

Hippocampal and Cortical Place Cell Plasticity: Implications for Episodic Memory

Loren M. Frank,^{1*} Emery N. Brown,^{2,3} and Garrett B. Stanley^{3,4}

ABSTRACT: In humans, the hippocampus is essential for storing episodic memories. These event memories require the rapid storage of novel associations, but little is known about the cellular correlates of such rapid plasticity. We studied patterns of activity and plasticity in the CA1 region of the hippocampus and in anatomically adjacent cortical regions as rats explored a novel arm of a maze to identify the neural correlates of hippocampally dependent memory formation. We found that hippocampal place fields exhibited three phenomena that may have direct relevance to the encoding of episodic memories: (1) very rapid plasticity upon exposure to the new environment, (2) instability in representations formed after short periods of exploration, and (3) a dissociation between the stability of a hippocampal representation and the apparent familiarity of a location. In contrast, cortical regions showed less dramatic changes. Taken together, these findings suggest that hippocampal activity undergoes a period of rapid reorganization during the encoding of novel information, and that even after this reorganization is complete, areas outside the hippocampus have not yet formed stable memories. © 2006 Wiley-Liss, Inc.

KEY WORDS: CA1; plasticity; learning; memory; encoding

INTRODUCTION

In humans, damage to the hippocampal formation results in a profound impairment in the ability to store new memories for events, known as episodic memories (Scoville and Milner, 1957; Squire, 1982). In rodents, these same structures play an essential role in the animals' abilities to learn about and remember complex associations (Cohen and Eichenbaum, 1993; Rudy and Sutherland, 1995). This is particularly apparent when the animal must encode the relationships among locations in its environment, as hippocampal damage causes profound impairments in these spatial tasks (O'Keefe and Nadel, 1978; Aggleton et al., 1986; Jarrard, 1993). Both episodic memory and spatial memory require storage of the relationships among a number of stimuli: an episode can be thought of as the relationship among a set of people, places, and things

over some period of time, while a place can be defined by the relationships among the various types of sensory information available at a location as well the relationships among that location and other locations in the environment (Eichenbaum et al., 1999). At the same time, it is important to note that a full account of episodic memories includes the fact that they allow for the recall of previous events and in particular one's own role in past occurrences. Episodic memory is therefore defined by at least one prominent author as requiring self-awareness and a sense of time (Tulving, 2002). Extending this definition to nonhuman species is difficult, as it seems unlikely that rodents, for example, are self-aware, and one may legitimately ask whether human episodic memories represent a fundamentally different sort of representation from that found in other animals. While full-fledged episodic memories are very unlikely to be present in rodents, it has been shown that rodents can remember conjunctions that are qualitatively similar to those present in episodic memories (Day et al., 2003). In our view and the view of many others, the anatomical and functional parallels across species argue that, while episodic memories clearly involve types of information (e.g., self-awareness) that are probably not available to the rodent hippocampus, the hippocampus and associated regions nonetheless carry out a qualitatively similar computation across species (O'Keefe and Nadel, 1978; Squire, 1992). Here, we focus on the physiological characteristics associated with two related elements of the hippocampal computation: the nature of the representation stored and the rapidity of storage.

THE HIPPOCAMPAL REPRESENTATION OF SPACE

As mentioned earlier, the hippocampus appears to be essential for storing representations involving relationships among multiple items (Eichenbaum and Cohen, 2001). In the case of memories for locations, each place is defined by a unique combination of cues. As an example, each room in a house may contain walls, a floor, furniture, and so on, but we are able to create a unique memory for each room we have visited, including representations of both their contents and their layout. We must therefore store information about the types of furniture, the color of the walls, etc., as well as information about the relative locations of the different pieces of furniture, the walls, etc. At the

¹ Department of Physiology, Keck Center for Integrative Neuroscience, University of California, San Francisco, San Francisco, California; ² Department of Brain and Cognitive Sciences, MIT, Cambridge, Massachusetts; ³ Harvard-MIT Division of Health Sciences and Technology, Cambridge, Massachusetts; ⁴ Division of Engineering and Applied Sciences, Harvard University, Cambridge, Massachusetts

Grant sponsor: NIMH; Grant number: MH59733; Grant sponsor: NIH/NIDA; Grant number: R01 DA015644; Grant sponsors: McKnight Foundation, John Merck Foundation, and Alfred P. Sloan Foundation; Grant sponsor: Whitaker Foundation; Grant number: RG-01-0087; Grant sponsor: Whitehall Foundation; Grant number: 2003-12-42-APL.

*Correspondence to: Loren M. Frank, S-859, 513 Parnassus Ave., San Francisco, CA 94143, USA. E-mail: loren@phy.ucsf.edu

Accepted for publication 10 June 2006

DOI 10.1002/hipo.20200

Published online 18 August 2006 in Wiley InterScience (www.interscience.wiley.com).

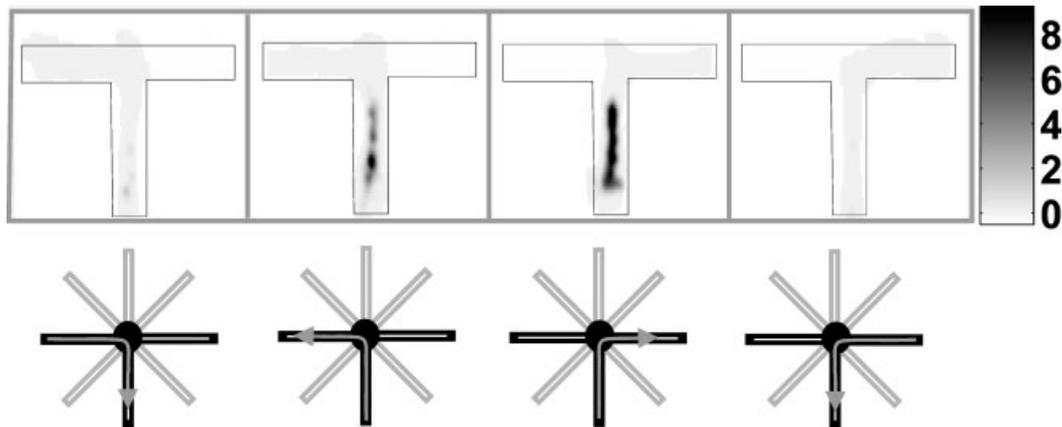


FIGURE 1. An example of directionality and prospective coding from a CA1 neuron. The grayscale colorbar indicates the firing rate of the neuron in Hz, and each of the four panels shows the rate along one path that the animal traversed through the T-maze envi-

ronment, depicted in the bottom row of drawings. This neuron was active only on outbound runs from the center arm, and fired more when the animal was heading toward the right arm than toward the left arm.

level of individual neurons, the hippocampal circuit must therefore process this information to create a unique representation of each place. As a result, individual hippocampal neurons (place cells) come to respond selectively in restricted regions of space (O'Keefe and Dostrovsky, 1971; Best et al., 2001; Ekstrom et al., 2003), and the ensemble activity of place cells accurately represents the animal's location in the environment (Wilson and McNaughton, 1993; Brown et al., 1998). These place-specific responses are present immediately upon introduction to a previously explored place (Mehta et al., 1997), suggesting that place cell activity in familiar environments represents the retrieval of a memory for that environment (Kentros et al., 1998).

