The Role of the Hippocampus in Prediction and Imagination

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Abstract

Traditionally, the hippocampal system has been studied in relation to the goal of retrieving memories about the past. Recent work in humans and rodents suggests that the hippocampal system may be better understood as a system that facilitates predictions about upcoming events. The hippocampus and associated cortical structures are active when people envision future events, and damage that includes the hippocampal region impairs this ability. In rats, hippocampal ensembles preplay and replay event sequences in the absence of overt behavior. If strung together in novel combinations, these sequences could provide the neural building blocks for simulating upcoming events during decision-making, planning, and when imagining novel scenarios. Moreover, in both humans and rodents, the hippocampal system is spontaneously active during task-free epochs and sleep, further suggesting that the system may use idle moments to derive new representations that set the context for future behaviors.

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INTRODUCTION

Patients with memory impairment often also have difficulties in imagining upcoming events and novel scenarios (Hassabis et al. 2007, Klein et al. 2002b, Korsakoff 1889/1996, Talland 1965, Tulving 1985). This observation in amnesia provides an important clue about the adaptive function of memory systems. Remnants of past events may serve as the building blocks for prediction and imagination. Here emerging findings are reviewed that suggest an essential role of the hippocampal-cortical system is to facilitate predictions about the future. At the center of this perspective is the idea that the capture of associations that define event sequences is adaptive because these sequences can be reassembled into novel combinations that anticipate and simulate future events. Traditional memory tests tap into hippocampal mechanisms because stored associations are necessary for veridical recall, but the functional role of the hippocampus is nonetheless best understood from an adaptive, forward-oriented perspective.

The idea that the hippocampal-cortical system is important to prediction is receiving growing attention. Cohen & Eichenbaum (1993) end their book by noting that the representational flexibility of the hippocampal system permits the ability to "manipulate" stored representations in the service of problem-solving behaviors. Such ideas are echoed in cognitive theories. Johnson & Sherman (1990) proposed that expectations about the future are an amalgamation of all past events that one has experienced and stored. Klein and colleagues (2002b; see also Klein et al. 2002a) poignantly noted, "a case can be made that information storage is intrinsically prospective, used to support future decisions and judgments that cannot be known in advance with certainty." Attance & O'Neill (2001), Ingvar (1985), Suddendorf & Corballis (1997), and Tulving (2005) have all thoughtfully discussed the role of memory in thinking about the future. Several recent reviews specifically elaborate on the possibility that the hippocampus plays a role in prediction or imagination (e.g., Bar 2007; Bird & Burgess 2008; Buckner & Carroll 2007; Buckner et al. 2008; Hassabis & Maguire 2007; Johnson et al. 2007; Lisman & Redish 2009; Schacter & Addis 2007, 2009; Schacter et al. 2007, 2008). These past ideas and papers serve as an important basis for the present review.

The review begins with a brief historical orientation to the problem by drawing from the

seminal work of Edward Tolman, who showed that learning can be flexibly expressed in novel contexts. Next, imaging and neuropsychological data in humans are reviewed that suggest the hippocampal-cortical system plays a critical role in envisioning the future. Following the description of findings in humans, recent electrophysiological studies in rodents are described that reveal the presence of preplay and replay sequences that might provide the building blocks for representation of upcoming events. These combined observations are then integrated into a mechanistic model of how the hippocampus might contribute to prediction and imagination.

TOLMAN'S THEORY OF EXPECTANCY

A classic series of studies by Tolman and colleagues provides a good beginning point for discussion. Confronted with the prevailing view that all learning results from direct reinforcement of specific behaviors, Tolman developed an alternative formulation that he called "theory of expectancy." He was motivated by the observation that purposeful behaviors often follow a route for which the animal has no direct prior experience. How could a system that only has access to reinforced responses act in such a flexible manner? Tolman constructed several ingenious experiments to show that rats combine remnants of past experiences to guide de novo behaviors. These studies were instrumental in his development of the concept of a "cognitive map" (Tolman 1948) and its later link to the hippocampus (O'Keefe & Nadel 1978).

As one illustrative example, Tolman et al. (1946) trained rats to go down a path making several turns away from, and then back toward, an eventual food reward (**Figure 1**). After several training sessions, the apparatus was modified for a single critical trial to test the flexibility of the rats' use of memory. Specifically, they blocked the learned route and observed whether the rats would take a correct alternative path or remain stereotyped in their response and choose the path closest to the original (rein-

forced) route. They hypothesized that rats can flexibly express their prior experience to navigate novel situations, and found that many rats correctly chose the direct path to the food reward even though they had no experience with the route and it was positioned distant from the original path.

A second study by Tolman & Gleitman (1949) illustrated that rats can combine information across temporally distinct events. In this later study, they had rats explore a standard T-maze (**Figure 2**). Across sequential trials, the rats foraged for food equally in both arms, sometimes receiving a reward after turning right and at other times after turning left. Following initial training, the rats were removed from the maze and placed directly in one arm of the box, where they received a series of foot shocks. On a single critical test trial, the rats were placed back in the original maze and allowed to forage. Eighty-eight percent of the rats chose the safe arm even though they had never previously chosen the to-be-shocked corner in the T-maze and received an aversive outcome. Sequences experienced across prior episodes must have been combined to make the adaptive response.

Tolman's elegant studies illustrate that the use of memory extends beyond the exact retrieval of reinforced sequences. Behavior requires the novel recombination of remnants of past experiences to make predictions. In this review, I explore the possibility that the hippocampal-cortical system contributes to the construction of de novo predictions such as tapped into by Tolman's paradigms and presumably relied upon, in elaborated form, to support the human capacity to think about the future.

THE HIPPOCAMPAL-CORTICAL SYSTEM

The hippocampal-cortical system includes the hippocampal region as well as its widespread cortical targets. Within the hippocampal region is a set of interconnected structures (the CA fields, the dentate gyrus, and the subicular complex) that are positioned as a loop

Hippocampal-cortical system: includes the hippocampal region, the immediately adjacent cortex (e.g., entorhinal cortex), and widespread cortical targets

Preplay: an activity sequence that anticipates an upcoming event sequence (sequence A-B-C is preplayed in anticipation of experiencing A-B-C)

Replay: activity sequences that repeat past events (experience of A-B-C leads to replay sequence A-B-C)

Hippocampal region: the CA fields, the dentate gyrus, and the subicular complex of the hippocampus

receiving and projecting information to neocortex (for a recent review, see Squire et al. 2004). The hippocampal region is connected to cortical areas through the adjacent entorhinal cortex that then projects to the perirhinal and parahippocampal cortices. In turn, the perirhinal and parahippocampal cortices project to widespread cortical regions. Much of the electrophysiology in rodents has focused on the CA fields within the hippocampus itself or the immediately adjacent entorhinal cortex. In this review, we refer to the hippocampal region and its broad cortical targets collectively as the hippocampal-cortical system.

Across rat, monkey, and human, the hippocampal region interacts with neocortex through parallel pathways. Anatomical convergence from multiple processing pathways allows the hippocampus to integrate both spatial and nonspatial information. In the monkey, the perirhinal and parahippocampal cortices are distinguished by separate connections with temporal and parietal pathways, respectively (Suzuki & Amaral 1994). Functional connectivity analysis in humans reveals a similar distinction (Kahn et al. 2008). The rat hippocampal system is divided between two major input pathways that converge on perirhinal and postrhinal cortex (the equivalent of primate parahippocampal cortex) (Burwell 2000). Thus, although there are differences across species, the general architecture of the hippocampal-cortical system is similar and includes parallel pathways that convey multiple sources of information to the hippocampus.

Figure 3 shows the cortical areas that are connected to the hippocampal region across the three species. The estimated cortical targets in the rat and macaque monkey come from studies of connectional anatomy (e.g., Burwell 2000, Insausti et al. 1997, Kobayashi & Amaral 2003, Lavenex & Amaral 2000, Suzuki & Amaral 1994). In humans, direct assessment of connectional anatomy is not possible; however, functional connectivity based on functional magnetic resonance imaging (fMRI) provides an approximation (Biswal et al. 1995; see Fox & Raichle 2007 for review).

The estimated cortical targets of the human hippocampal region bear a strong resemblance to expectations from monkey anatomy (Kahn et al. 2008, Vincent et al. 2006), with the caveat that several of the regions include areas disproportionately expanded in hominid evolution (e.g., inferior parietal lobule, medial prefrontal cortex; Öngür & Price 2000, Van Essen & Dierker 2007). The specific topography of the cortical targets illustrated in **Figure 3** are especially relevant to the review of findings from human neuroimaging studies in the next section.

THE HIPPOCAMPAL-CORTICAL SYSTEM IS ACTIVE WHEN PEOPLE ENVISION THE FUTURE

Traditional tests of memory ask subjects to retrieve information about their past. Was this or that item presented on the earlier study list? Or, recall what happened at your college graduation. The central thesis of this review is that brain systems involved in memory are best understood in terms of their adaptive, future-oriented functions.

