea when they found in the entorhinal cortex a precursor of the spatial map that is formed by a new class of cells known as "grid cells." Each of these space-encoding cells has a grid-like, hexagonal receptive field and conveys information to the hippocampus about position, direction, and distance (Fyhn et al., 2004; Hafting et al., 2005). The gross structure of the grid is largely maintained when place cells remap, indicating that it is perhaps a more "hard-wired" representation of space. Nevertheless, the involvement of entorhinal cortex in memory also is well established, based on both lesion and imaging studies (Squire et al., 2004; Suzuki, 2009). Recently, Killian et al. (2012) reported that in a visual recognition task in the monkey, grid cells displayed decreased rate of firing for repeated stimuli, suggesting a role in memory for this specific type of cell in the entorhinal cortex.

This question has been further addressed by Tsao et al. (2013) who recorded from the neurons of the lateral entorhinal cortex in an open field where they presented objects on a subset of the trials. They found that whereas some neurons fired at the objects, other cells developed specific firing at places where objects had been located on previous trials, thereby providing a readout of past experience in the environment. The latter cells generally did not respond to the object when it was present, suggesting that object cells and object-trace cells are two independent cell classes. These findings identify the lateral entorhinal cortex as a component of the hippocampal-cortical circuit for object-place memory.

Synaptic Plasticity in the Mammalian Brain

Nearly contemporaneous with the discovery of place cells, a cellular model of experience-dependent plasticity—long-term potentiation (LTP)—was discovered in the hippocampus that appeared to play a significant role in memory in the mammalian brain. LTP was initially described briefly by Lomo (1966) and more extensively by Bliss and Lomo (1973). They found that high-frequency electrical stimulation of the perforant path input to the hippocampus resulted in an increase in the strength of the stimulated synapses that lasted for many days. Subsequent studies (Wigström et al., 1986) found that LTP displayed the elementary properties of associability and specificity formulated by Hebb (1949) that (a) only synapses that are active when the postsynaptic cell is strongly depolarized are (specificity) potentiated and (b) inactive synapses were not potentiated. Thus, groups of synapses that are coordinately active and contribute together to the firing of the target postsynaptic neuron will be strengthened, providing a plausible mechanism for linking ensembles of neurons encoding different environmental features that are presented together and thereby forming memory associations.

The mechanism for initial induction of LTP varies in different regions of the hippocampus and in the same region with different patterns of stimulation. In the CA1 region, 100 Hz stimulation induces a form of LTP that is dependent on NMDA receptor activation. Moreover, the properties of this receptor can explain the associative and activity dependent properties of LTP. NMDA receptors are both voltage- and ligand-gated, and to become active, they require depolarization of the postsynaptic membrane in which they reside as well as concurrent release of glutamate from an opposed presynaptic terminal. Thus, NMDA receptors are functional only at synapses that are active and that synapse on a neuron that is strongly depolarized at or near the time of transmitter release. Activated NMDA receptors produce a strong postsynaptic Ca^{2+} influx that is required to induce LTP. This Ca^{2+} signal can activate a wide range of signaling pathways including CaMKII, PKC, PKA, and MAPK that have each been implicated in the induction of LTP as well as in its later stabilization (Malenka and Bear, 2004; Huang et al., 2013; Kerchner and Nicoll, 2008; Kessels and Malinow, 2009; Lisman et al., 2012). These general molecular signaling pathways are also altered by modulatory transmitters such as dopamine, previously found to be required for LTP in CA1 (Frey et al., 1991) providing the opportunity for control of plasticity based on attention, motivational state or reward, which these neuromodulators can mediate. The early phase of LTP involves activation of second messengers that leads to an increase in the incorporation of new AMPA type glutamate receptors into the synapse resulting in a strengthened response (Hayashi et al., 2000; Shi et al., 2001; Shi et al., 1999; Granger et al., 2013; Malinow et al., 2000). It appears that a complex of proteins in the postsynaptic density is involved in the capture of new glutamate receptors following LTP (Malinow et al., 2000; Ramachandran and Frey, 2009).

LTP has a distinct late phase (L-LTP) that is dependent on new gene expression and shares a number of cellular and molecular features with LTF in *Aplysia*. The transcriptional activation required for L-LTP is dependent on the activation of a number of protein kinases including PKA and MAPK signaling ultimately to the CREB-1 transcription factor (Abel et al., 1997; Bourtchuladze et al., 1994; English and Sweatt, 1997; Frey et al., 1993). L-LTP also appears to employ a mechanism of synaptic tagging and capture of the newly expressed proteins similar to that described earlier for LTF in *Aplysia* (Frey and Morris, 1997). Finally, L-LTP is associated with structural changes in the synapse with the NMDA-dependent enlargement of dendritic spines and possibly addition of new spines at certain developmental stages (Bosch and Hayashi, 2012).

Long-term potentiation is not a unitary phenomenon. Phenotypically similar forms of synaptic potentiation can be produced by quite different patterns of stimulation with different dependencies on NMDA receptor activation. Moreover not all forms of LTP are NMDA receptor dependent and some do not involve primarily postsynaptic mechanisms. LTP at the mossy fiber synapse on CA3 neurons is an activity-dependent form of plasticity that is NMDA receptor independent and expressed wholly through an alteration in presynaptic transmitter release (Mellor and Nicoll, 2001; Mellor et al., 2002). Very high-frequency

(200 Hz) stimulation produces a form of LTP in the hippocampus that is dependent on voltage-dependent Ca^{2+} channels rather than NMDA receptors (Grover and Teyler, 1990).

In addition, most stimulation patterns that induce LTP are very high frequency and are thought to be atypical and unlikely to occur during the normal, learning-related changes in firing patterns. As a result, although there are some important correlations between gene knockouts that affect LTP, leading to explicit memory deficits, the exact relationship between specific forms of LTP and memory storage is still debated. In an attempt to induce LTP with more physiological patterns of stimulation, Sakmann and his colleagues paired presynaptic stimulation with the generation of a postsynaptic action potential (Nevian and Sakmann, 2006). In this spike timing dependent LTP (STDP), the presynaptic stimulation must precede the postsynaptic action potential by a few milliseconds (as would be expected in the natural case of a synapse contributing to the firing of a neuron) to produce potentiation. If the order is reversed, the synaptic strength will actually be depressed and result in an NMDA-dependent form of plasticity called long-term depression (LTD) (Malenka and Bear, 2004).