In addition, individual place cells can respond not only to a unique conjunction of cues defining a location, but also to the relationships among locations. This can be most easily seen in linear environments, where it is possible to examine activity according to the path the animal is on. In these situations, most place cells show directionally biased firing, where the firing rate of the cell differs substantially depending on the animal's direction of motion (McNaughton et al., 1983; Muller et al., 1994). We and others have also shown that place cells can fire differently in the same location and direction of motion, depending on the animal's past or intended future position, providing retrospective or prospective information that could be used to guide behavior (Frank et al., 2000; Wood et al., 2000; Ferbinteanu and Shapiro, 2003). An example of a CA1 place cell, showing both directional and prospective activity, is shown in Figure 1. These patterns of activity suggest that place cells are part of a representation that includes spatial and perhaps temporal relationships.

STORAGE OF NEW REPRESENTATIONS IN THE HIPPOCAMPUS

Episodes generally occur only once, and yet we are capable of remembering strings of events across minutes or hours. The sys-

tem must therefore be able to store new information quickly to avoid excessive interference between temporally adjacent experiences. The idea that the hippocampus is essential for this rapid storage of new information is supported by studies in rats showing that blocking hippocampal activity or plasticity impairs one-trial learning (Morris, 1996; Izquierdo et al., 1997; Day et al., 2003). Further support for hippocampal involvement in the initial stages of memory formation comes from consolidation experiments, where investigators interfere with hippocampal processing after learning. In contextual fear conditioning, for example, hippocampal lesions made immediately after learning cause a profound deficit, but lesions 28 days after learning had no effect (Kim and Fanselow, 1992). Comparable effects have been seen in the social transmission of food preference task (Winocur et al., 2001), and conceptually similar findings have also been reported in a series of experiments testing the effects of focal infusions of pharmacological agents in the hippocampus and downstream structures (Jerusalinsky et al., 1992; Quillfeldt et al., 1996; Izquierdo and Medina, 1997; Izquierdo et al., 1997). These results support the hypothesis that the hippocampus is important for initial learning, but that other downstream structures may be able to "take over" for the hippocampus, once sufficient time has elapsed.

While it is clear that the hippocampus is essential for the rapid storage of new information, less is known about how the circuit constructs new memories. It is generally accepted that the storage of new memories is mediated by changes in synaptic strength, which result in changes in hippocampal activity (Morris et al., 1990), but the nature of those changes and their relationship to learning is not yet understood. In the context of spatial representations, investigators have begun to characterize the types of plasticity seen in both familiar and novel environments.

Here we focus on results from area CA1, the most commonly studied hippocampal subregion, and on adjacent cortical regions. Studies of CA1 place cell change in linear environments have shown that CA1 place fields shift and change shape in familiar environments (Mehta et al., 1997, 2000; Lee et al., 2004). Similarly, alterations in visual cues or environmental boundaries

in previously familiar environments can cause changes in CA1 place fields (Muller and Kubie, 1987; Bostock et al., 1991; Gothard et al., 1996, 2001). Detailed examinations of the time course of these changes have revealed that individual place fields can show large changes over the course of a few minutes of experience (Lever et al., 2002), suggesting that place field plasticity may provide a valuable model for studying rapid hippocampal encoding of new information.

Results from recordings of CA1 cells in entirely novel environments also indicate that place-related activity develops rapidly when animals are exposed to new places. Wilson and McNaughton (1993) reported that reconstructions of animals' positions from CA1 place cell data were more accurate once the animal had ~ 10 min of experience in the environment. These findings were interpreted to mean that CA1 place fields are initially disorganized, but become stable after sufficient experience in a new place, although our findings indicate that spatial selectivity is frequently present upon the first visit to a novel place. A similar time course for CA1 place cells was reported by Leutgeb et al. (2004), once again using 10-min time windows.

There is, to our knowledge, only one study that directly examined the formation of spatial representations in adjacent cortical regions. Recent results from recordings of the superficial entorhinal cortical (EC) "grid cells," which provide input to the hippocampus, have indicated that these cells are active in a grid-like pattern from the moment the animal enters a novel environment, although the pattern did not achieve complete stability until the animal had 10 min of experience in the place (Hafting et al., 2005). These grid-like patterns were very similar across different environments, however, suggesting that the superficial EC does not create a unique representation of each environment. However, the methodological tools used for previous place field formation analyses made it difficult to examine the rapid changes in place field structure, and so these results do not provide detailed pictures of the dynamics of the development of spatial representations.

ADAPTIVE METHODS FOR STUDYING PLACE CELL PLASTICITY

We have developed new analytical techniques to quantify the time course of neural receptive field development (Brown et al., 2001; Frank et al., 2002). These methods make it possible to accurately describe the time course of place field plasticity, and, more generally, allow the examination of the dynamics of learning-related neural activity in the brain. The adaptive framework explicitly models the firing rate of each neuron as a function of a set of covariates which can include not only the animal's position in space but also other variables, such as the time since the last spike. Mathematically, we have modeled the firing rate $\lambda(t|\theta_t, H_t)$ as $\lambda(t|\theta_t, H_t) = \lambda^S(x(t), \theta_t)\lambda^T(t - \zeta_t, \theta_t)$, where the spatial component $\lambda^S(x(t), \theta_t)$ is a function of the rat's position $x(t)$ at time t , and the temporal component $\lambda^T(t - \zeta_t, \theta_t)$ is a function of the time since the last spike. The temporal component models the history dependence of the spike train H_t as

the time since the last spike. The parameter vector θ_t relates the animal's position and the time since the last spike to the shape of the rate function.

The adaptive algorithm, derived as an approximation to an instantaneous maximum likelihood algorithm, uses data from the spike train to update the estimate of the firing rate at each moment in time. The algorithm computes the difference between the predicted and actual firing to update the firing rate model, making it more consistent with the data. This update uses a learning rate term to weigh the new information from the data relative to the current estimate. Mathematically, the simplest version of the algorithm updates each parameter as follows: $\theta_{t_k} = \theta_{t_{k-1}} + \varepsilon \frac{d\lambda}{d\theta} [N(t_{k-1}, t_k) - \lambda(t|\theta_{t_{k-1}}, H_{t_k})\Delta_{t_k}]$ where θ_{t_k} is the new value of a parameter at time t_k , $\theta_{t_{k-1}}$ is the value of that parameter at the last time step, ε is a learning rate that weights the contribution from the new data, $\frac{d\lambda}{d\theta}$ is a term that ensures that changes in θ_{t_k} will have the desired effect on the firing rate λ , $N(t_{k-1}, t_k)$ is the number of spikes observed in the last time step, and $\lambda(t|\theta_{t_{k-1}}, H_{t_k})\Delta_{t_k}$ is the firing rate at the last time step, $\lambda(t|\theta_{t_{k-1}}, H_{t_k})$, multiplied by the length of the time step, Δ_{t_k} . Thus, $[N(t_{k-1}, t_k) - \lambda(t|\theta_{t_{k-1}}, H_{t_k})\Delta_{t_k}]$ is a comparison between the number of spikes observed and the number expected based on the current estimate of the firing rate, and the algorithm uses that measure of the error in the current estimate to update the firing rate model. When these terms are combined, the result is a descriptive model that tracks the firing rate process over time.

