Hippocampal Place Cells: Parallel Input Streams, Subregional Processing, and Implications for Episodic Memory

James J. Knierim,* Inah Lee, and Eric L. Hargreaves

ABSTRACT: The hippocampus is thought to be involved in episodic memory in humans. Place cells of the rat hippocampus offer a potentially important model system to understand episodic memory. However, the difficulties in determining whether rats have episodic memory are profound. Progress can be made by considering the hippocampus as a computational device that presumably performs similar transformations on its inputs in both rats and in humans. Understanding the input/output transformations of rat place cells can thus inform research on the computational basis of human episodic memory. Two examples of different transformations in the CA3 and CA1 regions are presented. In one example, CA3 place fields are shown to maintain a greater degree of population coherence than CA1 place fields after a rearrangement of the salient landmarks in an environment, in agreement with computational models of CA3 as an autoassociative network. In the second example, CA3 place field appears to store information about the spatiotemporal sequences of place fields, starting with the first exposure to a cue-altered environment, whereas CA1 place fields store this information only on a temporary basis. Finally, recordings of hippocampal afferents from the lateral and medial entorhinal cortex (EC) suggest that these two regions convey fundamentally different representations to the hippocampus, with spatial information conveyed by the medial EC and nonspatial information conveyed by the lateral EC. The dentate gyrus and CA3 regions may create configural object + place (or item + context) representations that provide the spatiotemporal context of an episodic memory. © 2006 Wiley-Liss, Inc.

KEY WORDS: entorhinal cortex; spatial orientation; single units; associative memory; pattern completion

INTRODUCTION

It has been known for decades that the hippocampus and medial temporal lobe play a critical, although not fully understood, role in human learning and memory (Scoville and Milner, 1957). Patients with medial temporal lobe amnesia display both a limited retrograde and a profound, anterograde amnesia for explicit memory. This particular form of mem-

ory was termed "declarative memory," and it was suggested that the hippocampus was necessary for both episodic memory (conscious memory of specific events from one's past) and semantic memory (conscious memory of facts about the world, without any binding to a specific autobiographical event) (Squire, 1987). The exact nature and defining characteristics of these two forms of declarative memory are under considerable debate (Baddeley et al., 2002). Recent work suggests that the hippocampus may be particularly important for episodic memory, while other regions of the medial temporal lobe may be particularly important for semantic memory (Vargha-Khadem et al., 1997; Tulving and Markowitsch, 1998; Aggleton and Brown, 1999; Graham et al., 2000; Fortin et al., 2004). However, the debates about the distinctions between episodic and semantic memory and their correspondence to specific brain systems are ongoing.

For nonhuman animals, the question of hippocampal involvement in episodic memory is murkier, for it is difficult to assess the phenomenon of episodic memory in nonverbal creatures. Indeed, the originator of the concept of episodic memory, Endel Tulving, has claimed that episodic memory is possessed uniquely by humans, for no nonhuman animal possesses the self-conscious, autonoetic properties that are the essence of episodic memory (Tulving, 2002). The difficulties in evaluating this claim are profound. In a bird, mouse, rat, monkey, or ape, there are no well-established methods to determine whether the animal's learned change in behavior is the result of the animal's explicit recollection of a past event ("mental time travel," in Tulving's words) or merely the result of experience-dependent changes in certain neural pathways with no concomitant "reliving" of the past event. Because of the difficulties in assessing the autonoetic qualities of animal memory, animal researchers have adopted the term *episodic-like* to describe animal memories that appear to require the three elements regarded as fundamental to episodic memory: memory for what occurred, where it occurred, and when it occurred, without a requirement for autonoetic awareness. Many investigators have devised new tasks that require memory for these three elements as a way of assessing the role of the hippocampus in episodic-like memory (e.g., Clayton and Dickinson, 1998; Fortin et al., 2002).