While LTP is the most studied form of synaptic plasticity in the hippocampus, there are a variety of other plasticity mechanisms that make up the pallet of potential information storage mechanisms in the mammalian brain. Specifically there are several forms of activity-dependent LTD (Malenka and Bear, 2004). In the hippocampus prolonged synaptic stimulation at low frequency or presynaptic activity produced shortly after postsynaptic action potentials in spike-timing-dependent-LTP leads to an NMDA receptor-dependent form of LTD that requires the recruitment of Ca^{2+}-dependent protein phosphatases and reduces the number of AMPA receptors at the synapse in a molecular mechanism that seems a mirror image of LTP (Beattie et al., 2000). In the cerebellum, the parallel fiber-Purkinje cell synapse undergoes a form of LTD that has been implicated in motor learning and depends on the activation of G protein coupled metabotropic glutamate receptors and the PKC-mediated loss of AMPA receptors (Cho et al., 2008; Xia et al., 2000).

The above discussion of mammalian forms of plasticity is far from comprehensive. Moreover, many of these forms of plasticity are subject to modulation by other transmitter systems and by the past stimulation history of the individual synapse itself in what is referred to as metaplasticity (Abraham, 2008). For example, in a synapse that has recently undergone LTP, stimulation protocols that would previously have produced no synaptic change now produce LTD (Barr et al., 1995). With this rich array of potential mechanisms for sculpting brain circuits with learning, we will now explore the more difficult task of linking these various mechanisms for synaptic plasticity to specific forms of learning and memory.

Hippocampal Subregions and LTP in Explicit Memory

Tasks that require place learning are hippocampal dependent and therefore have been used extensively to investigate the role of LTP in explicit memory. In rodents these tasks commonly rely on a variety of mazes, such as the T-maze, radial arm maze, and the water maze. These tasks commonly require the animal to use distal cues to navigate to a specific goal location (Tolman, 1938; Olton et al., 1979; Morris, 1984). Another type of place learning task that is sensitive to hippocampal lesion is contextual fear conditioning, which requires recognition of place rather than navigation to a particular location (Anagnostaras et al., 1999). In this task the animal receives foot shocks in a conditioning chamber with multimodal sensory cues (visual, olfactory, tactile) leading to a fear memory for the shock box (context) relative to similar chambers containing a distinct constellation of sensory cues.

In the first direct test of the role of LTP in hippocampal-dependent forms of learning, Morris et al. (1986) used the NMDA receptor antagonist APV to block NMDA receptors in rats and tested their spatial memory in a water maze. Inhibition of NMDA receptors to levels sufficient to block LTP in the hippocampus also blocked the animal's ability to learn a new spatial location in the water maze. In the first genetic tests of the role of hippocampal LTP in declarative memory, the studies of Kandel and his colleagues (Grant et al., 1992) and Tonegawa and his colleagues (Silva et al., 1992) generated mice carrying a deletion in either the Fyn kinase or the CaMKII gene, and tested for LTP and memory. The knockout mice were viable and grew to adulthood but lacked hippocampal LTP and showed severe deficits in several hippocampal-dependent forms of learning. Subsequent genetic studies on CaMKII showed that even a single amino acid mutation that prevented the autophosphorylation, and thus the persistent activation of the kinase, was also sufficient to disrupt both LTP and memory (Giese et al., 1998).

While mouse genetic studies opened up the ability to test the function of essentially any gene in the whole animal, there were a variety of drawbacks in this approach that are particularly acute when applied to the study of behavior. Constitutive knockouts disrupt gene function in all cell types in the animal and throughout development. This makes it difficult to determine whether an observed phenotype (e.g., loss of hippocampal LTP and spatial memory) is due to the requirement for the gene in the adult hippocampus, or to some alteration in the molecular or circuit development in the animal, or to a deficit in some other brain region in which the gene is expressed. To address these issues, more recent work has focused on the use of anatomically restricted and temporally controlled genetic modification.

Studies of the role of NMDA receptors in the hippocampus provide a good example of this approach. A series of studies using cell-type specific expression of the enzyme CRE recombinase to delete the NMDA receptor gene flanked by loxP sites ("floxed") in different hippocampal subregions has attempted to refine our understanding the role of LTP in different elements of the trisynaptic circuit. For example, McHugh et al. (2007) deleted the NMDA receptor specifically in the dentate gyrus granule cells of mice, leading to a loss of LTP at perforant path synapses. The animals were examined in a contextual fear discrimination task in which they were placed in two different chambers over several days and received a foot-shock in one of the chambers. Control animals learned to discriminate between the chambers and expressed a fear response specifically to the shocked chamber, whereas the knockout animals showed fear in both chambers. Although the knockout mice eventually learned the discrimination task, the results suggest that NMDA-dependent plasticity in the dentate gyrus contributes to the ability of animals to discriminate pattern. This is consistent with a previously postulated role for the dentate gyrus based

on the connectivity properties of the hippocampal circuit (Marr, 1971).

The CA3 neurons have a dense network of recurrent collaterals, and it has been suggested that this type of circuit structure could perform pattern completion with incomplete input information (Marr, 1971; McClelland and Goddard, 1996). Nakazawa et al. (2002) tested this idea by deleting NMDA receptors specifically from CA3 neurons in mice. The animals were tested for spatial learning in the water maze task and were indistinguishable from control mice in their acquisition and retrieval of the spatial memory. However, when some of the distal visual cues were removed, the NMDA receptor knockout mice showed impaired spatial memory retrieval consistent with a difficulty in pattern completion. Interestingly, the place fields of neurons recorded in area CA1 from the CA3 NMDA receptor knockout animals showed a reduction in spatial specificity compared to controls that was specific to the partial cue environment.

While the loss of NMDA receptors in CA3 and dentate gyrus result in subtle differences in behavioral performance only when the task demands are increased, early studies of mice in which the NMDA receptor was deleted specifically in CA1 neurons produced severe deficits in spatial learning and contextual fear conditioning (Shimizu et al., 2000; Tsien et al., 1996). This suggested that plasticity in CA1 was critical to actually storing information while plasticity in the other hippocampal areas served a more refined role in recruiting the correct neural ensembles for encoding or recall.

However, a recent study revisited the role of NMDA receptors in CA1 neurons and found a much more subtle effect on spatial learning (Bannerman et al., 2012). In this study, a line of mice was generated in which the NMDA receptor was deleted in both CA1 and dentate gyrus neurons. Unlike in the previous reports, when examined in the water maze this new knockout line performed identically to controls. While the animals could develop a normal spatial memory for platform location, they showed a slight deficit only when a competing ambiguous cue was added to the maze, suggesting a more subtle role for LTP in the CA1 region, possibly a role in pattern separation that allows the animal to disambiguate competing or overlapping memories.