With the addition of goodness-of-fit tests that ensure that the resulting models are consistent with the neural data (Barbieri et al., 2001; Brown et al., 2002; Frank et al., 2002), the result is an analysis that describes the spatial and temporal structure of each neuron's spike train across time, in terms of a smooth, continuous firing rate function. We can then analyze this function to accurately characterize changes in neural activity over time. The same type of approach has also been used to characterize plasticity in the primate hippocampus, as animals learned a location scene association task (Wirth et al., 2003), and is generally applicable to analyses of neural plasticity.

CA1 AND DEEP EC PLACE FIELD PLASTICITY IN FAMILIAR ENVIRONMENTS

We have used this algorithm to examine place field plasticity in both familiar (Frank et al., 2002) and novel places (Frank et al., 2004). For the analyses of familiar data, we applied the adaptive analysis to the data recorded from rats running back and forth on a familiar U-shaped track (Frank et al., 2000). We recorded data from neurons in hippocampal area CA1 and in the deep layers of the EC. The deep EC is the primary target of hippocampal outputs, and thus comparing plasticity in these structures allows us to compare patterns of change in the hippocampus with that seen in downstream structures.

We found that the patterns of change differed substantially across the two structures. In CA1, as had been reported previously, the large majority of place cells became more active over time and shifted backwards along the animal's direction of

motion. In contrast, most deep EC neurons became less active over time, and the population showed no consistent spatial shifts. These results indicate that the basic properties of place-related plasticity differ between CA1 and deep EC. At the same time, we found that there were a minority of deep EC neurons which showed a pattern of spatial plasticity like that seen in CA1, and that these neurons tended to show higher spatial specificity in their firing than do their nonincreasing counterparts.

It is generally hypothesized that the consistent increase in firing rates and the backward shift of place fields seen in CA1 activity in familiar environments reflects the relative ease of inducing plasticity in the hippocampal circuit and, in particular, in the connections from upstream area CA3 to CA1 (Blum and Abbott, 1996; Mehta et al., 1997, 2000; Ekstrom et al., 2001). The functional significance of these changes for memory encoding or recall remains unclear, however. The fact that, in CA1, these changes reset after a day of rest between exposures to the familiar track (Mehta et al., 1997) suggests to us that the small changes in rate and center of mass may not be important for memory storage or recall, but are perhaps instead an epiphenomenon that inevitably results where there are plastic feed-forward synapses (e.g., from CA3 to CA1). In particular, as the shifts in location are generally in the order of a few centimeters, and as these shifts occur across the whole CA1 population, it is not clear how downstream neurons could detect the shift from their highly variable place cell inputs or how they would use the shifts if they were detectable. One possible effect, the propagation of these shifts to downstream structures, does not appear to occur, as our data indicated that deep EC fields did not shift. Thus, we feel additional work will be required to determine whether these shifts have an effect on information encoding in the circuit.

The deep EC's tendency to show decreasing firing rates is consistent with a large body of literature on the effects of repeated presentations of the same stimulus on the firing of neurons in the EC and related structures in both rodents and primates (Miller et al., 1991; Fahy et al., 1993; Li et al., 1993; Miller and Desimone, 1994; Zhu et al., 1995; Suzuki et al., 1997; Young et al., 1997; Xiang and Brown, 1998, 1999). Once again, it is not clear that these decreases have functional significance, although the increase in activity for the minority of cells with higher specificity leads to a more faithful representation of relevant variables (spatial location in this case) over time. In any case, the relative homogeneity of the CA1 change as compared to that seen in the deep EC suggests that most or all of the active CA1 neurons are engaged in representing the familiar place, while deep EC may contain multiple subpopulations, some tied to CA1 output, and others more independent of CA1. If so, then CA1 may be involved in representing a single memory at a given time, while downstream areas could act to integrate that memory with previously learned information.

CA1 AND CORTICAL PLACE FIELD PLASTICITY IN NOVEL ENVIRONMENTS

While studying that plasticity in familiar environments can be informative, the hippocampus' role in learning suggests that

understanding how the rat hippocampus creates a representation of a novel environment would be particularly useful in our efforts to understand memory storage. We hypothesize that the development of new spatial representations is a process of memory formation, and we therefore recorded data from neurons in CA1 and in adjacent cortical regions as animals developed a representation of a new place (Frank et al., 2004). We pretrained animals to run in a continuous alternation pattern in a T-maze consisting of three arms of an eight-arm maze (Fig. 2A). Animals were placed in the home arm of the maze and were rewarded with liquid chocolate, each time it reached the next correct arm in the sequence. The animals were not removed from the track until the end of the run session, and required ~1–3 weeks of pretraining to reach 80% correct, where a single correct trial involved a run from the home arm to the correct outside arm (arm 3 or arm 7) and back to the home arm. Once each animal reached criterion, we implanted a microdrive array with 30 independently moveable tetrodes targeting the CA1 region of the hippocampus and hippocampally associated cortical regions. After the animal recovered, we collected data both while the animal ran in the familiar configuration of the maze and while it learned to continuously alternate in a novel configuration, where either the left or the right arm was closed off and a novel arm was opened up (Fig. 2B). In this novel configuration, the reward contingencies were the same, with the novel arm replacing the adjacent familiar arm in the rewarded sequence.

The animals were exposed to each configuration for 2 or 3 days, and each animal was exposed to a total of four novel configurations. As CA1 and deep EC place cells are generally directional in familiar environments, we examined the two directions of motion through the novel arm separately. The details of the analysis methods and the CA1 results are presented by Frank et al.

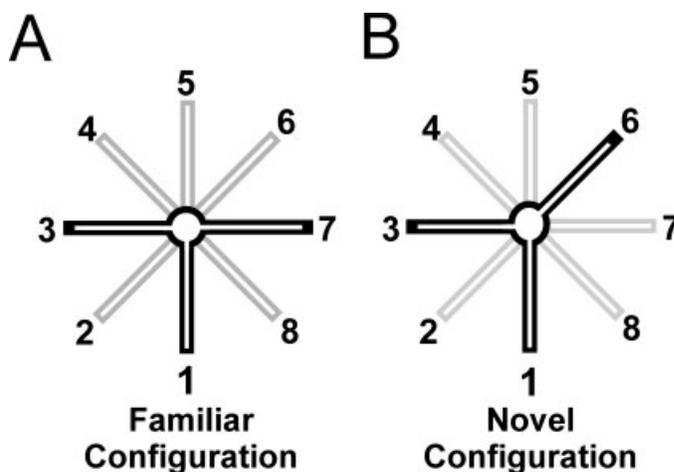


FIGURE 2. The task used to expose animals to novel environments. Animals were pretrained in the familiar configuration (A) to alternate from arm 1–3 to 1–7 to 1–3 and so on. Once trained, the microdrive array was implanted, and during each day of recording the animals ran first in the familiar configuration and then, after a 20–30-min rest, in the novel configuration (B) where either arm 3 or arm 7 had been closed off and a novel arm on the same side as the now closed arm had been opened (e.g., arm 6). The animals were rewarded for running in the same alternation pattern, including the novel arm, rather than the now closed familiar arm.