"Memory" systems are hypothesized to provide the building blocks that are used to construct predictions about upcoming events. Consistent with this possibility, accumulating evidence suggests that thinking about the future shares similar behavioral properties and uses the same hippocampal-cortical system as remembering the past.

Cognitive Observations

Behavioral studies have explored whether self-reported descriptions about possible upcoming events demonstrate properties that are shared in common with answers on typical memory tests. For example, recent memories are recalled with greater detail than distant memories (Johnson et al. 1988). Do projections about the future show a similar property? Several studies have adopted this approach (D'Argembeau & Van der Linden 2004, 2006; Spreng & Levine 2006; Szpunar & McDermott 2008). In one

of the first explorations, D'Argembeau & Van der Linden (2004) noted that temporally close events, both in the past and in the future, are experienced with more sensory and contextual details than are distant events. They had subjects re-experience memories or pre-experience possible future events. After each event, subjects rated the vividness of the experience for visual details, clarity of the spatial arrangements of objects and people, and several other features. For most features, temporally close future episodes were experienced with rich details, whereas distant events were relatively impoverished. This pattern is the same as that observed for past events. Psychiatric patients (D'Argembeau et al. 2008a) and older adults (Addis et al. 2008) show impoverished episodic details similarly for both recollection of the past and imagination of the future. These collective results demonstrate that people imagine future event scenarios in ways that parallel remembering the past.

Szpunar & McDermott (2008) recently expanded upon this procedure and provide evidence that future event constructions actively rely on past experience. In addition to probing content, they also manipulated the degree to which the future event could be based on past experience. In one study, subjects imagined future events in previously experienced environments (e.g., a friend's apartment) as compared to never-experienced environments (e.g., the jungle). In a second study, subjects imagined events in recently experienced environments (e.g., their university campus) as compared to environments lacking recent experience (e.g., their high school). In both studies, envisioned future events contained significantly more sensory and contextual details if they were built upon familiar environments. Although alternative explanations are possible, these findings suggest that acts of envisioning the future rely upon sampling memories from the past.

Evidence from Functional Brain Imaging

Direct evidence that the hippocampal-cortical system is used during future episodic thought emerges from functional brain imaging studies. Traditional retrieval tasks that encourage recollection, in particular from autobiographical memory, have reliably activated components of the hippocampal-cortical system or the system in its entirety (Cabeza & St. Jacques 2007, Maguire 2001, Svoboda et al. 2006, Vilberg & Rugg 2008, Wagner et al. 2005). In a particularly thorough analysis, Svoboda et al. (2006) aggregated data from 24 positron emission tomography and fMRI studies that examined autobiographical memory retrieval. The network of regions consistently activated across studies included the hippocampal region as well as the distributed cortical regions that comprise the hippocampal-cortical system. Critical to the present review, studies that examine tasks where subjects imagine future scenarios demonstrate that the same hippocampal-cortical system is active. Schacter et al. (2007, 2008) discuss in detail findings from such paradigms, so they are only briefly mentioned here.

In the prototypical paradigm, participants are given a cue and instructed to imagine a future situation related to that cue. For example, cued with the word "dress," a student tested by Addis et al. (2007) responded with the following imagined scene: "My sister will be finishing her undergraduate education... And I can see myself sitting in some kind of sundress, like yellow, and under some trees." Several such studies have been reported using positron emission tomography and fMRI (Addis et al. 2007, Botzung et al. 2008, D'Argembeau et al. 2008b, Okuda et al. 2003, Partiot et al. 1995, Sharot et al. 2007, Szpunar et al. 2007). Example data from Addis et al. (2007) are displayed in **Figure 4**. The network active for episodic future thought is strikingly similar to that for autobiographical recall.

Analyses that combine data across studies suggest there is convergent activation in the hippocampal-cortical system including the hippocampal region, the posterior cingulate extending into precuneus, the inferior parietal lobule, and the medial frontal cortex (Schacter et al. 2008, Spreng et al. 2009). Correspondence

is not perfect. Medial frontal regions implicated as components of the hippocampal-cortical system include ventral regions, while the studies of future thought converge on a region that is more dorsal (see Buckner et al. 2008 for anatomical review). Predictions are also likely dependent on more than just episodic processes (see Szpunar 2009). Addis and colleagues further provide evidence that activity within the hippocampal region tracks the amount of detail recollected or projected to an imagined future event (Addis & Schacter 2008) and also that the region (particularly the anterior hippocampal formation) is most active when imagined events about the future must combine details across episodes (Addis et al. 2009, Schacter & Addis 2009). Taken collectively, the functional imaging results suggest that (*a*) the same regions are active during envisioning the future as remembering the past, and (*b*) these regions include the hippocampus and cortical targets that (largely) overlap the hippocampal-cortical system.

MEMORY IMPAIRMENT DISRUPTS THE ABILITY TO IMAGINE FUTURE EVENT SCENARIOS

Neuropsychological studies of amnesia have long emphasized the profound memory loss that results from damage to the medial temporal lobe (MTL) and associated structures. Following bilateral MTL damage, the ability to recount recent events and learn new episodes is significantly impaired while global cognitive functions and procedural memory remain intact. Several prior reviews have discussed these classic neuropsychological findings (Milner et al. 1998, Squire et al. 2004). Here attention will be drawn to a lesser-studied aspect of amnesia that surrounds deficits in the ability to envision future events and imagination. Such deficits, which have been anecdotally reported since the earliest descriptions of amnesia, are emerging as an often-observed feature of memory impairment and have important implications for how we conceptualize the function of the hippocampal-cortical system.

Korsakoff (1889/1996) discussed the absence of imagination and flexible thinking in his memory-impaired patients, as reflected in his description below:

> This is why, after conversing at length with one of the patients, his initially striking perceptiveness and presence of mind seem somewhat deficient. We realize that: (1) the patient reasons by making use of old material, accumulated during a long period of time. Recent impressions have almost no role in his reasoning; (2) even with this old material, the patient makes only routine combinations and repeats phrases learned long ago; (3) the circle of ideas in which the patient's intelligence moves becomes very restricted, and even this narrow frame, he always makes the same connections.

Talland (1965) noted a similar loss of imagination in his case studies of amnesia. When asked about their future plans, his patients could only state generalities such as that they would return to work; their answers lacked details about possible future interactions with other people and events. Although the brain lesions in these patients confound medial temporal and frontal damage (e.g., Shimamura et al. 1990),[1] it is nonetheless intriguing that deficits in memory were intertwined with parallel deficits in imagining the future.

More recently, observations of patients H.M. and K.C. also revealed similar deficits. H.M., who became densely amnesic following bilateral resection of the hippocampus and adjacent structures in the MTL (Corkin 2002, Scoville & Milner 1957), did not make predictions about future autobiographical events. When pushed to do so, he responded with

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[1]The contribution of frontal systems to deficits in future thought, including foresight and planning, have been reviewed previously (e.g., Fuster 1989, Mesulam 2002, Shallice 1982). Interactions between frontal and hippocampal systems will undoubtedly be important to understanding how predictions are constructed and used to guide decisions. The emphasis on the hippocampal system in this review is a matter of focus and is not meant to minimize the importance of frontal systems (e.g., see Buckner & Carroll 2007).

a happening from the distant past or simply did not respond (S. Steinvorth and S. Corkin, personal communication). K.C., another well-studied individual with amnesia (Rosenbaum et al. 2005), also failed to respond in similar situations (Tulving 1985). In a recent test of K.C.'s deficits, Rosenbaum et al. (2009) observed that he could not imagine fictitious events with the same richness in detail as that of controls.

Deficits of envisioning the future were systematically studied in patient D.B., who developed amnesia following anoxia (Klein et al. 2002b). Motivated by the possibility that memory systems are intrinsically prospectively focused, Klein and colleagues probed D.B.'s deficits by asking him a series of questions about the future. They observed that D.B. either confabulated or did not know what he would be doing on most questions about his personal future, although he retained general knowledge. For example, he remarked that a future issue facing the environment was a "threat that weather and rainfall patterns are going to change because of industrial pollution." It is unknown the exact anatomy of D.B.'s lesion, which resulted from an anoxic episode during cardiac arrest. The hippocampus is affected during anoxia because it is among the structures most sensitive to damage and cell loss due to ischemia, although such damage is not typically limited to the hippocampus (Squire & Zola 1996).

The studies described above make a strong case that brain systems important to memory are also critical to imagining the future; impairments in one domain appear linked to the other. However, the findings do not allow a strong statement to be made about the exact anatomic structures damaged, especially in relation to determining whether lesions restricted to the hippocampus are sufficient to cause deficits. Among the above patients, the lesions sustained by H.M. have been the best characterized, but his behavioral deficits in this domain were insufficiently documented. Animal models and considerably more information than is available today will be required to resolve this issue.