Mechanisms Involved in the Maintenance of Memory

Memory Reconsolidation. A major development in research on consolidation in the past decade has been the revitalization of the idea (Misanin et al., 1968) that consolidation doesn't occur just once per item, but that under some circumstances it can be actively recruited during later retrieval of that same item (Sara, 2000; Nader et al., 2000; Nader and Hardt, 2009). When inhibitors of protein synthesis are given in a short time window after memory retrieval, they disrupt the subsequent storage of the memory, similar to what is seen with consolidation of initial learning, hence the term reconsolidation. The cellular mechanisms of the hypothetical reconsolidation process are currently less well understood than those of consolidation. Several research groups have reported molecular dissociations of consolidation and reconsolidation. Examples include the obligatory involvement for contextual fear conditioning in the rat hippocampus (Lee et al., 2004) of brain-derived neurotrophic factor (BDNF), but not the transcription factor Zif268, in consolidation, and the opposite in reconsolidation; the recruitment in reconsolidation of only a subset of immediate-early genes that are induced in consolidation (von Hertzen and Giese, 2005); and the requirement for interaction between eukaryotic initiation factors 4E and 4G in the lateral amygdala in consolidation, but not in reconsolidation, of fear conditioning in the rat (Hoeffer et al., 2011). It is yet unclear whether these differences stem from unique mechanisms of the postulated reconsolidation, or from differences in the context and the saliency of the cues in the encoding versus the retrieval sessions that are used to promote consolidation and reconsolidation, respectively (Tronson and Taylor, 2007).

As opposed to consolidation, which always takes place when a new item is encoded in long-term memory, reconsolidation does not seem to occur after each memory reactivation (Tronson and Taylor, 2007). Attempts have been made to identify the conditions that determine when reconsolidation will happen. Among the boundary conditions identified are the strength of the memory (Eisenberg et al., 2003), the duration of the reactivation trial (Pedreira and Maldonado, 2003; Suzuki et al., 2004), and the presence of new information in the retrieval trial (Pedreira et al., 2004; Morris et al., 2006).

Some studies show that susceptibility to reconsolidation is also a function of the age of the memory. In their initial reports of reconsolidation, Nader et al. (2000) reported that a reactivated 14-day-old fear memory in the rat is as susceptible to infusion of the protein synthesis inhibitor anisomycin into the amygdala as a 1-day-old memory. Similarly, Debiec et al. (2002) reported that a reactivated 45-day-old contextual fear memory is still blocked by anisomycin infusion into the hippocampus as is a 3-day-old memory. However, Milekic and Alberini (2002) reported that systemic administration of anisomycin after reactivation of inhibitory avoidance in the rat caused subsequent amnesia only when the memory was up to 7 days old but not later. Similarly, Eisenberg and Dudai (2004) reported that systemic administration of the amnesic agent MS222 blocked reactivated fear memory in the medaka fish only when the memory was 4 days old but not at 15 days. This has led to the proposal that reconsolidation is in fact a lingering consolidation process, and that when consolidation is ultimately completed, the memory does not reconsolidate anymore (Dudai and Eisenberg, 2004; Alberini, 2005).

Research on blockade of reconsolidation attracted much attention because it suggests a possible means to ameliorate posttraumatic stress disorder (PTSD) in humans. It is thought that if one reactivates the long-term memory of the trauma and triggers reconsolidation, administration of a behavioral manipulation that extinguishes the memory (Schiller et al., 2010) or of a pharmacological agent such as the beta-blocker propranolol that mitigates the emotional response (Lonergan et al., 2013) can result in reduction of the emotional valence of subsequent recollection of the original event.

To explore this idea further Monfils et al. (2009) blocked reactivated long-term fear memory in a rat by extinction training during the reconsolidation window. They conditioned rats to associate tone with shock, and after 24 hr activated the memory by the tone CS, followed by extinction training within or after the reconsolidation window. When tested for subsequent long-term memory, the rats that received extinction training within the reconsolidation window, but not afterward, displayed attenuated conditioned fear 24 hr later, and this memory did not return

spontaneously as is seen with simple extinction. Schiller et al. (2010) adapted a similar procedure in humans. They trained participants to fear a visual CS by associating it with a mild shock to the wrist. A day later they presented the CS only. The participants were then trained in an extinction paradigm after 10 min or 6 hr. In the 10 min group, long-term memory, as expressed in skin conductance response to the CS, was blocked even a year later. The identification of this renewed window of plasticity in humans opens valuable possibilities, ranging from ameliorating PTSD (see above), to enhancing learning in the classroom (Roediger and Butler, 2011) and understanding memory distortion (Schacter and Loftus, 2013).

Maintenance of Explicit Memory. In explicit, as in implicit memory, consolidated memory needs to be maintained. This raised the question: which molecular mechanisms subserve maintenance of hippocampal-dependent memory? Multiple candidate mechanisms were proposed, among them a variety of protein kinases (Huang et al., 2013, Lisman et al., 2012, Sacktor 2011). Some studies indicate similarity with molecular mechanisms identified in invertebrates (Glanzman, 2010; Pavlopoulos et al., 2011). For example, the cytoplasmic polyadenylation element-binding protein 3 (CPEB3), a regulator of local protein synthesis, is the mouse homolog of ApCPEB, a functional prion protein in *Aplysia*. Pavlopoulos et al. (2011) found that CPEB3 is activated by Neuralized1, an E3 ubiquitin ligase. In hippocampal cultures, CPEB3 activated by Neuralized1-mediated ubiquitination leads both to the growth of new dendritic spines and to an increase of the GluA1 and GluA2 subunits of AMPA receptors, two CPEB3 targets essential for synaptic plasticity. Conditional overexpression of Neuralized1 similarly increases GluA1 and GluA2 and the number of spines and functional synapses in the hippocampus, and is reflected in enhanced hippocampal-dependent memory and synaptic plasticity. By contrast, inhibition of Neuralized1 reduces GluA1 and GluA2 levels and impairs the maintenance of hippocampal-dependent memory and synaptic plasticity. These results suggest a model whereby Neuralized1-dependent ubiquitination facilitates the maintenance of hippocampal plasticity and hippocampal-dependent memory storage by modulating the activity of CPEB3 and CPEB3-dependent protein synthesis and synapse formation.

Memory Allocation in Neuronal Circuits

What defines a circuit in the mammalian brain? At one level there is a clear, developmentally controlled pattern of connectivity, for example, the hippocampal trisynaptic circuit or a cortical column. Although this canonical connectivity is clearly an important constraint on function, what is remarkable is that these circuits can represent many different external events and encode a wide range of memories. It is assumed that any individual neuron can participate in different representations or memories, and at a deeper level a neural circuit is defined by what it represents. How predetermined are these circuits? How are they differentially recruited during encoding and retrieval? And how can a new memory be formed through altered synaptic strength without overwriting a preexisting memory encoded in a neuron's synapses? Some new genetic techniques, along with novel electrophysiological approaches referred to below, are beginning to probe these questions.