(2004), and here we summarize the CA1 findings and discuss the results from the cortical recordings. The previously unreported cortical data were collected in conjunction with the CA1 data, using the methodologies described by Frank et al. (2004). All procedures were approved by the Animal Care and Use Committee at Harvard University and were in accordance with the guidelines established by the National Institute of Health. We should note, however, that all of the results from the cortical recordings must be interpreted cautiously. First, we did not target the subregion of EC where highly place-specific, grid-like firing has been seen (Fyhn et al., 2004; Hafting et al., 2005; Hargreaves et al., 2005). Second, cortical neurons were distributed across entorhinal and other adjacent neocortical regions, and as insufficient numbers of neurons were recorded to permit a separate analysis by region, there may be region-specific patterns of plasticity that our analyses do not capture. Third, we are analyzing plasticity as a function of position, but cortical neurons that respond, for example, to specific visual stimuli could show plasticity that might not correlate well with location. Nonetheless, there were clear trends in the cortical data, and as these trends are very different from those seen in CA1, we feel that the comparison can provide insight into the hippocampal cortical system.

CA1 and Cortical Plasticity—Day 1

The animals were always initially placed in arm 1 (Fig. 2), and thus they only became aware of the novel configuration once they reached the center platform. Upon arriving at the center in the context of a novel configuration, the animals immediately began to explore the entrance to the novel arm and the arm itself. This was in stark contrast to their behavior in the familiar configuration, where they would immediately go down an arm to reach the reward site at the end. This difference in behavior (see later for further discussion) was accompanied by large and rapid changes in CA1 place cell activity in the novel arm, but only small changes in the familiar arms.

Many CA1 place fields showed very pronounced changes in activity, including a large minority (18/91 or 20%), which were initially silent but then developed a place field (Figs. 3A,B). An examination of the patterns of change seen in these cells revealed several striking phenomena. First, these cells fired few spikes over the first passes through the novel arm (the end of each pass is marked by a vertical line on the top x -axis of the plots in Fig. 3) and then showed a sudden transition to a much higher firing rate. This can be seen in the rapid rise in the integrated spatial intensity graphs in the left column and in the spike rasters in the right column. The new firing was not distributed across the arm, however, but was instead limited to a restricted region, as can be seen in the snapshots of the place field shown in the middle column. Second, after this initial period of rapid place field growth, the fields became relatively stable. The fields continued to change in some cases, but these changes were small compared to the initial development of the field, suggesting that while the circuit continued to show plasticity, it was focused on refining the recently established representations. This process was accompanied by an overall increase in the activity of simultaneously recorded putative

interneurons. Third, when all cells active in the novel arm were considered, there was on average, a substantial increase in activity across the population from a level well below that initially seen in the familiar arms in both putative excitatory and putative inhibitory cells. The majority of cells had a place field that was apparent after the first pass through the environment, and both these cells and those that were initially silent tended to show marked increases in firing with experience.

Taken together, these findings suggest that when the animal encounters something new, the immediate result is a reduction in total CA1 activity relative to that seen in familiar places, followed by the rapid formation of new representations in the circuit. This plasticity is tightly regulated, however, as the rapid changes do not continue throughout the experience. Instead, there appear to be processes, including feed-back inhibition from interneurons, which clamp down on the increasing activity and subsequently allow only relatively small changes in the place fields, changes that are more comparable in magnitude to those seen in familiar environments. We therefore hypothesize that, when the hippocampus is engaged in the formation of a new memory for an episode, these same patterns of plasticity occur. Thus, when a new combination of people, places, etc., is experienced, individual CA1 neurons would rapidly come to represent the novel combinations of these elements. At the same time, even after the first memory has been formed, the observation of continued plasticity, albeit at a reduced level, suggests that the original representation can be modified by subsequently experienced events.

In contrast, our results from analyses of cortical plasticity suggest that changes in the cortical activity are generally slower than those in CA1. The recordings of these neurons were stable, and the cells were well-isolated, but only 1 of 70 cortical place fields met the criteria for rapid development that identified 20% of CA1 place fields as rapidly developing, and that single cell was not silent on the first pass, and showed highly variable activity across multiple passes through the novel arm. We show two cortical neurons that are representative of the most extreme changes seen in the cortex in Figures 3C and 3D. Comparing these patterns with those seen in CA1, we noted first that the patterns of change seen in these neurons illustrate that even those cortical cells which showed substantial plasticity over the course of the first novel exposure changed much more smoothly than do the rapidly developing CA1 neurons. These neurons were active on the first pass through the novel arm, and tended to be active across large portions of the arm, and generally across large portions of the familiar arms as well. Both the mean location and the peaks of activity tended to shift substantially over time. Second, there was no clear division between a period of initial, rapid plasticity and a subsequently less dynamic period. Third, for the majority of neurons, activity declined over the course of the novel exposure, just as it did for deep EC neurons recorded in familiar environments, as described earlier. We quantified the pattern of change by computing the derivative of the area of the place field and examining the distributions of derivatives. Figure 4A shows a comparison of the derivatives from the first minute of experience in the novel environment for CA1 and cortical place fields. The majority of the CA1 curve is on the right side of the $x = 0$ line,