Hassabis et al. (2007) recently tested patients with documented hippocampal amnesia providing some initial insight. Their study is important for two reasons. First, the anatomic analysis of the lesions and clinical description suggested that the hippocampus was specifically damaged in four patients showing the greatest functional impairments. As an example, **Figure 5** shows the MRI scan of patient P03, a 24-year-old male with a rare form of limbic encephalitis. His MRI revealed hyperintense signals in the bilateral hippocampus, and electroencephalogram (EEG) analysis showed bilateral epileptic discharges in the medial temporal regions (Samarasekera et al. 2007). Generalized atrophy was also present (note the enlarged ventricles), so it is not possible to conclude that his impairments result from focal hippocampal damage. However, in aggregate, the convergence of damage to the hippocampal region across patients supports the possibility that the hippocampus and interconnected structures are intimate to the origin of the deficits.

Second, Hassabis et al. (2007) explored the nature of the patient's impairment in considerable detail, including analysis of which components of imagination are disrupted. The paradigm involved asking patients and matched controls to imagine experiences in response to short verbal cues. For example, the participants were asked to describe scenes involving "lying on a white sandy beach in a beautiful tropical bay" and "a possible event over the next weekend." A composite index measuring the overall richness of the imagined experiences was markedly reduced in four of five patients compared to controls (**Figure 5**). The patients' own narratives also revealed these deficits. For example, when patient P03 was asked to imagine lying on a white sandy beach, he provided a vague description of objects that are typically associated with a beach but did not describe a coherent visual scene. As a final analysis, the patients were asked to judge the appropriateness of statements that described their internal mental experience. Some of the statements asked whether the imagined scenes were integrated (e.g., "I could see the whole scene in my mind's eye"), while others probed whether the scenes were fragmented (e.g., "It was a collec-

tion of separate images"). Results again confirmed that the patients' imagined scenes were fragmentary and lacked an integrated spatial context.

Taken together, these findings suggest that amnesia is associated with deficits in the ability to envision the future and other forms of events that depend on an imagined scene. A possibility is that such deficits result because of the loss of mechanisms to store and flexibly recombine the remnants of past events into novel, prospectively useful forms. In the section below, I review physiological studies of rats navigating environments that suggest mechanisms by which cell assemblies in the hippocampus might support such prospective functions.

HIPPOCAMPAL CELL ASSEMBLIES PROVIDE THE BUILDING BLOCKS FOR PREDICTION

The question addressed in this section is whether activity patterns exhibited by hippocampal cell assemblies are consistent with a role in prediction. That is, do hippocampal neurons fire in a manner that could contribute to expectations about the future? The most basic expected property is that activity should represent upcoming actions and events. Under appropriate conditions, prospective activity correlates should be detached from the stimuli in the immediate environment and current behaviors of the animal. A second property is that the activity should predict future behavior. Error trials are particularly informative for testing this property. Finally, manipulation or disruption of the activity should influence later behaviors. Ultimately, a prediction mechanism would be most convincingly demonstrated by showing experimental control over an animal's decision-making.

The vast majority of information about neuronal activity patterns in the hippocampus comes from studies in rodents navigating spatial environments. To foreshadow the observations that will be discussed, hippocampal cell assemblies exhibit firing patterns during navigation that (*a*) reflect past and upcoming locations, (*b*) are spontaneously emitted, and (*c*) correlate with the future behavior of the animal under specific conditions. As is discussed, caveats and open questions remain concerning the functions of these activity patterns because causal manipulations have yet to be demonstrated.

Two important discoveries provide the backdrop for understanding the potential role of hippocampal neurons in prediction. The first is the phenomenon of place fields (O'Keefe & Dostrovsky 1971; for recent review, see Moser et al. 2008) and the second is of theta phase precession (O'Keefe & Recce 1993, Skaggs et al. 1996; for recent reviews see Buzsáki 2005 and Maurer & McNaughton 2007). These two phenomena are discussed first, followed by a more extensive description of recent studies that provide evidence for prospective coding.

Place Fields

Place fields are spatial receptive fields that are present in hippocampal pyramidal cells in CA1 and CA3. As a rat moves through the environment, neurons exhibiting place fields will preferentially respond when the rodent transverses a specific location (**Figure 6**). The observation of place fields led O'Keefe & Nadel (1978) to propose that cells exhibiting such fields—place cells—are the building blocks of an internal map-like representation of the environment. Numerous studies have confirmed and extended these observations, including the remarkable discovery of neurons in the medial entorhinal cortex—grid cells—that map multiple locations of the environment in a grid-like pattern (Fyhn et al. 2004). A great deal of recent focus has been on unraveling the network properties that enable the computation of place fields and how the population signals are used for spatial navigation and memory (e.g., Burgess et al. 2007, Hasselmo & Eichenbaum 2005, Lisman 2005, McNaughton et al. 2006, Moser et al. 2008).

For the present purpose of exploring the role of the hippocampus in prediction, place fields provide a powerful way to measure what

Prospective coding: neural coding sequences that represent possible future events or event sequences

hippocampal cell assemblies are representing at any given moment in time. Once the receptive fields of multiple units have been mapped, it becomes possible to measure the ensemble activity to determine whether the neuronal population is representing the current position of the animal or a past or future position. That is, one can obtain a readout of what the animal's brain is representing. This is a major breakthrough because measurement of ensemble activity provides a direct way to peer into the rat's brain during navigation to determine what the hippocampus is representing without the need to infer what the animal is thinking.

Three further aspects of hippocampal response properties are relevant. First, spatial signals do not necessarily arise within the circuitry of the CA fields of the hippocampus. Inputs from the medial entorhinal cortex, as demonstrated by grid cells, are a likely source of spatial information relevant to navigation (Fyhn et al. 2004; see Moser et al. 2008 for review). The representational properties of hippocampal neurons should be considered as byproducts of larger circuit properties including interactions with cortex. Second, in paradigms where associations between nonspatial sources of information are demanded, hippocampal neurons respond in ways that suggest they also code aspects of the environment beyond location (Eichenbaum 2000). Consistent with this, the anatomic input streams to the hippocampus provide multiple sources of information with afferents from the lateral, in contrast to medial, entorhinal cortex, providing nonspatial information (Hargreaves et al. 2005; see also Lisman 2007). In this regard, while studies of rat navigation provide the richest source of information about hippocampal function, it is likely that the properties discussed here will generalize to other informational domains beyond spatial information conveyed to the hippocampus via external inputs (Eichenbaum 2004). Finally, place fields are not solely determined by the location of the animal but can respond to higher-order features such as where the animal has come from and where it will go to (Ferbinteanu & Shapiro 2003, Frank et al. 2000, Ji & Wilson

2008, Smith & Mizumori 2006, Wood et al. 2000; see Shapiro et al. 2006 for review). These properties suggest that there is substantial representational flexibility within hippocampal circuits.

Theta Phase Precession and Theta Sequences

In addition to exhibiting place-specific response firing at the level of individual neurons, hippocampal neurons as a population manifest remarkably regular oscillations during active navigation, referred to as theta oscillations. Six to eight times a second, the aggregate synaptic activity—measured by the local field potential—increases to a peak and then decreases. O'Keefe & Recce (1993) and Skaggs et al. (1996) observed a timing relationship between place cell firing and theta oscillations that provides an essential insight into the activity of hippocampal cell assemblies. They noted that as a rat approaches the location of a place field, the place cell fires late in relation to theta; as the animal leaves the critical location, the place cell fires early. Given that it typically takes 8 to 12 theta cycles for a rat to move through a place field, the timing of place cell firing appears to progress along the full phase of the theta oscillation—a process called theta phase precession.

What does the phenomenon of theta phase precession tell us about the structure of hippocampal cell assemblies? Recognizing that there are alternative possibilities (e.g., see Maurer & McNaughton 2007 for discussion), theta phase precession may be revealing the presence of firing sequences or chains across multiple neurons within a network. Using a computational model, Tsodyks and colleagues (1996) elegantly demonstrated how activity sequences could give rise to timing shifts observed in individual neurons. To conceptually illustrate how this possibility follows, consider the simple case where there exists only three neurons and only three locations that a rat transverses (**Figure 6**). Let's label the neurons A, B, and C. If the neurons were independent and the

animal ran through the three locations, one would observe sequential firing of neurons A, B, and C as the animal entered each location. Now consider the alternative, where A-B-C are linked in a chain such that when an animal enters the location coded by neuron A, it will fire, followed by B and C in succession. In this latter case, one would observe a more complex behavior when recording activity from the neurons. As an animal enters the location represented by A, neuron B will fire but will do so with a very brief delay (late from the relative perspective of neuron B firing). As the animal enters the location represented by B, neuron B will fire without delay (early from the relative perspective of neuron B firing). Thus, as the animal runs through the sequence of locations, recording from a single neuron will reveal a firing precession from late to early as the animal moves through the receptive field. An observer with access only to a single neuron sees theta phase precession.