Competition between neurons often is necessary for refining neural circuitry during development and use (Hebb, 1949; Changeux and Danchin, 1976; Changeux, 1997; Hübener and Bonhoeffer, 2010). This raised the question: does competition and preferential selection of subsets of neurons in the population play a role in encoding memories in the adult brain? In studies of fear conditioning, the introduction of excess or constitutively active CREB into a sparse subset of amygdala neurons caused those neurons to be specifically recruited to encode the memory to which the animals were subsequently trained (Han et al., 2007). Conversely, if such neurons are deleted after learning, that specific fear memory is blocked while other fear associations stay intact (Han et al., 2007). This study reveals that there is great flexibility in the particular group of neurons recruited to any given memory, at least in the amygdala, and that the resting state of the neuron at the time of learning governs the probability that it will be recruited to the circuit for that learning.

Synthetic Traces in the Mammalian Brain

The observation of learning evoked neural activity patterns has provided a great deal of insight into the possible information encoded in different brain regions. However, further examination of the role of distributed ensembles and of specific cellular mechanisms requires direct manipulation. Furthermore, by directly manipulating activity in candidate ensembles, one might hope to be able to simulate internal representations (i.e., to create "synthetic traces" in the behaving animal), and thereby establish that specific activity patterns are not only correlated with or necessary for memory but are actively sufficient for memory to take place.

One useful approach uses the *cfos* promoter to link the natural patterns of sensory evoked neural activity to genetic alteration such that the pattern of neurons activated during a behavioral session can be specifically altered to express essentially any desired protein (Reijmers et al., 2007). This allowed Liu et al. (2012) and Ramirez et al. (2013) to test the nature of the neural representation for a hippocampal-dependent memory. Using the *cfos*-based genetic tagging approach they expressed channelrhodopsin (ChR2) (Boyden et al., 2005), specifically in neurons that were activated during learning in a contextual fear-conditioning task (Figure 3). Animals received foot-shocks in the training context to allow ChR2 expression in neurons that were naturally active with learning. When light pulses were delivered to the dentate gyrus to stimulate the ChR2 expressing neurons, the animals showed fear. This suggests that artificial stimulation of the dentate gyrus neurons active during learning recruited a component of the fear memory representation, essentially causing the animals to "think" they were in the conditioning box.

An alternative to light-gated channel control of neural activity by optogenetics is a chemical genetic approach using *d*esigner *r*eceptors *e*xclusively *a*ctivated by *d*esigner *d*rugs (DREADDs). One such designer receptor (hM3Dq) is a Gq coupled human muscarinic receptor that has been mutated so that it no longer responds to acetylcholine but instead responds to the synthetic ligand clozapine-N-oxide (CNO) (Alexander et al., 2009). In hippocampal pyramidal cells, activation of hM3Dq by CNO results in a 5–8 mV depolarization and subsequent increase in action potential firing. Garner et al. (2012) used this *cfos*-based genetic

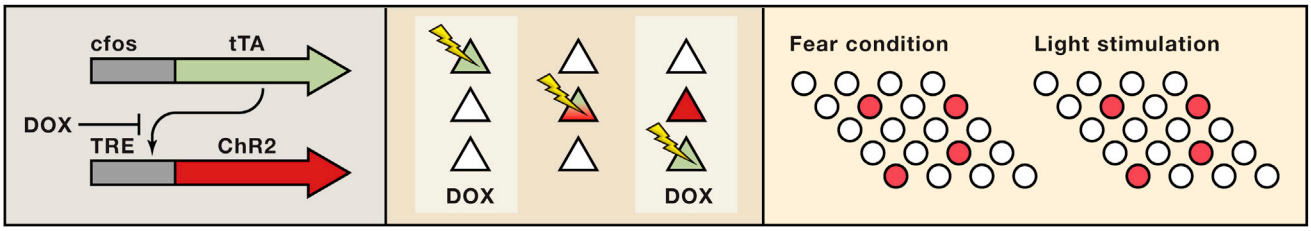

Figure 3. Genetic Tagging of Active Circuits
Two transgenes are required. The expression of tetracycline-controlled transactivator (tTA) is linked to neural activity by the cfos promoter. In the presence of doxycycline (DOX) tTA fails to activate the second gene (ChR2 in this example). During time periods when DOX is absent neurons activated by environmental stimuli express the Chr2 gene. This allows labeling of sparsely distributed neural ensembles and their subsequent reactivation.

tagging approach to control the activity of specific neural ensembles and used hM3Dq to probe the role of internally generated neural representations during contextual fear conditioning. Garner and colleagues tagged the ensemble of neurons activated in one context (BoxA) with the hM3Dq receptor and then stimulated those neurons with CNO while delivering shocks in a separate context (BoxB). The animals appeared to form a hybrid neural representation incorporating elements of the natural sensory activity from BoxB with the artificially generated activity of the CNO stimulated BoxA neurons.

Does this experiment, with highly artificial modes of neural activation, provide us with a picture of the learning and memory mechanisms that operate under natural conditions? One point that is often lost sight of in a typical study of memory is that the brain is not a blank slate at the start of the experiment. Also the brain is not silent in the absence of experimenter provided stimuli, nor is the brain responding exclusively to the stimuli provided by the experimenter during the experiment. It is now well established by many techniques, including EEG (Berger, 1929), intrinsic optical imaging (Kenet et al., 2003), and fMRI (Gusnard et al., 2001), that there is extensive internally generated "spontaneous" activity in the brain in addition to activity evoked by the experimental cues. What is the function of this spontaneous activity and how does it contribute to the formation of memory and its maintenance? One clue may come from recordings of place cells in the hippocampus during "rest" periods following a typical session in which animals explore a distinct environment. The "spontaneous" off-line activity under these circumstances tends to display a temporal structure that parallels that seen during the actual exploration (Ji and Wilson, 2007; Foster and Wilson, 2006; Wilson and McNaughton, 1994). Similar off-line replay of sensory evoked activity has been described in other brain areas such as visual cortex (Kenet et al., 2003; Ji and Wilson, 2007). This indicates that elements of previous experience are represented in internally generated activity. The neurons associated with the previous experience of exploring BoxA were internally activated while the animal was learning an aversive association in BoxB, and in order to produce fear recall, the conjunctive activation of BoxA neurons was also required (Garner et al., 2012). A similar process must be common in other complex forms of learning where new information is integrated with old previously existing internally generated information to form complex knowledge schemas (Bartlett, 1932; Tse et al., 2007).

Part III: Explicit, Declarative, Memory in the Human Brain

The rich molecular and cellular armamentarium available for the study of animal models is commonly invasive and, therefore, inapplicable to most research on people. Human brain research was, however, revolutionized 20 years ago with the introduction of functional magnetic resonance imaging (fMRI) capable of unveiling the activity of identified brain regions (Ogawa et al., 1992), including their role in memory storage in intact, alert, behaving human beings (Cohen et al., 1994). Despite its relatively limited spatial (mm) and temporal (sec) resolution, and its complex relevance to neuronal mechanisms (Goense et al., 2012), the fMRI blood-oxygenation level-dependent (BOLD) signals which are time-locked to performance in memory paradigms, are for the moment our main source of experimental data for exploring brain mechanisms of memory in the intact human brain. In recent years, fMRI methods, data analyses, and behavioral protocols have improved and these improvements have led to higher resolution of the location of memory functions, and to a better understanding of the functional interaction between brain regions, than have been possible in past studies.