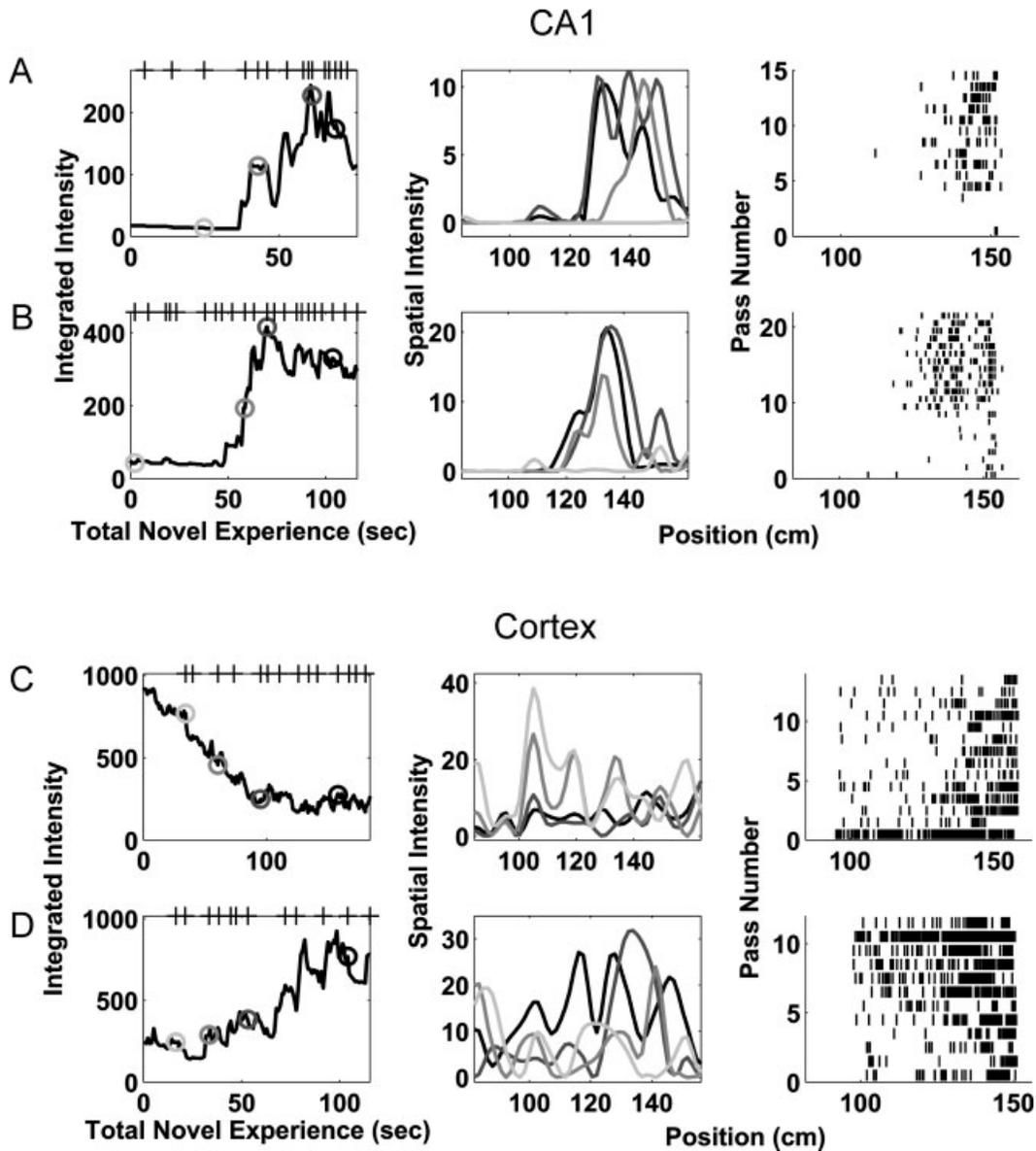


FIGURE 3. Examples of place field plasticity from CA1 and cortex. Each row represents a single neuron. The first column shows the integrated spatial intensity plotted as a function of the total experience in the novel arm. This represents the total size of the place field. The vertical lines along the top x -axis represent the times at which the animal completed a pass through the arm. The second column shows the shape of the place field at the four times indi-

cated by circles in the first column. Early times are represented by light gray, while later times are represented by progressively darker gray. The third column shows the spike rasters of the neuron's activity on each pass through the novel arm. (A) and (B) represent two CA1 neurons which were initially essentially silent but then rapidly developed place fields. (C) and (D) represent two cortical neurons that showed large, but more gradual, patterns of change.

indicating that CA1 place fields were more often growing than shrinking in area. In contrast, the majority of the cortical curve is to the left of the $x = 0$ line, indicating that their fields generally decreased in size over time. The two curves are highly significantly different according to a Komolgorov–Smirnov test ($P < 0.0001$).

These findings suggest that the large and rapid changes seen in CA1 are not accompanied by similar changes in adjacent cortical regions. Instead, these areas appear to show more gradual dynamics that are more similar to those seen in familiar environments. This finding may help explain why the hippocampus is essential for the

formation of new episodic memories. Our results suggest that cellular and circuit level properties that allow for both the rapid formation of new representations and the subsequent stabilization in the hippocampus are not present in adjacent cortical regions, and thus that these regions are not capable of the rapid formation of new memories required for encoding episodic memories.

CA1 and Cortical Plasticity—Days 2 and 3

The second day of exposure to the novel arm occurred ~ 18 h after the first exposure. We expected that the experience on day 1

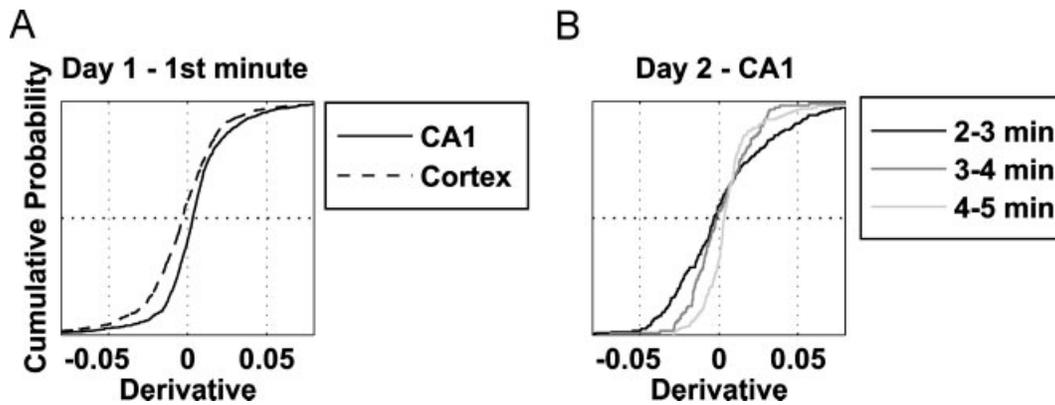


FIGURE 4. Cumulative distributions of the derivatives of the area of the spatial intensity function for CA1 and cortex. Wider curves represent greater amounts of change. (A) A comparison of the distributions for the first minute of experience for CA1 and cortical neurons. The majority of the cortical distribution is to the left of the

$x = 0$ line, while the majority of the CA1 distribution is to the right, indicating that cortical activity tended to decrease in the novel arm while CA1 activity increased. (B) A comparison of the distributions for different total lengths of experience on day 2. Short day 1 experiences were associated with increased plasticity on day 2.

and the subsequent consolidation period would result in stable place fields on day 2, resembling those in the familiar arms. Instead, we found that many CA1 place cells showed plasticity on day 2 that closely resembled the rapid dynamics on day 1. The animals were free to spend as much or as little time in the novel arm as they chose, and when the animal had spent only a short time in the novel arm, the place fields changed, on average, even more quickly than during the first minute of experience on the first day, as though the previous experience had primed the circuit to be plastic. In contrast, place fields from animals that had spent more time in the novel arm on day 1 tended to exhibit less plasticity on day 2. This is illustrated in Figure 4B, where three cumulative distributions of derivatives for CA1 place fields are shown. The three curves show the amount of change associated with different total amounts of experience. The curve corresponding to 2–3 min of experience is clearly much wider than the other curves, implying that when the animal had relatively little experience on day 1 (<2 min), there was substantial place field change on day 2. When we examined these neurons, we found instances of the same types of place field change seen on day 1 in the novel arm, with the appearance of new fields in neurons that were initially silent as well as large changes in initially active cells.