One critical aspect of episodic memory is its one-trial, single-shot nature. Events happen once, and later they are either remembered at some level of detail or

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not. Rehearsal or reactivation of these memories can strengthen or decrease the memory trace, but the actual event happens once. Thus, a brain system that underlies episodic memory must be able to rapidly and robustly encode neural representations of single experiences. This one-trial learning is a necessary but not sufficient property of episodic memory, for various forms of one-trial learning (e.g., fear conditioning to a CS, conditioned taste aversion) do not require a specific recollection of a past event or knowledge about the spatiotemporal context of the learned item. They merely require that an animal change its behavioral response to a certain stimulus as the result of a single, past experience. Similarly, spatial and temporal components of the remembered item are not sufficient markers of episodic memory, at least in Tulving's definition, as even Pavlovian classical conditioning requires a temporal component (i.e., the CS must precede the US) and spatial/contextual conditioning may occur in the absence of specific, autonoetic recollection of the spatial context being conditioned. Thus, although one-trial learning of *what, where,* and *when* may be necessary components of an episodic memory, they can also be important components of other forms of learning and memory.

Given these considerations, what is the most profitable strategy for investigating the neurophysiology of episodic memory, at the level of single-unit response properties, and the unique contribution played by the hippocampus to this form of memory? Presumably, the neural signature of an episodic memory is a reactivation of the neural representation (or some part thereof) that was active during the event itself (McNaughton, 1998). If the hippocampus plays a crucial role in episodic memory, then this role should be evident at some level in the mnemonic properties of location-specific place cells, the most salient and well-studied behavioral correlate of hippocampal CA3 and CA1 neurons in the rat. In their landmark book, O'Keefe and Nadel (1978) proposed that "the hippocampus is the core of a neural memory system providing an objective spatial framework within which the items and events of an organism's experience are located and interrelated" (p. 1). According to their original theory, hippocampal place cells were the anatomical locus of Tolman's (1948) cognitive map, which provided the organism's innate sense of space and its location in that space. They proposed that this mental map was the spatiotemporal framework used to organize the various internal and external stimuli that compose a behavioral event into an explicit memory, in a way that allows adaptive and flexible learning. Although subsequent experimental work has necessitated changes to the details of the original theory, much work on place cells can still be parsimoniously explained in terms of its essential constructs. For example, for many years, the field was mired in a debate over whether space was the only correlate of hippocampal cell firing or whether these cells had nonspatial correlates as well (O'Keefe, 1999; Shapiro and Eichenbaum, 1999). It is now clear that the answer is the latter. However, in experiments that tested simultaneously both spatial and nonspatial correlates, the nonspatial correlates were shown to ride on top of a spatial signal (Wiebe and Staubli, 1999; Moita et al., 2003). That is, the cells responded to unique combinations of locations and nonspatial stimuli. In one of the best examples, Moita et al. (2003) demonstrated that hippocampal cells showed place fields in the initial stages of a fear conditioning paradigm, but they did not respond to the conditioning stimuli. After training, the cells that were selective for location became additionally responsive to the auditory conditioned stimulus (CS), but the rat had to occupy the place field of the cell in order for the cell to respond to the CS. This result can be interpreted as the nonspatial CS being integrated into the spatial framework provided by place cells. Other examples of nonspatial firing of hippocampal neurons also appear to have a consistent, spatial signal, including the "misplace" cells originally reported by O'Keefe (1976) (i.e., cells that fire in a specific location in the presence of an unexpected object or in the absence of an expected item). Indeed, the activity of the original "place cell" described by O'Keefe and Dostrovsky (1971) required not only that the animal occupy a particular place, but also that the experimenter at the same time lightly restrain the animal with the hand behind the animal's back and the thumb and index finger on its arms.

Although the relationship between the spatial and nonspatial firing of hippocampal neurons is far from settled ("does the nonspatial information always ride on top of a spatial signal?"), an eventual resolution would still leave unsettled the question of whether this representation is critical for episodic memory. How can we make progress in understanding the role of the hippocampus in human episodic memory from studying place cells in rats? The most profitable approach is to make the assumption that, even though the rat may not have episodic memory as experienced by humans, the computational functions of the hippocampus are preserved across species. That is, the basic neuroanatomy and circuitry of the hippocampus is very similar (although not identical) in rodents and primates (Amaral and Insausti, 1990; Witter and Amaral, 2004), and evidence from monkeys and humans suggests that there are basic similarities in the information processing that occurs in both species (Nishijo et al., 1997; Rolls et al., 1997; Ekstrom et al., 2003; Ludvig et al., 2004). It is reasonable to assume that the hippocampus performs the same basic computation on its inputs in all species (with perhaps some species-specific modifications to optimize its performance for the idiosyncratic tasks of that species). In humans, the inputs to the hippocampus may have certain properties that enable hippocampal processing to create representations that downstream regions need for the storage/recall of explicit, episodic memories. In rats, however, the input and output regions of the hippocampus may not have the requisite complexity to support the self-conscious, autonoetic properties that are ascribed to episodic memory. Nonetheless, if one understands the basic nature of hippocampal processing in the rat—the transformations of input representations within the different stages of the hippocampus and the properties of hippocampal output representations—the assumption of computational homology among species will allow such studies of place cells on rats to inform the research on human and nonhuman primates, which may have more complex neural representations that are indeed capable of true, episodic memory.