To identify regions of brain that are important for the encoding of explicit memory, studies in humans commonly employ the "subsequent memory paradigm." In this paradigm, brain activity is monitored during a learning (encoding) session, and memory performance is tested in a subsequent session, which occurs minutes to months later, depending on the protocol. The difference in brain activity in identified brain regions during the encoding of items subsequently remembered and that of items subsequently forgotten (Dm, *d*ifference based on later *m*emory performance), is taken to identify candidate circuits required for productive encoding (Brewer et al., 1998; Wagner et al., 1998). Converging evidence from several such studies has led to the identification of a set of regions in which the BOLD activity commonly predicts successful encoding (for meta-analysis see Kim, 2011; Spaniol et al., 2009). Commonly, memory-predicting activity is identified in areas including (but not restricted to) the medial temporal lobe, as expected from clinical findings of the role of medial temporal lobe damage in amnesia, and from animal models of explicit memory (see above); as well as subregions of the prefrontal cortex and the posterior parietal cortex (Figure 4A).

Within the medial temporal lobe, a functional division has emerged between the hippocampus and the surrounding

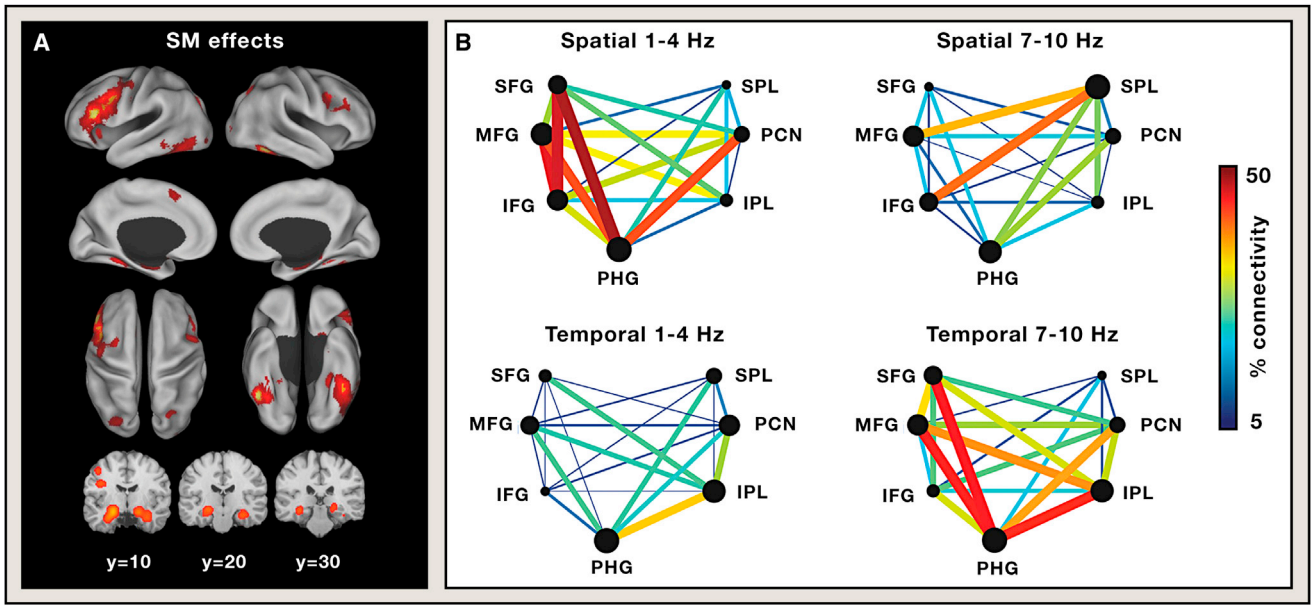

Figure 4. Brain Correlates of the Encoding and Retrieval of Human Declarative Memory

(A) Brain activity in encoding that predicts subsequent memory. The figure depicts statistical BOLD-signal maps produced by metaanalysis of data from 74 fMRI studies of subsequent memory of verbal items and their associations and of visual items and their associations. The memory-predicting regions revealed by this set of studies include the bilateral mediotemporal lobe (MTL), left inferior frontal cortex, bilateral fusiform cortex centered on the intraprietal sulcus, and bilateral posterior parietal cortex. Images reproduced by permission from Kim (2011).

(B) Diagrams depicting the dynamics of brain network fast functional connectivity in memory retrieval revealed by electrocorticographical (ECoG) recording in patients undergoing seizure monitoring. The patients were engaged in retrieving spatial and temporal episodic contexts. Phase synchronization between brain areas was used as a measure of connectivity. The panels display the connectivity correlated with correct spatial and temporal retrieval in the 1–4 Hz and 7–10 Hz bands. PHG, parahippocampal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; PCN, precuneus; SPL, superior parietal lobule. Successful retrieval was associated with greater global connectivity among the sites with the MTL acting as a hub for the interactions, but while correct spatial context retrieval was characterized by lower frequency interactions across the network, temporal context retrieval was characterized by faster frequency interactions. These results provide insight into how multiple contexts associated with a single event can be retrieved in the same network. Reprinted by permission from Watrous et al. (2013).

cortices (MTLc). The nature of the computations remains unclear. However, various models share the view that the hippocampus combines information from medial temporal lobe cortices to support binding of multiple stimulus attributes (Eichenbaum et al., 2007; Diana et al., 2007; Wixted and Squire, 2011). Similarly, attempts are being made to discern distinct encoding-related functions within the hippocampus proper. Most studies currently use high-resolution fMRI combined with advanced analyses (Rissman and Wagner, 2012), as well as data from intracranial electrophysiology in human patients (Suthana and Fried, 2012). Studies of the long (anterior-posterior) hippocampal axis indicate a bias in the anterior hippocampus for the representation of context. By contrast the bias in the posterior hippocampus is for the representation of detail (Poppenk et al., 2013).

In parallel with studies of animal models discussed above, analyses of the role of hippocampal subfields in human memory attempt to explore the degree to which certain memories rely on the ability to perform pattern separation on the one hand, and pattern completion on the other (McClelland and Goddard, 1996). Pattern separation is postulated to be particularly instrumental in encoding, and pattern completion is thought to be important in retrieval. High-resolution imaging of the hippocampus revealed differences between hippocampal subfields, with activity consistent with pattern separation in the CA3/dentate gyrus region and activity consistent with pattern completion in CA1 and subiculum (Bakker et al., 2008). The engagement of pattern separation and pattern completion computations at any point in time may relate to the activation of encoding versus retrieval modes while learning takes place. Since, in real life, the subject is not naive to at least part of the information presented (see above), a tension is expected between episodic encoding and retrieval in the learning situation, with the two modes temporally segregated and interchanging within fractions of a second to seconds (Hasselmo et al., 1996; Kunec et al., 2005; Lisman and Grace, 2005). The effect of such postulated switching on the outcome of learning was recently studied by Duncan et al. (2012), who found that recent encoding of novel objects improved subsequent identification of subtle changes in stimuli, indicating bias for pattern separation carried over from the encoding mode. By contrast recent retrieval of old objects increased subsequent integration of new information into old memories, indicating a carried-over bias for pattern completion.