Foster & Wilson (2007) recently demonstrated directly the presence of neuronal activity sequences time-locked to theta, appropriately calling them "theta sequences" (see also Dragoi & Buzsáki 2006, Itskov et al. 2008). In their experiment, they had rats run back and forth on a linear track; the investigators simultaneously recorded the place fields of many neurons. Typical of such paradigms, CA1 neurons exhibited place fields that temporally precessed in relation to theta. Critically, when activity patterns across multiple neurons were examined, Foster & Wilson (2007) observed sequences of firing that rapidly (<100 ms) recapitulated the sequential patterns of place cell firing experienced by the animal during navigation. Neurons that sequentially fired during multisecond navigation fired in rapid, sequential bursts as the animal moved through the place fields. The theta-phase precession observed at the level of individual cells could be accounted for by the sequences of activity across multiple neurons.

The functions of hippocampal theta-phase precession and theta sequences are presently unknown. The kind of rapid temporal prediction afforded by theta sequences might be useful to bridge processing events that unfold over hundreds of milliseconds or to compress the timescale of experiences to optimize plasticity (e.g., Buzsáki 2002, Itskov et al. 2008). They are almost certainly not, in isolation, responsible for the forms of prediction that span multiple event contingencies or anticipate distant upcoming events. Perhaps the lesson most relevant for our present purposes is to raise the possibility that networks of hippocampal neurons code predictive event sequences. That is, neurons within the cell assemblies do not simply fire based on inputs that specify a single location but rather are triggered by inputs to earlier locations that anticipate them (see also Lisman & Redish 2009 for discussion).

Evidence for Prospective Coding

The preceding sections review observations that suggest hippocampal circuits have the capacity to encode sequential associations. However, they do not necessarily reveal activity patterns used as prospective codes for planning or decision-making. All of the results concerned generation of spiking sequences triggered by entry or exit of a specific location, so the simplest interpretation is that they are stimulus bound. It is in this context that one can appreciate the importance of recent demonstrations that nonlocal activity sequences are spontaneously emitted independent of immediate cues arising from the environment (Csicsvari et al. 2007, Davidson et al. 2009, Diba & Buzsáki 2007, Foster & Wilson 2006, Johnson & Redish 2007, Karlsson & Frank 2009, Pastalkova et al. 2008).

The first example of such a phenomenon was reported during sharp-wave ripple events. Ripple events occur when theta oscillations are minimal, such as during resting moments and slow-wave sleep (Buzsáki 1989). At a circuit level, ripple events reflect the coordinated discharge of large numbers of pyramidal cells. Foster & Wilson (2006) recorded multiunit activity while rats ran back and forth on a linear track as described earlier for their documentation of theta sequences. However, unlike

the typical analysis of activity sequences that emerge during active navigation, they focused on the time periods after the rat had completed its lap and received a food reward. During these stop periods, structured activity sequences were observed that mimicked the navigation path, but in reverse order. These reverse replay events were common and preferentially occurred during sharp-wave ripple events.

Diba & Buzsáki (2007) observed a similar phenomenon but, critically, also observed ripple-linked sequences that evolved in forward order—"preplay" events. Taking advantage of the high percentage of place fields that were directionally selective, they were further able to quantify the number of forward preplay and reverse replay events that occurred at the beginning versus the end of the journey. Consistent with an anticipatory role in upcoming behavior, the vast majority (95%) of preplay events took place before the journey was initiated. Thus, hippocampal cell assemblies can emit prospectively oriented firing patterns prior to an event journey. These firing patterns anticipate upcoming work toward a reward as distinct from what just happened following reward delivery (**Figure 7**).

An unresolved question concerning the relation of preplay (and replay) events to prospective behavior surrounds their brevity. The activity sequences observed during ripple events, which last upwards of about 100 milliseconds, represent track positions spanning only 1–2 meters in length. Navigation in the wild rodent spans large environments with many distantly encountered choice points. There are likely other mechanisms at work, as it is difficult to imagine how an extended trajectory could be represented.

Davidson et al. (2009) provide evidence that brief activity sequences can be chained together to represent extended epochs. Their study deviated from the earlier work by using a longer track (∼10 meters) that included angled and hairpin turns. Despite the added complexity, there were no choice points; the activity sequences could be analyzed in reference to a linear path. Under such conditions, extended

sequences were observed that spanned the full 10-m length of the path. Detailed analysis of the ripple events showed that the extended sequences were played back across chains of discrete ripple events possibly mediated by reentrant processes between the hippocampus and entorhinal cortex (Davidson et al. 2009). This result reinforces the growing consensus that the hippocampus can represent nonlocal positions in the environment and further documents mechanisms that string together chains of sequences representing distant locations and extended paths.

How do such activity sequences relate to decision processes? This is perhaps the most critical open question as well as the most difficult to resolve. There are two challenges. The first challenge is that decision paradigms are inherently more complicated than those amenable to linear paths where cues and cue-sequences can be held constant. Second, decisions presumably occur during active navigation, when theta oscillations are dominant, making it difficult to link the preplay sequences observed during ripple events to choice behaviors. Providing a clue that decision processes are being engaged, rodents move slower during novel trajectories (Ji & Wilson 2008) and engage exploratory behaviors at choice junctions (Johnson & Redish 2007, Lisman & Redish 2009). Nonetheless, there are many unresolved questions about how activity sequences spanning theta oscillations and sharp-wave ripple events might contribute to choice decisions.

Important initial observations are provided by two recent studies that explored paradigms with choice points. The first study, reported by Johnson & Redish (2007), had rats navigate a maze with multiple T-junctions. A sophisticated behavioral paradigm allowed multiple choice-point locations to be probed for nonlocal activity patterns. The investigators recorded from the dorsal CA3 region and observed prospective activity sequences that aligned to theta oscillations, although the sweeps showed evidence for spanning multiple theta cycles. Most interestingly, there was a tendency for the activity sequences to sweep forward down the

Reverse replay:
activity sequences that repeat past events but in reverse order (experience of A-B-C leads to replay sequence C-B-A)

alternative paths at the choice points. Although these nonlocal sweeps of activity have yet to be linked to the animal's behavioral decision, they provide intriguing evidence that hippocampal cell assemblies can represent alternative paths during navigation, including entry into routes ultimately not taken by the animal.

Pastalkova et al. (2008) provide the most compelling link to date between spontaneous hippocampal activity and choice behavior. In their study, rats alternated arms through a figure-eight maze. Prior to initiating each journey, the rats ran on a wheel, creating an extended delay. Alternation under these delay conditions was dependent on intact hippocampal function as demonstrated using bilateral lidocaine injections. Multiunit activity recorded from the intact hippocampus during the delay period revealed remarkably robust spontaneous firing patterns. In aggregate, the cells showing place fields were more active during wheel running than during actual navigation. Such an observation reinforces the point that spontaneous emission of nonlocal activity reflects a prominent component of hippocampal physiology. Second, the activity of several units correlated with the eventual choice of the animal (left versus right turn) and also predicted error trials. Predictive firing patterns were most prevalent during the earliest periods of wheel running, ten seconds or more before the decisions were made. An open question is to what extent the wheel running contributed to the observation of activity sequences. It remains possible that the predictive signals observed by Pastalkova et al. (2008) are an illusion of active navigation induced by wheel running. These results are compelling because they reveal that spontaneous hippocampal activity predicts future behavior on a task demonstrated to be dependent on intact hippocampal function.

A HIPPOCAMPAL PREDICTION MODEL

Findings reviewed above suggest that (*a*) the hippocampal-cortical system is active when people envision the future, (*b*) human amnesia

is often accompanied by deficits in imagining the future, and (*c*) activity patterns in the rat hippocampus reflect both preplay and replay of event sequences. In the following section, a provisional model is provided that suggests how the observed prospective coding sequences in the hippocampus might contribute to future-oriented thinking. The proposal is in the spirit of Buzsáki (2005), who outlines a possible relationship between hippocampal theta sequences observed in rats and the human capacity for memory recall. The present model explores the question of what relationship, if any, exists between the behavior of the hippocampal cell assemblies described above and the ability in humans to think flexibly about the future. The model can be summarized as follows:

1. Experiences are characterized by repeated and novel sequences. Through some form of Hebbian plasticity, short spans of novel event sequences are linked together through modification of synaptic strengths.

2. Hippocampal cell assemblies have the capacity to replay and preplay event sequences when appropriately cued (such as when triggered by a related input).

3. Extended event sequences can be produced by chaining together multiple, shorter sequences. In its most basic form, the terminating event of one sequence might serve as the beginning trigger for another. The mechanisms of this chaining are presently unclear and may involve reentrant processes between the hippocampus and cortex. As a result of this process, temporally extended complex event sequences will be produced that span many theta oscillations or ripple events.

4. Sequences may also be triggered by extremely weak cues or through purely spontaneous processes. Constraints from the environment via cortical inputs and the current state of the hippocampal cell assemblies presumably bias which sequences are produced. Yet, the process is expected to be somewhat stochastic, and

thus novel combinations of sequences will chain together to yield de novo extended sequences that represent novel events.