CA1, CA3, AND ASSOCIATIVE MEMORY FUNCTIONS

What are the computational functions of the hippocampus? The seminal ideas of Marr (1971) still dominate computational theories of the associative memory functions of the hippocampus. According to many current theories (McNaughton and Morris, 1987; O'Reilly and McClelland, 1994; McClelland and Goddard, 1996; Rolls, 1996), hippocampal processing is characterized as an interaction between two, sometimes competing, processes. Pattern separation refers to the ability of a network to create and store independent representations of two input patterns that are overlapping and similar. For example, an episodic memory can be thought of as a set of stored associations among the representations of the many distinct cues and stimuli that the animal experiences at a moment of time. Many experiences share a host of common elements, and storage of such representations in the synaptic matrix of an associative network can easily lead to errors in recall when the network attempts to store many similar memories (e.g., where did I park my car this morning and yesterday morning?). One solution to this problem is to create new representations from the originals, in which the new representations share fewer common elements. With such a recoding, the network can store many more memories before interference between the representations begins to cause recall errors.

In contrast to pattern separation, pattern completion refers to the ability of a network to reactivate the entire, stored representation based on incomplete or degraded input patterns. Thus, a single retrieval cue (the smell of cinnamon in a kitchen) can reactivate a vivid memory of a childhood experience watching grandma bake cinnamon rolls in her kitchen. Similar to pattern completion is the phenomenon of generalization, in which the system may store two slightly different input patterns as the same representation, ignoring the differences between the inputs and extracting the similarities.

A number of theorists have proposed that the DG is the region of the hippocampus that is critical for pattern separation, whereas the recurrent collateral system of CA3 makes it a natural candidate for the autoassociative memory functions required of a pattern completion device (McNaughton and Morris, 1987; Rolls, 1996). In simultaneous recordings from CA1 and CA3 place cell ensembles, Lee et al. (2004b) obtained evidence in support of the autoassociative functions of the CA3 network (Fig. 1). In these experiments, rats were trained to run for food reward on a circular track with four distinct visual and textural cues, each covering 90° of the track. On the circular curtains surrounding the track were six salient landmarks. After many days of training in this standard environment, the place cells were recorded under standard conditions and under conditions in which the circular track and the set of distal landmarks were rotated in opposite directions ("mismatch" sessions). In the mismatch sessions, both CA1 and CA3 place field representations showed evidence of remapping, as some place fields from the standard session disappeared, some place fields
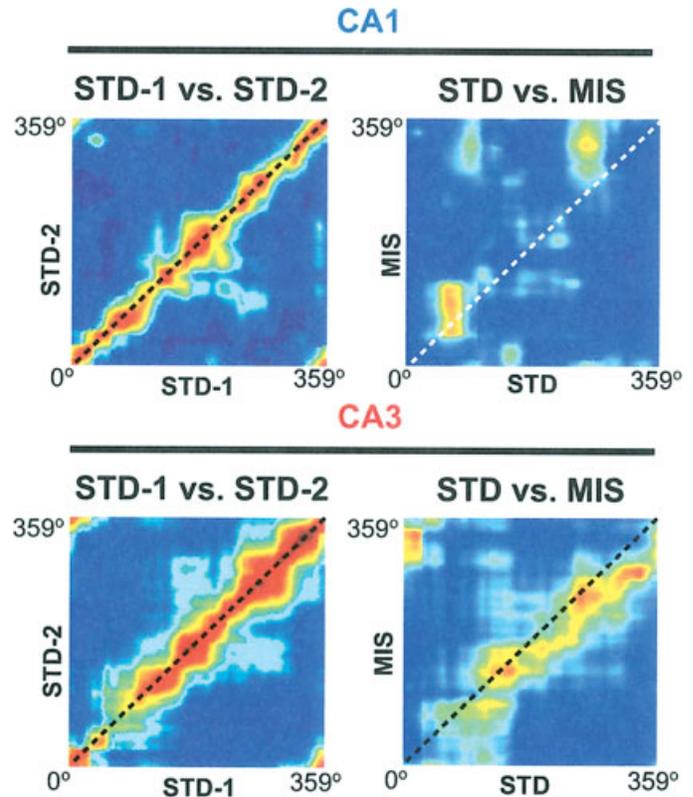