Studies of the role of the hippocampus in human memory also reveal the involvement of cognitive processes that modify or bias memory implicitly. Thus Edelson et al. (2011) examined how socially induced memory errors are generated in the brain. Groups of five participants each watched a narrative movie

and were tested a few days later. The participants remembered most of the information with high accuracy and confidence. Each of the participants was then presented inside the fMRI scanner with fake replies of the other four participants in the group, which negated the original correct high-confidence response to the same questions. A substantial part of the original correct responses were changed (in line with earlier behavioral results on the power of social conformity such as those by Sherif [1936]). The long-lasting, but not the temporary, false memory was predicted by enhanced amygdala activity and hippocampal-amygdala functional connectivity during the exposure to the social influence. Posttest debriefing indicated that most participants were unaware of the manipulation, let alone of the extent of their long-lasting memory change. In other words, this largely unconscious hippocampal-amygdala crosstalk was required to bring about the implicit change in explicit memory. Wimmer and Shohamy (2012) identified the role of hippocampus in implicit decision bias. They induced new associations between pairs of neutral visual stimuli, S1 and S2, and then associated value with part of the S2 stimuli by conjoining them with monetary reward. In the final phase of the experiment, they asked participants to select between pairs of S1 items, S1+, previously associated with a rewarded S2, and S1−, associated with a nonrewarded S2. Participants tended to choose the rewarded S2 over unrewarded S2. Most participants displayed a bias toward S1+ as well. Wimmer and Shohamy found that this bias was predicted by BOLD activity during the reward learning phase in the posterior hippocampus, in visual cortical areas related to the category of the specific S2 (body, face or scene), and functional connectivity between the hippocampus and the striatum, a brain area implicated in reward. Postscanning debriefing showed no explicit memory for the reward associations or awareness of task structure, indicating that in value-based decision the hippocampus is involved in automatic selection of alternatives.

Functional neuroimaging also linked subregions of the prefrontal cortex (PFC) to encoding of new memories in the human brain (meta-analysis in Spaniol et al., 2009; Kim, 2011). The frontal cortex is much more developed in humans than in other primates, and therefore might be expected to have a role in these complex forms of memory that are most developed in humans. The involvement of PFC has recently received particular attention in the context of integration of information across episodes and into existing schemas, knowledge frameworks that filter and facilitate the incorporation of new information. For example van Kesteren et al. (2010) manipulated prior schema by exposing participants to the first 80 min of a movie, which was presented in a consistent order to half of the participants and in a temporally scrambled order to the other half. The next day, the participants underwent fMRI scanning while watching the movie's final 15 min in the correct temporal order. Performance on prior schema knowledge and item recognition was associated with increased intersubject synchronization of activity in the ventromedial PFC (vmPFC) and less hippocampal-vmPFC functional connectivity during encoding. This interregional connectivity pattern persisted during the postencoding rest period of 15 min. The authors interpreted the data to indicate that to compensate for difficulty integrating novel information in the absence of a prior schema additional crosstalk between hippocampus and vmPFC is required, and that this crosstalk persists to support immediate postencoding consolidation. Based on these and other studies, the efficiency of memory was found to be augmented by congruency-dependent interactions between medial temporal lobe and vmPFC interactions (van Kesteren et al., 2012). This is consistent with the schema-accelerated system consolidation found in the rat (Tse et al., 2007, and see above.)

As noted above, fMRI has low temporal resolution and measures neuronal activity only indirectly via BOLD, therefore, many fMRI studies have initially focused on the localization of function. However, as evident in the literature on rodents (e.g., Buzsáki and Moser, 2013), it is unlikely that we will understand the mechanisms of memory at the brain systems level without tapping into the temporal dynamics of neural activity. In humans, such temporal dissection has so far been mostly limited to the recording of classical event-related potential (ERP) recordings. These have good temporal resolution (in the ms range) but lack proper spatial resolution (cm). Attempts to combine both ERP and fMRI to extract the advantage of each provide information unavailable by the fMRI data alone (Rugg et al., 2002). For example when examining two types of verbal tasks, one relating words to animate objects and the other probing the alphabetical order of the first and last letter in the words, the fMRI memory signatures were similar, yet the ERP signatures were qualitatively different, indicating different brain mechanisms at the higher temporal resolution. In addition, the ERP data revealed activation immediately before and right at the onset of the encoding task, masked by the slower BOLD signal.

The impressive advances in high resolution functional imaging at the cellular level in animal models and the recent advances in human brain neurophysiology (Staresina et al., 2012; Suthana and Fried, 2012; Watrous et al., 2013), have reinvigorated the search for methods that achieve better temporal resolution of memory mechanisms in the human brain. One example is provided by studies of the role of synchronization over theta and gamma rhythms in binding items to be encoded and relegating them to memory (e.g., Nyhus and Curran, 2010; Lega et al., 2012; Buzsáki and Moser, 2013); theta rhythm is the neural oscillatory pattern typically in the range of 4–10 Hz as evident in the electroencephalography [EEG], whereas gamma rhythm is the pattern of neural oscillations at a higher frequency, typically 25–40 Hz. Lega et al. (2012) recorded intracranial EEG from neurosurgical patients as they performed an episodic memory task, and identified two patterns of hippocampal oscillations at the theta range, slow (3 Hz) and fast (8 Hz). One of their findings was that the power of the slow theta rhythm was correlated with successful encoding and that the theta rhythm was in synchrony with oscillations in the temporal cortex, indicating an instantaneous crosstalk between the hippocampus and the temporal cortex in productive encoding.

Systems Consolidation and Transformation of Declarative Memory

Over the years, the term "memory consolidation" has been used in two different yet interrelated meanings, referring to a level of description (Dudai and Morris, 2000). Synaptic, cellular, or immediate consolidation refers to the gene-expression-dependent transformation of information into a long-term form in the neural circuit that encodes the memory. Its molecular underpinnings

were described earlier in this review. Systems consolidation refers to a slower postencoding reorganization of long-term memory over distributed brain circuits into remote memory lasting months to years, and is commonly studied within the context of the cortico-hippocampal system that subserves explicit memory.