Figure 8 diagrams the main properties of the model in the context of Tolman's classic study of shock avoidance (Tolman & Gleitman 1949). The model proposes that sequences of learned associations can be replayed in novel combinations. This model illustrates an important difference between the current proposal and traditional models of memory. The hippocampal-cortical system is postulated to generate activity sequences that, while constrained by past events, fundamentally reflect novel predictions. This property, in an elaborated form, may have allowed our distant ancestors to evolve from primarily trial-and-error learners to mental explorers who solve problems by imagining the alternatives.

The Importance of Randomness

A central feature of the model is that a certain level of randomness is explicitly required for the process to unfold properly and flexibly. Given weak inputs, there should be a tendency for the circuits to chain together similar sequences, but the exact chains will vary from moment-to-moment and trial-to-trial. That is, the activity patterns emitted by the circuit should be constrained, but not dictated, by the past. Intrinsic properties or small differences in cortical inputs might contribute to the emergence of chaotic activity fluctuations (see Levy et al. 2005 for relevant discussion). As a result, rare complex event sequences should periodically emerge that allow internal exploration of radically different routes than have actually been experienced. It is this hypothesized feature of the circuit that may have allowed Tolman's rats to navigate using a shortcut (Tolman et al. 1946). In their expanded forms, such internal explorations may also contribute to human creativity and imagination (see Campbell 1960).

The notion that variability can be a critical feature of a neural circuit has precedent. A striking example is found in songbird learning, where young finches produce randomly patterned songs akin to human babbling (Aronov et al. 2008). Recent ablation studies have demonstrated that a specific structure within the finche forebrain—lateral magnocellular nucleus of the nidopallium (LMAN)—is required to produce variability. Adult, stereotypic behaviors do not require LMAN. Although it is presently unexplored, the model predicts that the architecture of the hippocampal-cortical system will be shown to have similar properties that promote some level of stochastic behavior. All sequence alternatives and chains are surely not equiprobable. Nonetheless, uncommon chains linked by weak associations or even jumps between previously linked sequences are expected to emerge with some frequency.

Linking Rodent Navigation to Flexible Human Cognition

The model outlined above is based largely on physiological properties observed during rodent navigation. A critical question is whether the response properties observed in the rodent generalize to the human, and if so, how they are expanded to support cognitive abilities that are elaborated in the human. Human hippocampal recordings obtained during surgical cases show response properties that parallel rodent recordings, which suggests that the basic circuitry is more similar than different. For example, single-unit recordings in people reveal place fields similar to those observed in rodent (Ekstrom et al. 2003). Also similar to rodents, theta oscillations are observed in the human temporal lobe including the hippocampus during navigation of virtual environments (Ekstrom et al. 2005, Kahana et al. 1999). Finally, physiological response properties in the hippocampus and surrounding cortex identify distinct populations of neurons that likely reflect the differences between pyramidal and interneurons described in animals models (Viskontas et al. 2007).

The presence of characteristically similar firing patterns in the rat and human hippocampus supports the possibility that our ability to

think about the future may extend from the same circuit properties that have been studied in the rodent. This does not mean that rats and humans have similar capacities—the question at hand is whether preplay and replay observed in the rodent provide insight into mechanisms that are co-opted to support more complex cognitive abilities in people.

Relevant to this question, Gelbard-Sagiv et al. (2008) provide evidence that human hippocampal neurons show spontaneous replay events (**Figure 9**). In their study, they focused on neurons exhibiting stimulus-preferential responses in the hippocampus and entorhinal cortex. Subjects first viewed video clips that depicted short episodes of famous people and characters. For example, one clip was of the actor Tom Cruise being interviewed by the talk-show host Oprah Winfrey; another clip depicted a scene from the popular television show *The Simpsons*. Many neurons responded strongly to only one or a few of the episodes. Subjects were then asked to freely recall the video clips with no stimulus cues provided. Remarkably, units that selectively fired while watching the videos were again selectively active when the clips were recalled. These results demonstrate that hippocampal neurons encoding episodes are active during the mental representation of those episodes. Going beyond what is possible to probe in the rodent, Gelbard-Sagiv et al. (2008) were further able to link the hippocampal activity to conscious perception. During neural replay, subjects reported vivid re-experiences of the originally encoded events. These findings add weight to the possibility that the hippocampal-cortical circuitry observed in the rodent is preserved in the human and put toward considerably more elaborated use.

Relationship to Prior Frameworks

The idea that the hippocampal-cortical system is important to future-oriented thinking and imagination has received growing interest over the past decade. Many contemporary proposals have their antecedents in the seminal work of Edward Tolman, David Ingvar, and Endel Tulving discussed above. Among recent proposals, Suddendorf & Corballis (1997, 2007) thoughtfully considered the possibility that memory systems evolved to aid constructive aspects of representing the future. They noted that "the real importance of mental time travel applies to travel into the future rather than the past; that is, we predominantly stand in the present facing the future rather than looking back to the past." They further suggested that "the constructive element in episodic recall is adaptive in that it underlies our ability to imagine possible scenarios rather than the actual ones." Schacter & Addis (2007) echo a similar perspective: "Since the future is not an exact replica of the past, simulation of future episodes may require a system that can draw on the past in a manner that flexibly extracts and recombines elements of previous experiences—a constructive rather than a reproductive system."

The model proposed above is consistent with these earlier themes and suggests specific circuit mechanisms linked to the hippocampus that may contribute to these functions. At the center of this model is the idea that the adaptive function of the hippocampal-cortical system is the capture of sequential associations and relations that define events because these sequences can be reassembled into novel combinations that anticipate and simulate future events. The intent of the model is to provide a framework to link the findings in rodent studies of hippocampal physiology with the growing body of data on the homologous system in humans.

Lisman & Redish (2009) previously discussed the possibility of a relation between rodent hippocampal physiology and constructive processes, but also noted that no result to date has provided direct evidence that the hippocampus emits activity sequences that are functional recombinations of past events. They further noted that traditional memory tasks relying on simple expectations do not require hippocampal integrity. Rather, an intact hippocampus becomes necessary as more complex

changes in contingencies are added, which suggests that flexible forms of sequence generation are likely present even though empirical data are so far lacking. Cohen & Eichenbaum (e.g., 1993) have long emphasized the particular role of the hippocampus in establishing novel associations that allow for the flexible expression of memory, referring to them as relational associations. Thus, there are many reasons to postulate that the two sets of observations—those from rat physiology and those from humans—may be linked.

A BRIEF COMMENT ON THE ROLE OF SLEEP AND IDLE MOMENTS

To this point, activity sequences that occur just prior to upcoming events have been the focus of discussion. However, it is also possible that constructed event sequences are adaptive independent of a targeted decision. That is, even without a specific task goal, spontaneous event sequences may result in adaptive, novel representations that are stored for later use (Bar 2007). It is difficult to speculate on the specific nature of these derived representations, but some possibilities seem more likely than others. For example, derived sequences that link temporally distinct episodes may be adaptive because they create new relations that are not present at the time of encoding.

Paradigms requiring judgments about stimuli that are encoded across separate presentations provide a nice illustration of the value of recoding. One such example is the transitive inference paradigm. During training, a subject learns that A is better than B, B is better than C, C is better than D, and D is better than E. Then, during the critical probe trial, the subject is asked if B is better than D. The relations across the stimuli suggest the answer is yes even though B itself was never simultaneously presented with D. Of interest, lesions to the hippocampal region in rat (Dusek & Eichenbaum 1997), monkey (Buckmaster et al. 2004), and human (Smith & Squire 2005)

impair performance on transitive inference tests.[2] It is also interesting to note the similarities between this form of inference task and the original paradigm studied by Tolman (**Figures 2** and **7**). Both require decisions that are based on novel relations drawn from multiple past events. Although it is possible that transitive inferences rely on the retrieval of the exact encoded events and then a secondary process of comparison, it is also possible that the needed relations are derived spontaneously in advance of their use.

Ellenbogen and colleagues (2007) provide evidence that such relations emerge spontaneously. In their study, subjects studied a series of abstract picture pairs, one of which was arbitrarily designated the correct item within the pair. The pairs followed a hierarchy as described above but were presented in random order so that the hierarchy was difficult to discern. The task was further made challenging by training the initial pairs to a high, but not ceiling, level of performance. Under these conditions,[2] they observed that subjects performed poorly on transitive judgments shortly after studying the pairs (20-minute delay). However, the subjects were significantly better following 12- and 24-hour intervals. And, if sleep intervened, they were particularly adept at succeeding on the most difficult judgments that spanned multiple event pairs (e.g., B versus E). Although further study will be required to extend this observation, the findings suggest that certain relational links emerge gradually following learning.