FIGURE 1. Difference in population coherence between CA1 and CA3 place cell ensembles in a cue-mismatch environment. Each graph is a population correlation matrix for neural firing at different locations on a circular track (linearized from 0° to 359°) in two different sessions. On the left are correlation matrices for two different standard sessions (STD-1 and STD-2), in which the cue configurations were identical. The red regions along the diagonal indicate that the same place cells fired at the same locations in each of the two sessions. On the right are correlation matrices between a standard (STD) and a mismatch (MIS) session. The CA3 matrix (bottom) still shows a band of high correlation (shifted slightly off the diagonal), indicating that there is a tendency for the population to maintain coherence between the representations of the standard and mismatch environments (although note that the correlations are lower than in the STD-1 vs. STD-2 matrix, indicating some degree of change in the CA3 representation). The CA1 matrix (top) shows no band of high correlation, as the place fields tended to remap, rotate in opposite directions, or become otherwise disrupted. (Modified from Lee et al., Nature, 2004, 430:456–459.)

appeared from previously silent cells, and some place fields were altered in various ways. Other cells maintained their place fields, which either rotated clockwise with the distal landmarks or counterclockwise with the circular track. In agreement with prior studies (Shapiro et al., 1997; Knierim, 2002), the CA1 place field representation split, as equal numbers of cells rotated with each set of cues, and a large number of cells remapped. In contrast, CA3 place fields were less likely to remap, and the place fields that were maintained in both sessions were more likely to rotate with one set of cues (typically the circular track) as a coherent ensemble. This representational coherence in the face of altered input is predicted from the pattern completion/

generalization properties of an autoassociative memory network. These results are in agreement with other behavioral studies with CA3-specific lesions (Gold and Kesner, 2005) and combined recording and behavioral experiments with CA3-specific NMDA-receptor knockout mice (Nakazawa et al., 2002).

Another study with recordings of CA1 and CA3 ensembles came to an opposite conclusion (Leutgeb et al., 2004). In that study, the CA3 representations of two environments were more orthogonal (independent) than the CA1 representations, suggesting that CA3 actually performed a pattern separation function. This apparent discrepancy between the studies can be interpreted as a result of the competition between pattern completion and pattern separation in associative networks (McClelland and Goddard, 1996; Rolls and Treves, 1998; Guzowski et al., 2004). In the Lee study (Lee et al., 2004b), the animals ran in the same room, with the same cues, but the cue arrangement was altered. Under these conditions, the input representations to the hippocampus may not have been sufficiently different, and the CA3 network therefore outputs a more coherent representation. In the Leutgeb study (Leutgeb et al., 2004), in contrast, the two different recording environments were in two separate rooms, which may have altered the input representations enough to cause the CA3 network to form a completely separate representation. A study utilizing the Arc transcription factor activity marker supported this interpretation (Vazdarjanova and Guzowski, 2004). These results may be consistent with the standard model of pattern separation being performed by DG and pattern completion being performed by CA3 (McNaughton and Morris, 1987; Rolls, 1996) by viewing CA3 as the arbiter of the pattern completion/separation competition. The DG may automatically create more dissimilar (not necessarily completely orthogonal) representations of its different entorhinal inputs under all conditions, as expected from a pattern separator. CA3 may receive this orthogonalized input from the mossy fiber synapse of the DG, but CA3 also receives a direct input from the EC, from the same layer (layer 2) that projects to the DG. If the combined input from the DG and from the EC representations of environment B is similar to that of environment A, the activity induced in CA3 may fall within the basin of attraction of environment A and the CA3 network state will naturally relax into the original representation of environment A (pattern completion/generalization). However, as the EC representation of environment B is altered further by increasing changes to environment B, and the DG orthogonalizes the EC inputs to an even greater extent, at some point the EC and DG representations become different enough to induce an activity pattern in CA3 that falls outside the basin of attraction of environment A. If the activity falls within the basin of attraction of another, already established, attractor, CA3 will relax into that attractor state. If the activity does not fall within the basin of attraction of an established attractor, synaptic plasticity may establish a new attractor at the current network state. In either case, the presumed orthogonalization from DG reduced the similarity between the EC representations of environments A and B and allowed the CA3 representation to escape the environment A attractor (pattern separa-

