Leading Edge
Review
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The Molecular and Systems Biology of Memory

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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.

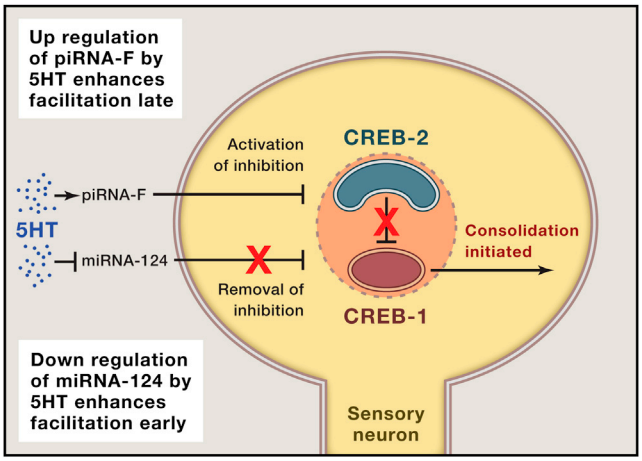

Figure 1. Epigenetic Mechanism in Memory

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

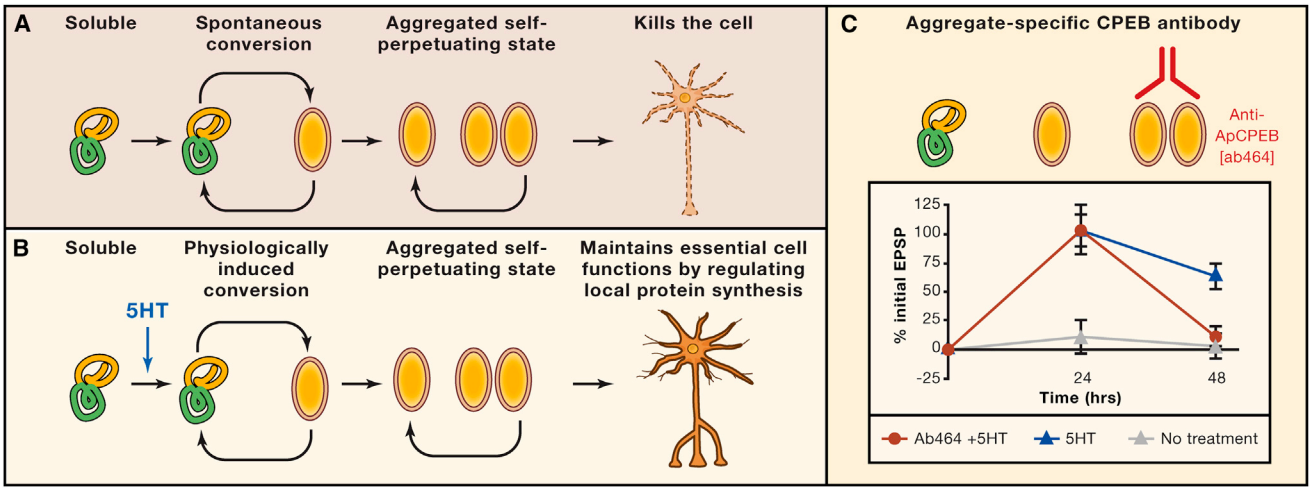

Figure 2. Prions in Memory

(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

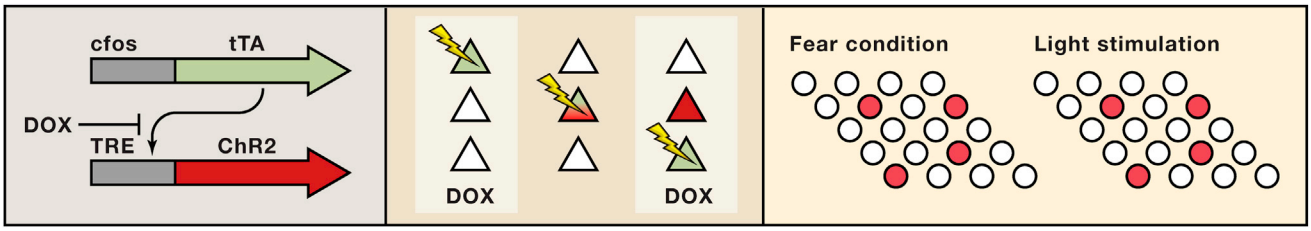

Figure 3. Genetic Tagging of Active Circuits
Two transgenes are required. The expression of tetracycline-controlled transactivator (tTA) is linked to neural activity by the cfos promoter. In the presence of doxycycline (DOX) tTA fails to activate the second gene (ChR2 in this example). During time periods 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

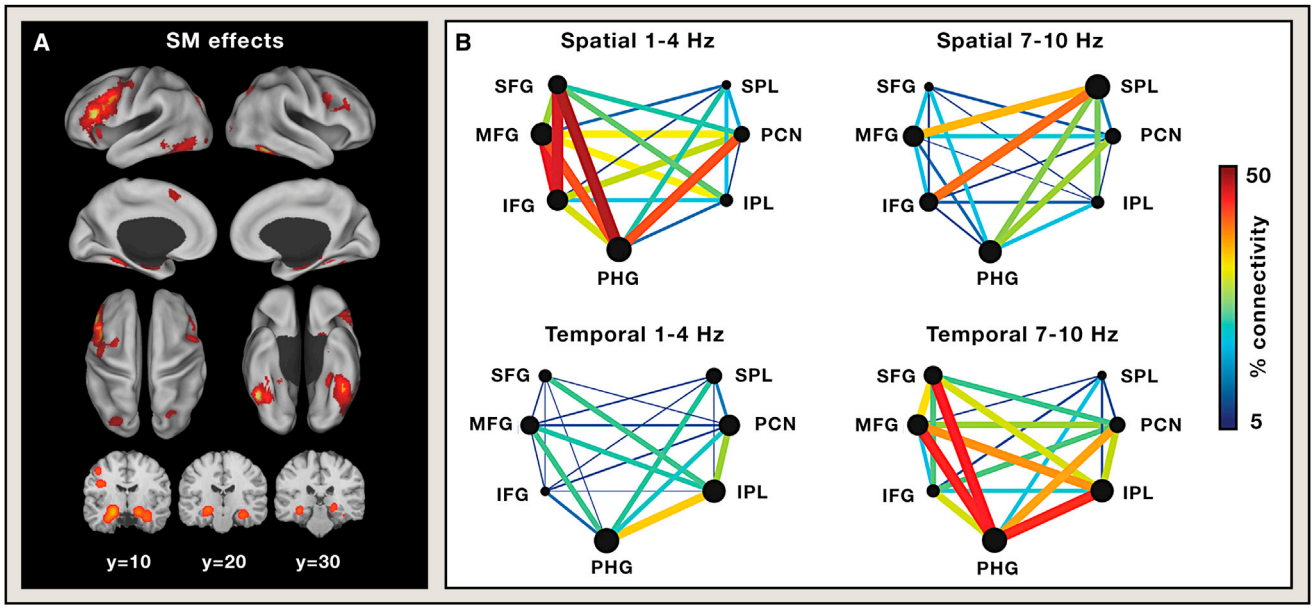

Figure 4. Brain Correlates of the Encoding and Retrieval of Human Declarative Memory

(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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