Spontaneous activity events during idle moments may function to build a repository of derived information that is considerably richer

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[2] Studies of transitive inference in amnesic participants also show impairment on the acquisition of the initial premise pairs (B-C, C-D, etc.), suggesting that people use hippocampal-dependent processes even for simple learning situations (Smith & Squire 2005). Performance of normal participants in transitive inference paradigms is influenced by differences in the awareness level of the participants during training, whether premise pairs are learned to ceiling and whether premise pairs are presented hierarchically or in random order.

than that captured at the time of encoding. This process can be called "prospective consolidation" to make clear that the stored representations are recoded, chunked, or otherwise derived forms of the original experiences. The stored representations are not expected to be replicas of the original experiences but rather derived representations that extract relations among past events in prospectively useful forms. Relevant to this possibility, hippocampal replay events have been repeatedly documented during sleep, in particular slow-wave sleep when sharp-wave ripple events are prominent. Pavlides & Winson (1989) first noted that if a rat spends extended awake time exploring a particular location, the firing rates of the associated place cells increase during the next period of sleep. In a compelling extension of this observation, Wilson & McNaughton (1994) demonstrated that cell pairs showing correlated firing during awake navigation replay their correlated firing patterns during sleep and further that the correlated events occur preferentially during sharp-wave ripple events. Sleep replay involves coordinated reactivation across the cortex and hippocampus (Euston et al. 2007, Ji & Wilson 2007) and preserves the temporal order of the original firing patterns (Lee & Wilson 2002, Skaggs & McNaughton 1996). In a recent analysis, O'Neill et al. (2008) observed that correlated replay during sleep mimics the frequency of the rat's awake experiences.

Such findings provide strong evidence that activity sequences experienced during awake behavior are replayed during sleep. The leading hypothesis about the functional role of sleep replay is that it participates in consolidating long-lasting representations of the day's events (for relevant reviews see Maquet 2001, Walker & Stickgold 2006). An implication of the hippocampal prediction model presented above is that spontaneous activity events during sleep may be important to prospective consolidation. That is, although methods to date have identified replay sequences that replicate earlier events, it may also be the case that novel sequences that emerge spontaneously during sleep form new links between episodes.

Evolution may have co-opted periods of sleep and idle moments to precompute adaptive information. An interesting topic for future investigation will be to reexamine spontaneous activity events occurring during sleep and rest states to determine if novel sequences are emitted that can be shown to be adaptive and predict upcoming decisions.

In its most elaborated form, offline processing in humans has been proposed to facilitate problem solving (Stickgold 2005). Support comes from insight learning, where an unexpected, novel relationship must be discovered to solve a problem. In an elegant study, Wagner et al. (2004) presented subjects with an arithmetic puzzle that required a series of digits to be sequentially transformed into a new pattern. Unbeknownst to the subjects, there was a hidden rule that would allow them to complete the transformation rapidly. The majority of subjects never discovered the rule. However, allowing the subjects to sleep on the problem more than doubled their chances of gaining insight into the shortcut. Control studies established that it was not sleep per se that facilitated insight, but rather specifically sleep following training exposure to the task. Replay of hippocampal cell assemblies during the intervening sleep may have facilitated a qualitative restructuring of the memory representation into a prospectively adaptive form.

CONCLUSIONS

The hippocampus and associated cortical structures are active when people envision future events, and studies of amnesic patients suggest that damage to the hippocampal region impairs this ability. As rodents navigate, the hippocampus spontaneously emits forward-oriented activity sequences that predict future choices under certain conditions. These findings collectively raise the possibility that a core function of the hippocampal-cortical system is to use remnants of past experiences to make predictions about upcoming events.

Eichenbaum, Cohen, and colleagues have previously emphasized the importance

of the hippocampus for establishing novel associations that allow for the flexible expression of memory, referred to as relational associations (e.g., Cohen & Eichenbaum 1993). As one example, Eichenbaum et al. (1990) demonstrated that rats fail to navigate novel paths following hippocampal lesions, consistent with an important role for the hippocampus in solving Tolman-type paradigms (also Dusek & Eichenbaum 1997, Eichenbaum & Fortin 2009).

In this review, the idea of flexible expression of memory was extended to the possibility that a fundamental role of the hippocampal-cortical system is to provide building blocks, based on past experiences, that can be strung together in novel combinations to predict and mentally explore upcoming events (e.g., Buckner & Carroll 2007, Lisman & Redish 2009, Schacter & Addis 2007). The shift from a retrospectively oriented model of hippocampal function to a prospectively oriented model pushes the field to consider novel paradigms and theoretical orientations, including those that can link observations in rodents, monkeys, and humans. It will be interesting to develop human testing paradigms, perhaps based on navigation and interactions in virtual environments, that create situations where moments of prediction can be isolated and manipulated.

To paraphrase Aspinwall (2005), future-oriented thinking—our plans, goals, daydreams, worries, predictions, and the various scenarios through which these potential outcomes may or may not be realized—is the stuff of mental life. Humans can imagine far into the future and spend a great deal of time engaged in such thoughts. To gain insight into underlying mechanisms of such abilities, it will be necessary to rely heavily on animal models where the neural circuitry of human-like processes, or their proto-forms, can be explored. The present review provides a beginning framework to integrate recent observations from rodent physiology and the human abilities to predict and imagine the future.

DISCLOSURE STATEMENT

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

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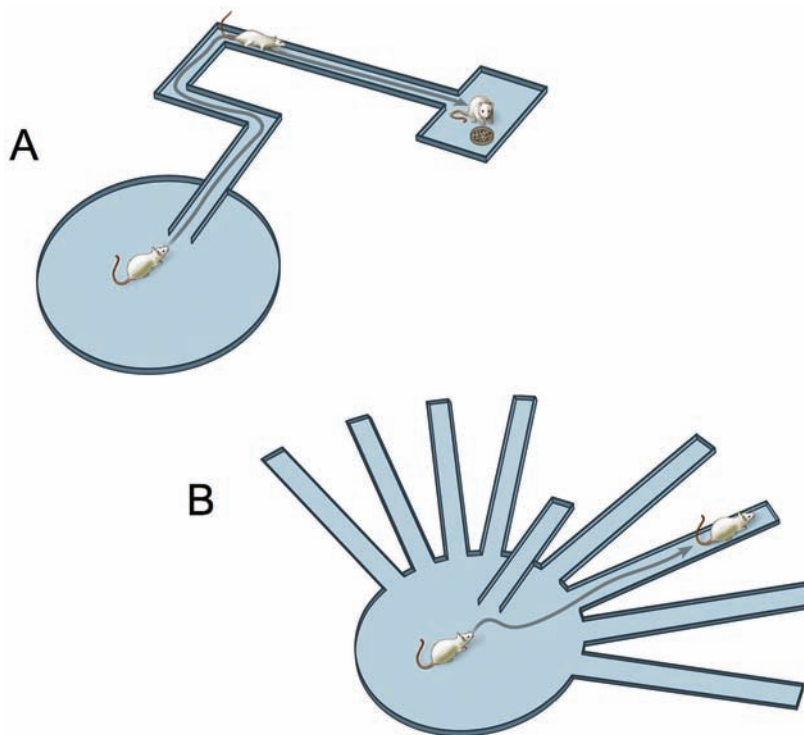
Figure 1

Edward Tolman's classic paradigms demonstrate that rats can use past experience to make de novo predictions. When confronted with a barrier that prevents a learned route, rats will often take a novel direct path—a shortcut—to the food reward. Tolman illustrated this behavior by first training the animals on a circuitous route to a food reward (*A*). Then, following training during a single critical trial, the learned path was blocked. The animals tended to take the angled path that could lead directly to the food reward. Adapted from Tolman et al. (1946).
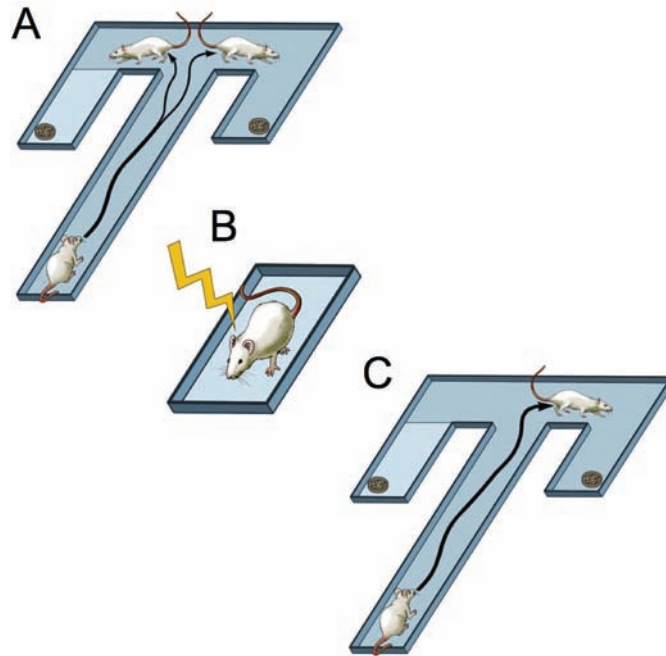
Figure 2