Longer experiences on day 1 were associated with relatively little plasticity on day 2, and our findings for CA1 indicate that the representation of space was stable once the animal had at least 5–7 min of experience in the new place, which occurred late on day 2 or on day 3. In particular, the pattern of place field change was very similar in the novel and familiar arms by this point, as was the pattern of inhibitory cell dynamics. We also found that the clear dependence on the total length of experience in the novel arm was not clearly visible when the data were organized by the number of complete passes through the arm, indicating that time, rather than number of traversals, was the more important variable in determining the pattern of plasticity. In addition, our analysis of place cell directionality indicated that the less directional fields seen on days 1 and 2 became more directional on day 3, although there was still a trend for the fields in

familiar arms to be more directional than the fields in the novel arms. Finally, the number of neurons active in the novel arm was significantly greater than the number active in the familiar arms on days 1 and 2, but not on day 3. Thus, there are a number of lines of evidence that suggest that CA1 place fields stabilize by day 3. The cortical data on place field area change was more difficult to interpret, and further investigation will be required to accurately establish the time course of plasticity as a function of total experience in the cortex.

The CA1 findings imply that short experiences may not be sufficient to establish lasting memories, and that there is a critical minimum length of experience required to create a representation that will be stable over time. We should note, however, that the 5–7-min time course for the formation of new place fields is likely to depend on a number of factors, including the overall novelty and complexity of the environment. We are currently exploring these possibilities.

The increased plasticity on day 2 following short day 1 experiences suggests that whatever changes occurred during the initial encoding of the new space on day 1 and during the subsequent sleep were not sufficient to establish a complete CA1 representation of the space. Had a complete representation been established on day 1, we would expect that the first time the animal entered the previously novel arm on day 2, it would retrieve the memory for the arm. That would suggest that only the normal “familiar” pattern of plasticity would be seen. Instead, the network appeared to be creating a new representation. We should note, though, that as we did not track the same neurons across days, it is possible that for each place cell rapid plasticity on day 2 occurred in the same place as plasticity on day 1 and thus that there was a stable underlying spatial structure. In either case, the effect of this large change in CA1 would be a very different pattern of activation in downstream neurons. This finding, in combination with the observation that CA1 place cells continue to undergo some plasticity even in familiar environments, may help provide a circuit level explanation for the observations about the relatively frequent occurrences of errors in episodic memories

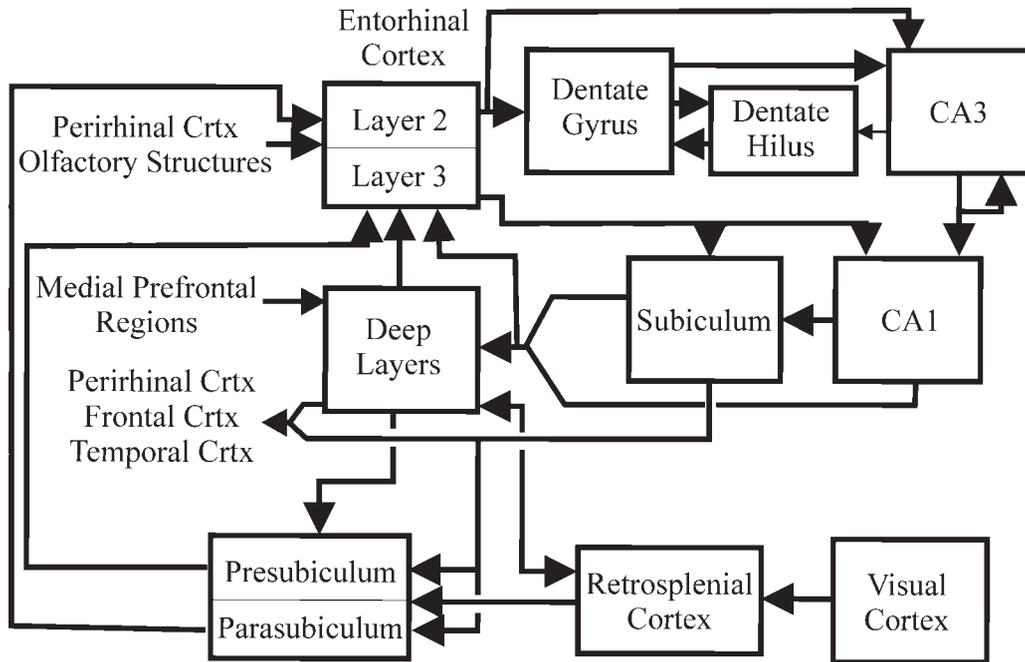


FIGURE 5. The anatomy of the hippocampal–cortical circuit, adapted from Amaral and Witter (1995). Input from association areas comes in primarily to the superficial layers of the EC, which then sends outputs to the dentate gyrus (DG), CA3, CA1, and the

subiculum. The outputs of the circuit primarily target the deep layers of the EC, although some subicular outputs target layer 3 of the superficial EC, and the deep EC projects back to the superficial EC, both directly and through the pre- and parasubiculum.

(Loftus, 1980; Hyman and Loftus, 1998). We hypothesize that the encoding of episodic memories puts the hippocampus in a high plasticity state, and that unless sufficient time is available to solidify the newly formed memories, these memories may be easily disrupted by subsequent experiences.

the hippocampus with their ongoing activity and as there are a number of synapses between the hippocampus and motor planning regions, we suspect that plasticity in multiple regions may be necessary to translate a hippocampal memory into behavior.

Place Field Dynamics and Behavior Change

We also examined the relationship between place field dynamics and behavior. One might predict that once CA1 had formed a stable representation of the novel arm, the animal would behave as though that arm were a familiar place. As the transition from novelty to familiarity is accompanied by a transition from exploration to directed motion to and from reward locations, we used the animals' speed as a measure of familiarity. We found that the animals moved significantly more slowly in the novel arm from the beginning of the first session, and their errors rates in the task increased. Surprisingly, animals continued to move more slowly through the novel arm even on day 3, after the hippocampal place fields had stabilized. Thus, stable hippocampal place fields are not sufficient to cause the animal to treat a place as familiar.

These findings offer further support for the hypothesis that the hippocampus is specialized for rapid encoding of complex relationships, and that other brain areas process new information more slowly. From one perspective, the new pattern of activity that develops in the hippocampus during the initial encoding of a new memory constitutes a new pattern of input to downstream regions, such as the deep layers of the EC. These downstream regions may need additional time to integrate the new output from

INTEGRATION WITH OTHER FINDINGS ON THE FORMATION OF NEW REPRESENTATIONS IN THE HIPPOCAMPAL CIRCUIT

As mentioned earlier, recent work has investigated the formation of novel representations in the dorsolateral portion of the medial superficial EC (Hafting et al., 2005). Their results, based on correlations of place field structure over time, showed that superficial EC grid-like fields were present immediately in a new environment, although they were not entirely stable at first. They also found that unlike CA1 place cells, superficial EC neurons showed very similar firing patterns across environments. It has also been shown that neurons in the lateral superficial EC show little place specificity (Hargreaves et al., 2005). As the superficial EC is the main source of neocortically originating inputs to the hippocampus (Fig. 5, adapted from Amaral and Witter (1995)), these results suggest that one important function of CA1 is to take patterns of input that are similar across environments or episodes and rapidly form unique representations. This formation may depend on the integration of the nonspatial information from the lateral EC, which may be different across environments, with the common grid cell representation of the medial EC.