The current models of systems consolidation in humans draw from behavioral and anatomical investigations of amnesic patients, and fMRI studies that monitor time-dependent alterations in recollection-correlated brain activity in healthy human participants. These models fall into two types: the "standard consolidation theory" (Alvarez and Squire, 1994; McClelland et al., 1995) and models that challenge the "standard consolidation theory," including the "multiple trace theory" (Nadel and Moscovitch, 1997) and the more recent "trace transformation theory" (Winocur et al., 2010).

In "global amnesics," like H.M., who suffered damage to the MTL and particularly to the hippocampus and entorhinal cortex (Scoville and Milner, 1957; Corkin, 2002; Squire, 2009), performance on many explicit tasks show temporally graded retrograde amnesia, implying that the older memories are less dependent on an intact MTL. The standard consolidation theory attempted to explain this observation by suggesting that the hippocampus is only a temporary repository for memory whereas the neocortex stores the memory thereafter (Alvarez and Squire, 1994; McClelland et al., 1995). Specifically, the model postulates that the encoding, storage and retrieval of declarative information is initially dependent on both the hippocampus and related MTL structures, and on neocortical areas relevant to the encoded stimuli. With time, the information reorganizes, involving replay of the hippocampal representation to the neocortex. This reinstates the corresponding neocortical memory, resulting in incremental adjustments of neocortical connections, and establishment of a long-lasting, reorganized representation, while the hippocampal memory decays.

Some recent evidence seems incompatible with the standard consolidation theory. First and foremost, MTL lesions have differential effect on types of facts and events, with autobiographical episodes being most severely affected: the retrograde temporal gradient for this type of memory is either entirely absent or very shallow. Driven by these observations and corresponding findings in animal models, Nadel and Moscovitch (1997) proposed the "multiple trace theory," which posits that the hippocampus rapidly and obligatorily encodes all episodic information. This information is sparsely encoded in distributed ensembles of hippocampal neurons, acts as an index for neurocortical neurons that attend the information, and binds them into a coherent representation. The resulting hippocampal-neocortical ensemble constitutes the memory trace for the episode. Since reactivation of the trace commonly occurs in an altered context, it results in newly encoded hippocampal traces, which in turn bind new traces in the neocortex. This results in multiple traces that share some or all the information about the initial episode. Over time, multiple related traces facilitate the extraction of factual information into a semantic representation of the gist of the episode. This information integrates into a larger body of semantic knowledge and becomes independent of the specific learning episode. Contextual information about the episode, which is required for episodic recollection, continues, according to this model, to depend on the hippocampus as long as the memory is viable.

Opponents of the multiple trace theory claimed that patients with well-characterized MTL lesions do show intact remote memory, including the autobiographical type, unless the damage exceeds the MTL (Squire and Bayley, 2007). This argument was challenged based on data from patients with lesions restricted to the MTL (Rosenbaum et al., 2008; Race et al., 2011). The argument also does not explain why functional neuroimaging identifies hippocampal activation in retrieval of remote autobiographical memory in healthy individuals (Gilboa et al., 2004; Viard et al., 2010). As a result we are now left with several open questions about the functional imaging data. These include: (1) to what extent is hippocampal activation the result of cue-induced imagining processes that promote memory reconstruction and re-encoding (Hassabis et al., 2007) as opposed to genuine recollection and (2) does the activation reflect processes essential for retrieval or just a process correlated with it?

The new technologies now available in animal models also cast additional light on aspects of systems consolidation. Many groups have reported retrograde gradients in contextual fear conditioning in rodents, with hippocampal lesions severely affecting recall at early time points after learning but having no effect on recall at remote time points. But there are conflicting reports, echoing the conflicting reports on amnesic gradients in human declarative memory (Frankland and Bontempi, 2005; Broadbent and Clark, 2013). This question was recently revisited using rapid optogenetic silencing of the hippocampus (Goshen et al., 2011). Halorhodopsin is a light-gated chloride pump that acts on a millisecond timescale to hyperpolarize neurons, thereby preventing action potential generation. At remote time points after contextual fear conditioning halorhodopsin-based silencing of the hippocampus disrupted memory recall suggesting an ongoing involvement of the hippocampus in remote memory. Paradoxically, there was no effect on memory if the silencing was extended for 30 min prior to the recall trial, to mimic previous pharmacological and lesion-based studies. This suggests that at remote time points after learning, the hippocampus is still normally recruited and required for retrieval, but that with a prolonged loss of the hippocampal pathway there are compensatory mechanisms that allow retrieval independent of the hippocampus. This finding emphasizes the importance and distinction between permanent lesions and temporary ones.

The Role of Sleep in Consolidation

Both animal studies and human studies indicate that consolidation benefits from sleep or even a short nap (Diekelmann and Born, 2010). The evidence for the role of sleep in consolidation of implicitly acquired sensory and motor skills was initially considered more robust than that for other types of memory (Walker and Stickgold, 2004). It is now well established, however, that consolidation of explicit memory benefits from sleep as well (Diekelmann and Born, 2010; Walker and Stickgold, 2010). Sleep may promote the preferential strengthening of emotional memoranda and of items that are expected to be subsequently retrieved (Sterpenich et al., 2009; Wilhelm et al., 2011; Rauchs et al., 2011); Rudoy et al. (2009) trained awake participants to associate object locations with sound and found that only

those associations that were cued during sleep with their relevant sound were strengthened. This suggests that specific associations are preferentially reactivated and strengthened during sleep.

How does consolidation occur in sleep? Extending earlier proposals that sleep had evolved to maintain homeostasis (Crick and Mitchison, 1983; Borbély and Achermann, 1999), Tononi and Cirelli (2006) posited that plastic processes during wakefulness result in a net widespread increase in synaptic strength in the brain, and the role of sleep is to downscale synaptic strength to a baseline level that is energetically sustainable and possibly also more useful for acquiring new learning the next day. This implies that sleep plays a necessary role in sustaining memory systems, and is at least permissive for consolidation. A different, though not mutually exclusive, view is that sleep involves active processes that consolidate memory, and is therefore necessary and instrumental in implementing the steps required for consolidation. This is the "active consolidation in sleep hypothesis" of Diekelmann and Born (2010). Their proposal is that during slow-wave sleep (SWS), the characteristic neuronal activity patterns and low cholinergic activity act together to promote the reactivation and redistribution to neocortex of hippocampal-dependent memories, thereby instantiating systems consolidation. Subsequently, during rapid eye movement (REM) sleep, high cholinergic- and theta activity promote synaptic consolidation of the newly redistributed representations in the neocortex. Seen this way, synaptic consolidation is a subroutine in systems consolidation. Similar systems-synaptic sequences may take place in certain implicit memories as well (Dudai, 2012).