Rats were trained to forage freely in an environment (*A*). After being foot shocked in a chamber that was associated with one of the chamber's endpoints (*B*), rats avoided the path in the maze that led to the chamber (*C*) even though they had never actually experienced the aversive chamber when foraging. Adapted from Tolman & Gleitman (1949).
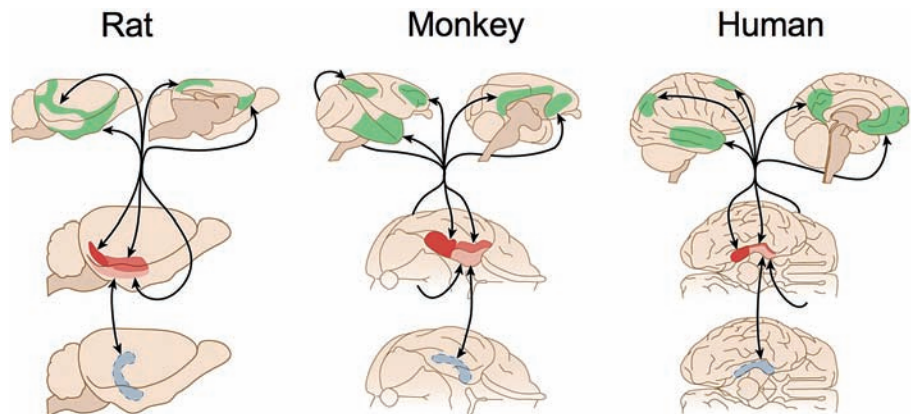
Figure 3

The hippocampal-cortical system in rat, monkey, and human. In each species, the hippocampus proper (*blue*) projects to the entorhinal cortex (*pink*). The entorhinal cortex projects to the perirhinal (*red*) and parahippocampal (postrhinal in rat) (*orange*) cortices that, in turn, project to widespread regions of cortex that include the posterior midline, lateral parietal cortex, and medial prefrontal cortex in monkey and human. The general architecture of the hippocampal region is preserved across species. Estimates of rat and monkey cortical projections redrawn from Eichenbaum (2000). Estimates of human cortical projects are based on Vincent et al. (2006) and Kahn et al. (2008).
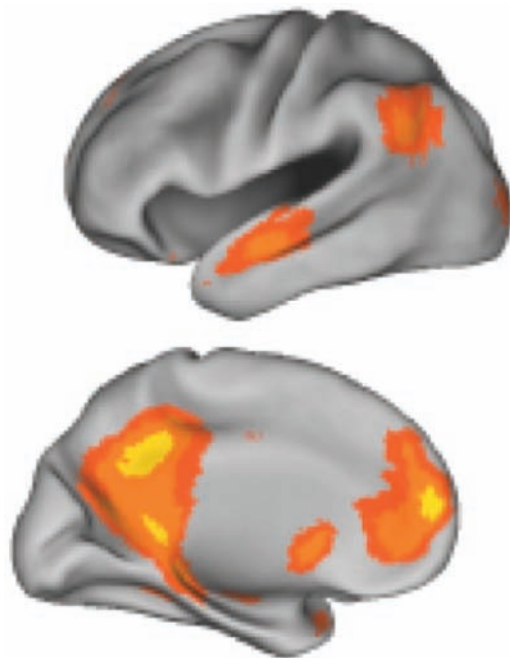
Figure 4

Autobiographical memory retrieval and envisioning the future both activate the hippocampal-cortical system. Cortical activation during a functional MRI task that targets imagining the future is shown for a group of subjects from Addis et al. (2007). Note the overlap between the regions active and the hippocampal-cortical system as diagrammed in **Figure 3**. The representation is a left hemisphere surface based on the Population-Average, Landmark- and Surface-based (PALS) atlas of Van Essen (2005).
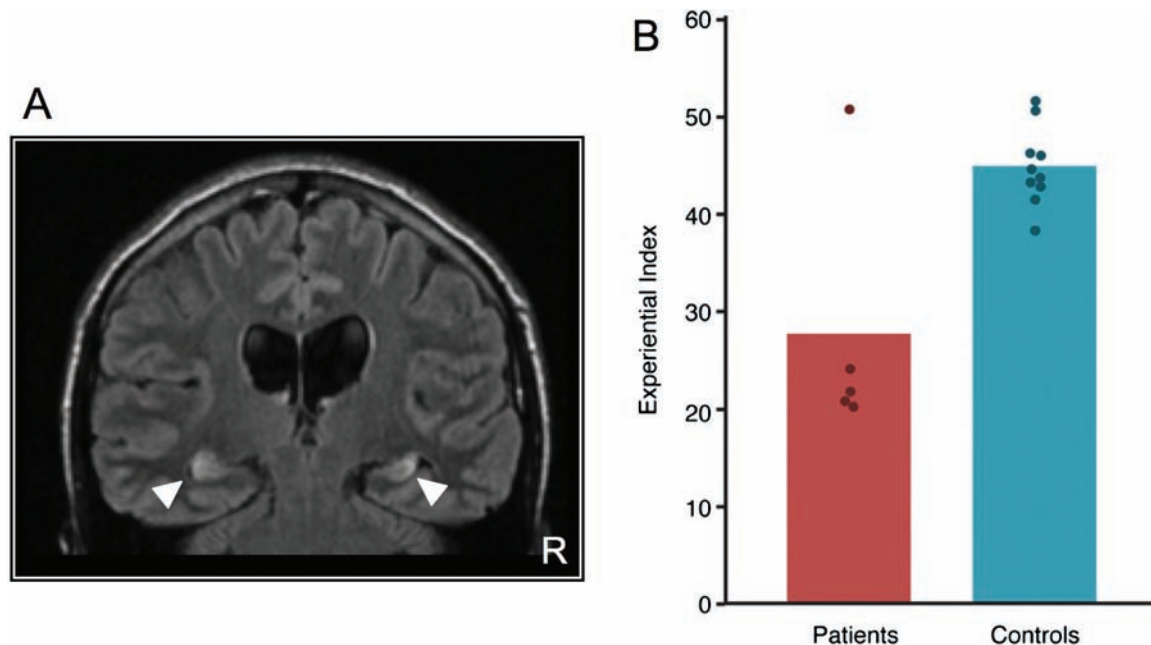
Figure 5

Patients with brain lesions that include the hippocampus are impaired at envisioning novel scenarios. (*A*) An example of a 24-year-old male patient (P03) studied by Hassabis et al. (2007). The patient's MRI scan showed bilateral hippocampal damage following limbic encephalitis (*arrows*), and he had significant autobiographical memory deficits. (*B*) Data plotted for five amnesic patients, including P03, on a test of their ability to imagine novel scenarios (e.g., "Imagine you are standing in the main hall of a museum containing many exhibits"). The plotted index, referred to as the experiential index, reflects the overall richness of the imagined experience. Note that the patients provide relatively sparse descriptions of imagined scenarios that are devoid of the elaborate and detailed content typical of normal subjects. Adapted from data reported by Hassabis et al. (2007).
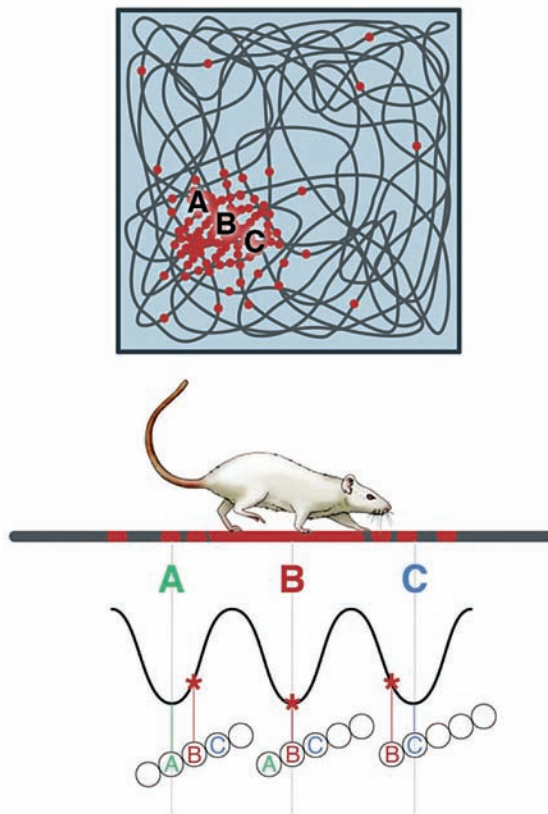
Figure 6