Two studies have also examined the formation and modification of spatial representations in CA3, the area immediately upstream of CA1. Leutgeb et al. (2004) showed that while CA1 place cells became stable in the first 10 min of foraging in a novel environment, CA3 place cells continued to change over 30 min. In contrast, Lee et al. (2004) reported that after a double rotation of local and distal cues, CA3 cells showed immediate place field shifts on the first exposure to the cue rotation, while CA1 cells did not show these characteristic shifts until day 2. These results suggest that CA3 plasticity may differ between novel and modified environments, and suggest that CA1 is largely decoupled from CA3 during the initial formation of new memories. One possible explanation for this pattern is that CA3 may be important for creating representations that require more experience than those seen initially in CA1, perhaps involving sequences of locations or events rather than single locations or events.

CONCLUSIONS AND FUTURE DIRECTIONS

Our results indicate that the patterns of place field plasticity in the CA1 region of the hippocampus differ from those seen in the neurons we recorded from adjacent cortical regions.

Our data support the idea that the hippocampus is essential for episodic memory, because it is the only structure that can rapidly reorganize its pattern of activity in response to new information to create a new memory, a finding consistent with results from the primate hippocampus (Wirth et al., 2003). At the same time, there are many other regions in the hippocampal–cortical circuit, and an examination of the anatomy of the hippocampal formation and the effects of region-specific manipulations (Lee and Kesner, 2002; Nakazawa et al., 2003) make it clear that each region may make a unique contribution to memory storage. Thus, understanding how new episodic memories are formed will require examining the patterns of activity and plasticity in each of these structures. In particular, we feel it is essential to compare the patterns of activity and plasticity seen in each region to those present in upstream and downstream structures under the same behavioral conditions, as we do not yet understand how differences in task or environment geometry will affect the formation of new hippocampal representations. We also need to begin to understand how the various feedback loops present in the hippocampal–cortical circuit, including those from the deep entorhinal outputs back to the superficial entorhinal inputs, contribute to learning. We believe that a careful examination of neural dynamics and its relationship to behavior across the hippocampal system will provide a powerful framework for identifying the computations that occur during memory storage and retrieval.

REFERENCES

Aggleton JP, Hunt PR, Rawlins JN. 1986. The effects of hippocampal lesions upon spatial and non-spatial tests of working memory. *Behav Brain Res* 19:133–146.

- Amaral DG, Witter MP. 1995. Hippocampal formation. In: Paxinos C, editor. *The Rat Nervous System*. San Diego, CA: Academic Press. pp 443–493.
- Barbieri R, Quirk MC, Frank LM, Wilson M, Brown EN. 2001. Construction and analysis of non-Poisson stimulus response models of neural spike train activity. *J Neurosci Methods* 105:25–37.
- Best PJ, White AM, Minai A. 2001. Spatial processing in the brain: The activity of hippocampal place cells. *Annu Rev Neurosci* 24:459–486.
- Blum KI, Abbott LF. 1996. A model of spatial map formation in the hippocampus of the rat. *Neural Comput* 8:85–93.
- Bostock E, Muller RU, Kubie JL. 1991. Experience-dependent modifications of hippocampal place cell firing. *Hippocampus* 1:193–205.
- Brown EN, Frank LM, Tang D, Quirk MC, Wilson MA. 1998. A statistical paradigm for neural spike train decoding applied to position prediction from ensemble firing patterns of rat hippocampal place cells. *J Neurosci* 18:7411–7425.
- Brown EN, Nguyen DP, Frank LM, Wilson MA, Solo V. 2001. An analysis of neural receptive field dynamics by point process adaptive filtering. *Proc Natl Acad Sci USA* 98:12261–12266.
- Brown EN, Barbieri R, Ventura V, Kass RE, Frank LM. 2002. The time-rescaling theorem and its application to neural spike train data analysis. *Neural Comput* 14:325–346.
- Cohen NJ, Eichenbaum H. 1993. *Memory, Amnesia, and the Hippocampal System*. Cambridge, MA: MIT Press.
- Day M, Langston R, Morris RG. 2003. Glutamate-receptor-mediated encoding and retrieval of paired-associate learning. *Nature* 424:205–209.
- Eichenbaum H, Cohen NJ. 2001. *From Conditioning to Conscious Recollection*. New York: Oxford University Press.
- Eichenbaum H, Dudchenko P, Wood E, Shapiro M, Tanila H. 1999. The hippocampus, memory, and place cells: Is it spatial memory or a memory space? *Neuron* 23:209–226.
- Ekstrom AD, Meltzer J, McNaughton BL, Barnes CA. 2001. NMDA receptor antagonism blocks experience-dependent expansion of hippocampal “place fields.” *Neuron* 31:631–638.
- Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Neuman FL, Fried I. 2003. Cellular networks underlying human spatial navigation. *Nature* 425:184–188.
- Fahy FL, Riches IP, Brown MW. 1993. Neuronal activity related to visual recognition memory: Long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. *Exp Brain Res* 96:457–472.
- Ferbinteanu J, Shapiro ML. 2003. Prospective and retrospective memory coding in the hippocampus. *Neuron* 40:1227–1239.
- Frank LM, Brown EN, Wilson MA. 2000. Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron* 27:169–178.
- Frank LM, Eden UT, Solo V, Wilson MA, Brown EN. 2002. Contrasting patterns of receptive field plasticity in the hippocampus and the entorhinal cortex: An adaptive filtering approach. *J Neurosci* 22:3817–3830.
- Frank LM, Stanley GB, Brown EN. 2004. Hippocampal plasticity across multiple days of exposure to novel environments. *J Neurosci* 24:7681–7689.
- Fyhn M, Molden S, Witter MP, Moser EI, Moser MB. 2004. Spatial representation in the entorhinal cortex. *Science* 305:1258–1264.
- Gothard KM, Skaggs WE, McNaughton BL. 1996. Dynamics of mismatch correction in the hippocampal ensemble code for space: Interaction between path integration and environmental cues. *J Neurosci* 16:8027–8040.
- Gothard KM, Hoffman KL, Battaglia FP, McNaughton BL. 2001. Dentate gyrus and CA1 ensemble activity during spatial reference frame shifts in the presence and absence of visual input. *J Neurosci* 21:7284–7292.
- Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. 2005. Microstructure of a spatial map in the entorhinal cortex. *Nature* 436:801–806.