Retrieval of Explicit Memory

Our brain can retrieve complex explicit information and act on it within a fraction of a second (e.g., Thorpe et al., 1996), but we still do not know how. Behavioral models (Tulving, 1983; Roediger et al., 2007) lead us to expect that the brain does this through a combination of sequential and parallel distributed processes that involve multiple brain circuits. The involvement of the medial temporal lobe in retrieval in at least the early stages of long-term explicit memory is not disputed, and more recent studies indicate that the medial temporal lobe is normally required for contextually rich explicit retrieval as long as the memory exists. The prefrontal cortex interacts with the medial temporal lobe during retrieval (Eichenbaum, 2000; Rugg et al., 2002; Shimamura, 2011), providing top-down selection of information, updating episodic features, and acting on the product of retrieval in a way that aligns our response with the task at hand. In addition, regions of the parietal cortex are implicated in attention-driven retrieval efforts and search (Burianová et al., 2012; Cabeza et al., 2012) and in binding and representing episodic features (Rugg et al., 2002; Shimamura 2011).

How can we gain insights into a process as complex as memory retrieval when fMRI gives us only snapshots of brain states averaged over a period of time that is much longer than that in which the machinery of retrieval functions? Previous studies using noninvasive scalp EEG have yielded some data on temporal phases of retrieval (Conway et al., 2001; Rugg et al., 2002), but the low spatial resolution of this technology presents a serious obstacle. A recent study illustrates that invasive electrophysiology in human patients, similar to that recently introduced to the study of explicit encoding (see above), can lead to better analyses.

Watrous et al. (2013) made electrocorticographical (ECoG) recordings of brain activity in patients undergoing monitoring for seizure who were engaged in retrieving the spatial and temporal contexts associated with their memory (Figure 4B). These recordings report large-scale activity with a time resolution of milliseconds. Watrous and his colleagues recorded simultaneously from various areas of the medial temporal lobe, the prefrontal cortex, and the parietal cortex—the major components of the retrieval network—and used phase synchronization between brain areas as a measure of network connectivity. As shown in Figure 4B, they found that successful retrieval is associated with greater overall connectivity among sites and, moreover, that successful retrieval of temporal context occurs at higher-frequency interactions than retrieval of spatial context.

These results provide insight into how multiple contexts associated with a single event can be retrieved in the same network. They also illustrate that to understand retrieval in the human brain, studies of the localization of function must be complemented with studies capable of measuring fast electrophysiological dynamics. Moreover, such studies must be done in healthy participants. As this discussion makes clear, understanding how explicit memory is retrieved remains one of the major challenges facing the neuroscience of human memory.

Open-Ended Questions

Systems Biology of the Synapse. The biochemical and genetic characterization of the protein complexes in the pre- and postsynaptic terminal has provided a view of the molecular machinery responsible for synaptic transmission and neuronal plasticity. The modification of synaptic strength and behavior, as we have seen, involves a complex array of molecular signaling mechanisms operating in the synapse and cell-wide over different time scales. A challenge for the future that faces the biology of memory, as it faces all of biology, is to understand the interaction of these components as part of complex molecular machines and the signaling circuits in which they participate. This systems approach to biology is now coming into view aided by new technologies for imaging such as cryo-EM, a new means of collecting structural data on large protein complexes, and fluorescent imaging for assessing in real time a range of molecular processes extending from protein-protein interactions to the activity of signal transduction pathways. Finally we have a range of genomic and proteomic-based strategies for assessing global changes in gene and protein expression, modification, and signaling. This big data approach to biology is now appropriately matched by sophisticated computational modeling that is constrained by the biological data and provides testable predictions for experimental assessment and model refinement. The evolution of a realistic computational neuroscience and its incorporation into memory research has already proven of great value and will become even more important in the future.

Systems Neuroscience of Memory. Much of what we know of the cellular and molecular mechanisms of memory comes so far from relatively simple invertebrate and mammalian systems processing unimodal sensory information in a defined circuit. Understanding the neural code for more complex memory embedded in sparsely distributed networks is a significant

challenge and here advances in the study of mammalian, including human, memory is expected to add significantly. Are complex forms of memory encoded and expressed in relatively simple population rate codes or in dynamic spatiotemporal codes? If so, what are the concrete type and token elements of these codes? Is the representation distributed, requiring coordinated activation of multiple brain regions, or is it convergent, with small groups of cells representing specific items? How stable is the code and what is the signal to noise ratio? How and where does use-dependent plasticity alter these circuits and how does that alter subsequent processing at multiple levels of organization of the nervous system to instantiate a memory? Recently developed tools for calcium imaging of large populations of neurons in behaving animals combined with optogenetic manipulation and activity-based genetic modification, supplemented with computational approaches, will likely cast light in the foreseeable future on these critical questions in memory research. Advances in human brain electrophysiology in patients undergoing monitoring and treatment, in brain activation using brain-machine interfaces, and further down the road in brain-inspired technology and neuromorphic devices, are also expected to add new facets to our understanding of the systems neuroscience of memory.

Systems Problems of Brain Disorders. Some animal models of human cognitive disorders involving memory deficits have been developed and could yield new basic insights into these defects. For further advance in understanding how aberrations in the activity of synapses, cells, and circuits contribute to mnemonic deficits, we are in need of batteries of rigorous and informative basic behavioral task variants, which can, in principle, be used in mice as they are in people. This might allow one to develop progressively more reliable and informative imaging and cognitive psychological criteria for distinguishing the behavioral and anatomical differences between age-related memory loss from those of early Alzheimer's disease and to try to develop therapies selective for each.

In addition animal models of human cognitive disorders associated with schizophrenia, and of the memory disorder associated with depression, are needed to provide further insights into these diseases. Progressively more sophisticated approaches to reversing these disorders are desperately needed, since no new antischizophrenic agent has been developed in the last 40 years and no new antidepressant has been developed in the last 20 years.

Summary

A great deal of progress has been made over the past 40 years in uncovering the biological mechanisms of learning and memory. In a simple circuit that controls behavior, the tools of cellular and molecular biology have revealed how individual neurons and molecular signaling pathways are modified by learning. Changes in synaptic strength produced by specific patterns of electrical activity or the action of modulatory transmitters can alter the processing of information to control behavior. Both memory storage and synaptic plasticity have varying temporal phases, with the switch from short- to long-lasting synaptic and behavioral memory requiring new gene expression. The long-term phase uses a number of cellular mechanisms, such as synaptic tagging, changes in protein synthesis at the synapse, and possibly protein kinase-based cascades and functional self-perpetuating prion-like mechanisms for maintenance.

We are beginning to uncover the structure of neural circuits in more complex forms of explicit memory, which involve the hippocampus, adjacent mediotemporal cortex and additional neocortical areas, as well as the location and dynamics of their connections. Recent techniques for the genetic manipulation of neurons based on their natural activity during learning and recall are enabling direct tests of the function of distributed neural ensembles and their role in generating representations in complex explicit memory. Finally, advances in functional imaging, combined with new electrophysiological and computational techniques for assessing neural activity in large populations of neurons, are helping us to determine what regions of the human brain are involved in complex explicit memory and explore the coding properties of the neurons in those regions.

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