Place fields and theta phase precession provide insight into hippocampal function. (*Top*) A schematic diagram of a rat's path through a square environment. The view is from above, and the black path reflects the path of a freely foraging rat. Each time the rat transverses the bottom left, the place cell fires (*red dots*). The preferential firing in the specific location is the place field. (*Bottom*) Theta phase precession is illustrated for the rat running through the place field. The place field is represented by the red area under the rat's position, and locations A, B, and C are demarcated. The red dots reflect the firing of a single cell labeled B, and the oscillating line schematically illustrates theta. As the rat approaches the place field, the B cell fires relatively late in theta. As the rat moves through the field, the cell fires earlier and earlier in relation to theta. This property, known as theta phase precession, can be explained if the cell is embedded within firing sequences among multiple cells, some of which anticipate the upcoming location. The cell sequences are illustrated at the bottom of the panel as chains of circles with the A, B, and C cells labeled.
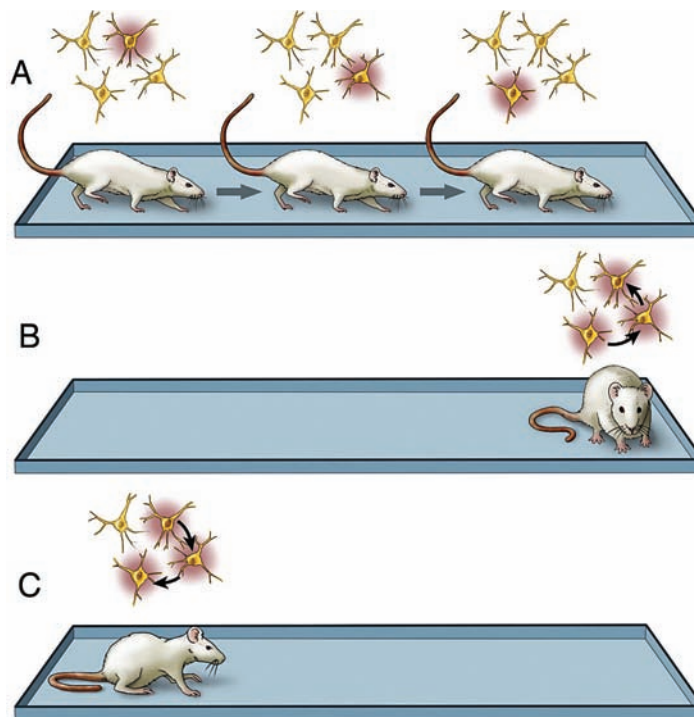
Figure 7

Replay and preplay sequences in the hippocampus. (*A*) As rats navigate, multiple place cells fire in
sequence, reflecting the changing location of the animal. When multiple units are recorded, the place of
the rat can be accurately estimated based on the firing pattern among the cells. (*B*) When rats stop follow-
ing reward delivery, place fields sometimes spontaneously fire in reverse order to their original sequence.
These firing events are referred to as "reverse replay" sequences and occur during sharp-wave ripple events
at the ends of reinforced journeys (Foster & Wilson 2006). (*C*) Anticipatory activity sequences are also
observed during sharp-wave ripple events. "Preplay" sequences occur almost exclusively at the beginning of
journeys and anticipate the upcoming sequential positions of the animal (Diba & Buzsáki 2007).
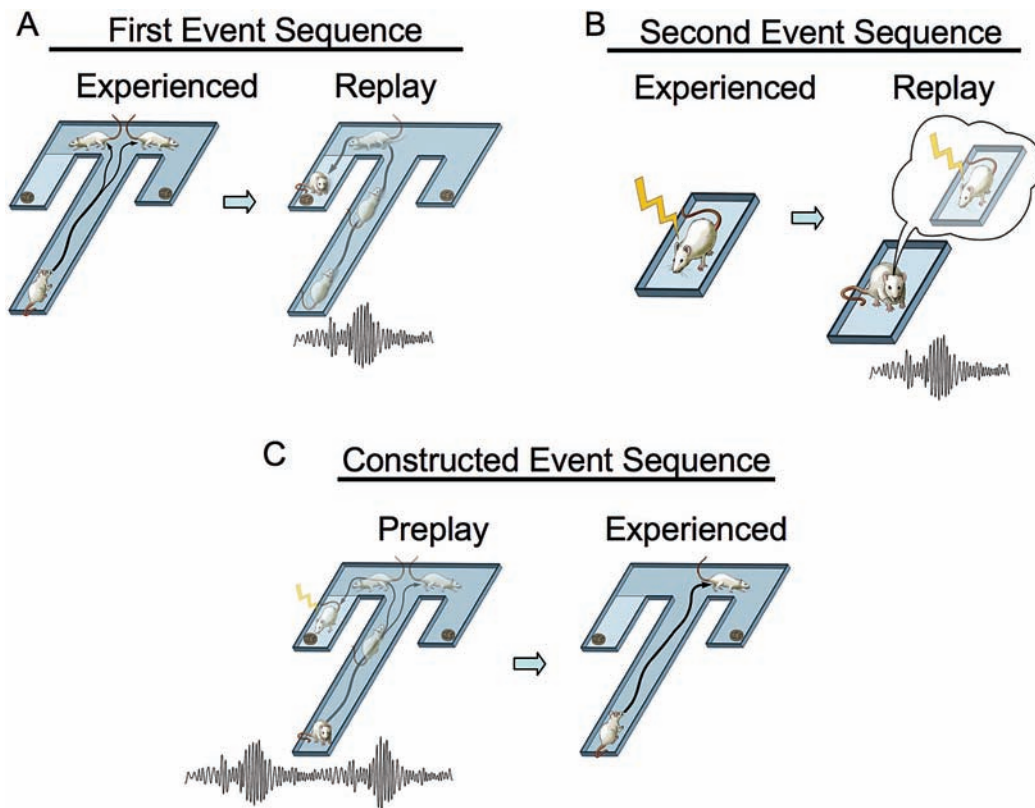
Figure 8

The hippocampal prediction model. Diagrams show how replay and preplay activity within hippocampal cell assemblies might allow for construction of de novo predictions. The model is applied to the paradigm studied by Tolman and Gleitman (1949) for illustrative purposes, but the framework is meant to be quite general and extend to humans in an elaborated form. (*A*) Activity sequences associated with experienced events are captured and can be replayed. The sequences are consolidated through replay that occurs at the end of journeys during sharp-wave ripple events or perhaps at other times. (*B*) Sequences are consolidated for distinct, isolated events using similar mechanisms. Presumably as exploration is undertaken, numerous sequences associated with experienced events are captured and available to future needs. (*C*) By chaining together multiple past event sequences in constructed combinations, complex event sequences that represent novel predictions emerge. In this instance, by chaining together the past experience of traveling down the left arm and the distinct experience of being shocked, the rat presumably predicts the aversive event and turns right to avoid it. Note that this is a de novo prediction because the rat never experienced turning left and receiving a shock.
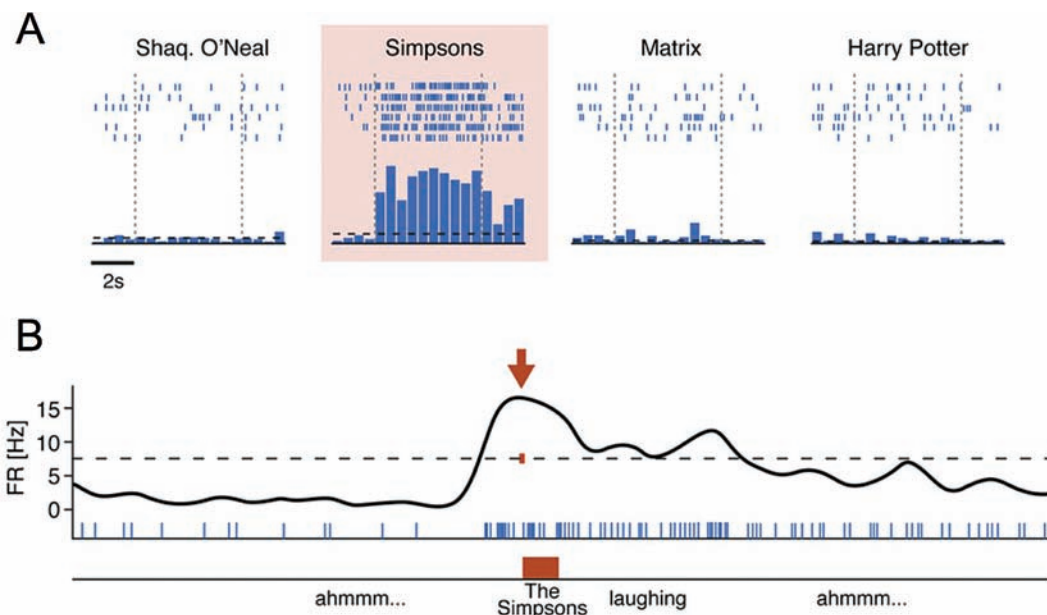
Figure 9

Human hippocampal cells exhibit spontaneous activity when episodes are imagined. (*A*) Single-unit recordings from an entorhinal cortex cell while the patient viewed video episodes of Shaquille O'Neal, *The Simpsons* cartoon, and movie scenes from *The Matrix* and *Harry Potter*. The small dash marks represent an action potential, with each line representing a different epoch of stimulus viewing. The histogram below represents the summed action potentials across the viewing epochs. Note that this particular cell is selectively responsive when the Simpsons cartoon is viewed. (*B*) Single-unit recordings from the same cell while the participant freely recalled the viewed epochs from memory. The words below represent the utterances of the patient as he reported what he was recalling. The spontaneous activity increase in the cell corresponded to the report of the patient imagining the episode of *The Simpsons*, which suggests that the hippocampal-cortical system is involved in replay. Adapted from Gelbard-Sagiv et al. (2008).

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Contents

Errata

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