- Hargreaves EL, Rao G, Lee I, Knierim JJ. 2005. Major dissociation between medial and lateral entorhinal input to dorsal hippocampus. *Science* 308:1792–1794.
- Hyman IE Jr, Loftus EF. 1998. Errors in autobiographical memory. *Clin Psychol Rev* 18:933–947.
- Izquierdo I, Medina JH. 1997. Memory formation: The sequence of biochemical events in the hippocampus and its connection to activity in other brain structures. *Neurobiol Learn Mem* 68:285–316.
- Izquierdo I, Quillfeldt JA, Zannata MS, Quevedo J, Schaeffer E, Schmitz PK, Medina JH. 1997. Sequential role of hippocampus and amygdala, entorhinal cortex and parietal cortex in formation and retrieval of memory for inhibitory avoidance in rats. *Eur J Neurosci* 9:786–793.
- Jarrard LE. 1993. On the role of the hippocampus in learning and memory in the rat. *Behav Neural Biol* 60:9–26.
- Jerusalinsky D, Ferreira MB, Walz R, Da Silva RC, Bianchin M, Ruschel AC, Zannata MS, Medina JH, Izquierdo I. 1992. Amnesia by post-training infusion of glutamate receptor antagonists into the amygdala, hippocampus, and entorhinal cortex. *Behav Neural Biol* 58:76–80.
- Kentros C, Hargreaves E, Hawkins RD, Kandel ER, Shapiro M, Muller RV. 1998. Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. *Science* 280:2121–2126.
- Kim JJ, Fanselow MS. 1992. Modality-specific retrograde amnesia of fear. *Science* 256:675–677.
- Lee I, Kesner RP. 2002. Differential contribution of NMDA receptors in hippocampal subregions to spatial working memory. *Nat Neurosci* 5:162–168.
- Lee I, Rao G, Knierim JJ. 2004. A double dissociation between hippocampal subfields: Differential time course of CA3 and CA1 place cells for processing changed environments. *Neuron* 42:803–815.
- Leutgeb S, Leutgeb JK, Treves A, Moser MB, Moser EI. 2004. Distinct ensemble codes in hippocampal areas CA3 and CA1. *Science* 305:1295–1298.
- Lever C, Wills T, Cacucci F, Burgess N, O'Keefe J. 2002. Long-term plasticity in hippocampal place-cell representation of environmental geometry. *Nature* 416:90–94.
- Li L, Miller EK, Desimone R. 1993. The representation of stimulus familiarity in anterior inferior temporal cortex. *J Neurophysiol* 69:1918–1929.
- Loftus EF. 1980. Impact of expert psychological testimony on the unreliability of eyewitness identification. *J Appl Psychol* 65:9–15.
- McNaughton BL, Barnes CA, O'Keefe J. 1983. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp Brain Res* 52:41–49.
- Mehta MR, Barnes CA, McNaughton BL. 1997. Experience-dependent, asymmetric expansion of hippocampal place fields. *Proc Natl Acad Sci USA* 94:8918–8921.
- Mehta MR, Quirk MC, Wilson MA. 2000. Experience-dependent asymmetric shape of hippocampal receptive fields. *Neuron* 25:707–715.
- Miller EK, Desimone R. 1994. Parallel neuronal mechanisms for short-term memory. *Science* 263:520–522.
- Miller EK, Li L, Desimone R. 1991. A neural mechanism for working and recognition memory in inferior temporal cortex. *Science* 254:1377–1379.
- Morris RG. 1996. Further studies of the role of hippocampal synaptic plasticity in spatial learning: Is hippocampal LTP a mechanism for automatically recording attended experience? *J Physiol (Paris)* 90:333–334.
- Morris RG, Davis S, Butcher SP. 1990. Hippocampal synaptic plasticity and NMDA receptors: A role in information storage? *Philos Trans R Soc Lond B Biol Sci* 329:187–204.
- Muller RU, Kubie JL. 1987. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *J Neurosci* 7:1951–1968.
- Muller RU, Bostock E, Taube JS, Kubie JL. 1994. On the directional firing properties of hippocampal place cells. *J Neurosci* 14:7235–7251.
- Nakazawa K, Sun LD, Quirk MC, Rondi-Reig L, Wilson MA, Tonegawa S. 2003. Hippocampal CA3 NMDA receptors are crucial for memory acquisition of one-time experience. *Neuron* 38:305–315.
- O'Keefe J, Dostrovsky J. 1971. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res* 34:171–175.
- O'Keefe J, Nadel L. 1978. *The Hippocampus As a Cognitive Map*. London: Oxford University Press.
- Quillfeldt JA, Zannata MS, Schmitz PK, Quevedo J, Schaeffer E, Lima JB, Medina JH, Izquierdo I. 1996. Different brain areas are involved in memory expression at different times from training. *Neurobiol Learn Mem* 66:97–101.
- Rudy JW, Sutherland RJ. 1995. Configural association theory and the hippocampal formation: An appraisal and reconfiguration. *Hippocampus* 5:375–389.
- Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20:11–21.
- Smith AC, Frank LM, Wirth S, Yanike M, Hu D, Kubota Y, Graybiel AM, Suzuki WA, Brown EN. 2004. Dynamic analysis of learning in behavioral experiments. *J Neurosci* 24:447–461.
- Squire LR. 1982. The neuropsychology of human memory. *Annu Rev Neurosci* 5:241–273.
- Squire LR. 1992. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychol Rev* 99:195–231. [Published erratum appears in *Psychol Rev* 1992, 99:582].
- Suzuki WA, Miller EK, Desimone R. 1997. Object and place memory in the macaque entorhinal cortex. *J Neurophysiol* 78:1062–1081.
- Tulving E. 2002. Episodic memory: From mind to brain. *Annu Rev Psychol* 53:1–25.
- Wilson MA, McNaughton BL. 1993. Dynamics of the hippocampal ensemble code for space. *Science* 261:1055–1058. [See comments; Published erratum appears in *Science* 1994, 264:16].
- Winocur G, McDonald RM, Moscovitch M. 2001. Anterograde and retrograde amnesia in rats with large hippocampal lesions. *Hippocampus* 11:18–26.
- Wirth S, Yanike M, Frank LM, Smith AC, Brown EN, Suzuki WA. 2003. Single neurons in the monkey hippocampus and learning of new associations. *Science* 300:1578–1581.
- Wood ER, Dudchenko PA, Robitsek RJ, Eichenbaum H. 2000. Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* 27:623–633.
- Xiang JZ, Brown MW. 1998. Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior temporal lobe. *Neuropharmacology* 37:657–676.
- Xiang JZ, Brown MW. 1999. Differential neuronal responsiveness in primate perirhinal cortex and hippocampal formation during performance of a conditional visual discrimination task. *Eur J Neurosci* 11:3715–3724.
- Young BJ, Otto T, Fox GD, Eichenbaum H. 1997. Memory representation within the parahippocampal region. *J Neuroscience* 17:5183–5195.
- Zhu XO, Brown MW, Aggleton JP. 1995. Neuronal signalling of information important to visual recognition memory in rat rhinal and neighbouring cortices. *Eur J Neurosci* 7:753–765.