tion). Changes in the relative weight of DG versus EC inputs to CA3 may also tip the balance of pattern completion/separation in CA3. Thus, the DG may perform a pattern separation function, but it is the putative attractor dynamics in CA3 that determines whether an input pattern is similar enough to a previously stored pattern and performs pattern completion/generalization by settling into the attractor basin of the stored pattern, or whether the orthogonalized input pattern is so different from other stored patterns that it settles into a completely new attractor state.

THE HIPPOCAMPUS AND THE 1-TRIAL LEARNING AND LONG-TERM STORAGE OF SPATIOTEMPORAL SEQUENCES

Episodic memory has temporal components at different time scales. A classic example of a temporal tag of episodic memory is remembering parking one's car each day in the same parking lot. When returning to the car, one can recall parking the car in a particular spot that morning and distinguish this from the memory of parking the car in a different spot the morning before. At a finer resolution, individual episodic memories can consist of a brief temporal sequence of events that occurred in a particular episode. For example, one can remember the temporal order of driving down the parking lot aisle, turning the steering wheel, and maneuvering the car into the parking space. How are these fine-scale sequences of events encoded in the brain? Hebb (1949) postulated the notion of a phase sequence, in which neural cell assemblies that represent different time points of a sequence of events become bound by the Hebbian learning rule, such that later reactivation of one assembly can cause the subsequent activation, in order, of the remaining assemblies that represent that experience. The temporally asymmetric nature of long-term potentiation (LTP)-induction (the presynaptic cell must fire within a specific time window before the postsynaptic cell) and spike-timing dependent plasticity are potential mechanisms by which the temporal order of activation of these assemblies may be preserved (Levy and Steward, 1983; Magee and Johnston, 1997; Markram et al., 1997).

Evidence that such phase sequences may be stored in the hippocampus came from a series of experiments by Mehta et al. (1997, 2000). According to theoretical models (Levy, 1989; Blum and Abbott, 1996), temporally asymmetric LTP between place fields should cause a predictable shift in the firing of place cells when the rats run stereotyped routes. If a rat always runs in the order of locations A, B, and C, place cells that represent location A (PC_A) will preferentially increase their connection strengths with place cells that represent location B (PC_B). Similarly, place cells that represent location B will preferentially enhance their connections onto place cells that represent location C (PC_C). As a result, over time, when the rat occupies location A, PC_A will fire and their enhanced connections to PC_B will also cause PC_B to fire, even though the rat has not yet arrived at location B. Consequently, the measured place fields of PC_B expand backward, in a direction opposite to
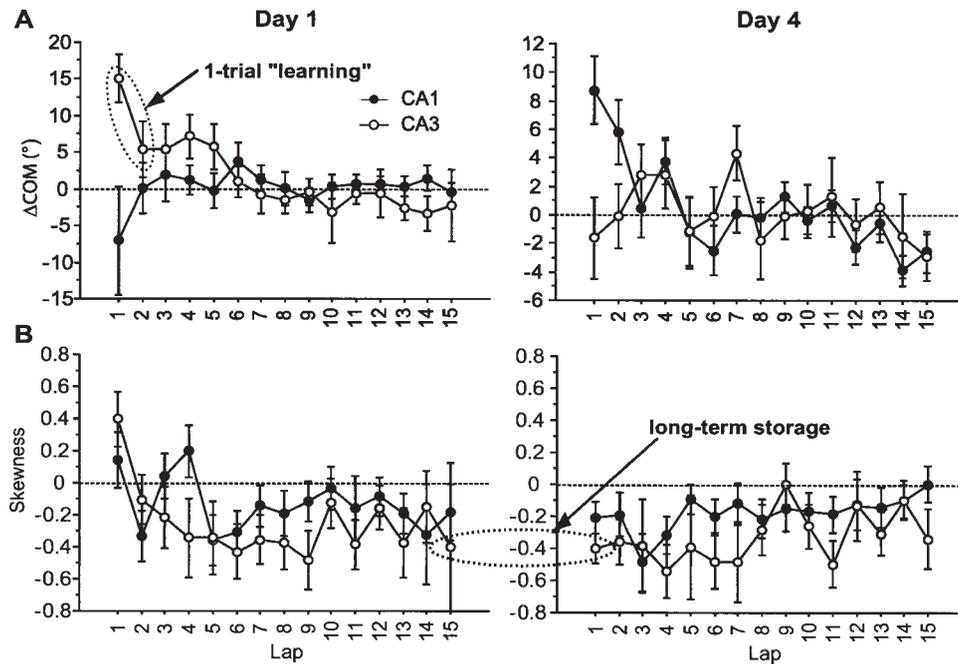
FIGURE 2. Difference between CA1 and CA3 in time-course of backward-shift of place fields in a cue-mismatch environment. (A) On the first day of exposure to the novel arrangement of cues, CA3 place fields demonstrate a strong backward shift of their place field center of mass (ΔCOM) from the very first lap (trial), whereas CA1 place fields display no significant shifts. By day 4, the reverse pattern is obtained, as CA1 place fields show the shift and CA3 place fields no longer shift backward. The pattern on day 4 is similar to the pattern in the familiar, standard environment. (B) On day 1, the CA3 place fields also develop a negative skewness in the shape of the place fields, which may be the cause of the change in place field location shown in A (Mehta et al., 2000). By day 4, the place fields are significantly skewed from the very first lap, and they do not become further skewed. The absence of backward shifts in CA3 after day 1 is presumably due to the long-lasting change in synaptic weights caused by the experience in day 1; that is, the place fields shift back to the maximum extent in CA3 on day 1, and they remain shifted backward and skewed indefinitely. In CA1, after day 1, the place fields reset each day, indicating that the long-term storage of the place field sequences probably resides in CA3. (Modified from Lee et al., Neuron, 2004, 42:803–815.)

the travel of the rat. Similar backward shifts occur for PC_C, which become driven by PC_B over time. Thus, the sequence of locations becomes encoded in the synaptic weights of the network. When the rat is at location A, the inputs that define that location (a combination of external cues and idiothetic cues) cause PC_A to fire and PC_A subsequently causes PC_B to fire as a prediction that the rat will soon arrive at location B (Levy, 1996). A number of recording studies have shown the predicted backward-shift of CA1 place fields when rats run stereotyped, linear routes (Mehta et al., 1997, 2000), and this effect was shown to be dependent on NMDA receptors and to be deficient in aged rats, which show deficits in spatial learning and LTP (Shen et al., 1997; Ekstrom et al., 2001). Moreover, there may be a connection between the backward expansion of place fields and theta-phase precession (O'Keefe and Recce, 1993), resulting in a compression of temporal sequences within a theta cycle allowing a current network state to activate predicted future states within each theta cycle (Skaggs et al., 1996; Samsonovich and McNaughton, 1997; Lisman, 1999; Mehta et al., 2002; Dragoi and Buzsaki, 2006).

In a familiar environment, the backward shift of place fields in CA1 occurs every day that the animal performs the task (Mehta et al., 1997). However, the backward shift does not occur, at the CA1 population level, the first time an animal experiences a cue-altered environment, although it occurs in subsequent exposures (Lee et al., 2004a). The opposite pattern of results occurs in CA3 place fields (Fig. 2). These fields show the backward shift on the animal's first experience in a cue-altered environment, but they fail to show the effect in subsequent exposures to the cue-altered environment and they do not show the effect in a familiar environment (Lee et al., 2004a). Thus, it appears that when an animal experiences novel configurations of environmental landmarks, CA3 place fields begin to encode the spatiotemporal sequences of place fields in that altered environment immediately. Notice that the backward shift occurs between the first and second trials in the newly altered environment, demonstrating that there is a robust, one-trial aspect to the plasticity. In contrast, CA1 does not show the effect at first, but it does show the backward shift on subsequent exposures. These results are similar to other studies that suggest that plasticity in CA3 is necessary for rapid, one-trial learning, whereas CA1 can support learning over a slower time course (Lee and Kesner, 2002; Nakazawa et al., 2003).

Why do CA3 place fields fail to show the backward shift after the first exposure to the new environment and in the familiar environment? In these cells, the backward shift co-occurs with the development of a negative skewness of the place fields
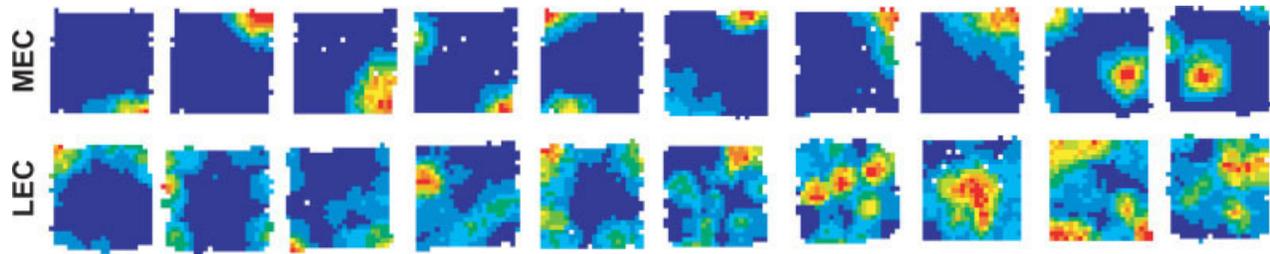
FIGURE 3. Differences between the medial EC (MEC) and the lateral EC (LEC) in spatial specificity. For each area, the spatial firing rate maps of the top 10 spatially selective neurons are displayed. MEC neurons displayed robust spatial tuning, which was, on average, less specific than CA1 place fields (not shown) but was much stronger than LEC neurons. (Modified from Hargreaves et al., Science, 2005, 308:1792–1794.) [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

(Mehta et al., 2000). In the familiar environment and in the subsequent exposures to the cue-altered environments, the CA3 place fields are skewed from the outset and do not change with each lap. It appears that in CA3, place fields shift backward and become negatively skewed beginning with the very first lap in an altered environment, and the synaptic changes that cause this effect are maintained for a long time. This long-term change in CA3 solves a conundrum from the original studies by Mehta et al. (1997, 2000). From those studies, the plasticity in CA1 appeared to be temporary, as the place fields reset back to their initial starting locations and shift backwards anew each day. The backward shift in CA1 was thus unlikely to be a reflection of long-term sequence memory if the effect was so short-lived. The resolution appears to be that the long-term memory resides in the CA3 network (perhaps in the recurrent collateral synapses). The relatively rapid reset in CA1 may be a reflection of the role of this region as a comparator of current input from neocortex (via the EC) with stored sequences in CA3 (Levy, 1989, 1996; Hasselmo and Schnell, 1994; Lisman, 1999; Vinogradova, 2001; Mizumori et al., 2004). That is, CA1 may be specialized for the online creation of sequences that reflect the current entorhinal input into the hippocampus (i.e., "what are the current sequences I am experiencing?"). It compares this sequence with the learned sequence stored in CA3 (i.e., "what are the sequences that usually occur in this context?"). If the current and stored sequences match, then there is nothing new to learn, and the system does not change. However, if there is a mismatch between the current sequences (conveyed by the EC) and the stored sequences in CA3, this may trigger new encoding of the sequences in CA3 to store the new information.

PARALLEL PROCESSING STREAMS INTO HIPPOCAMPUS

In addition to a temporal component, episodic memories have a spatial/contextual component. Hippocampal neurons respond to both spatial and nonspatial stimuli, but a number of studies suggest that the nonspatial inputs may be integrated into a pre-existing spatial framework (O'Keefe and Nadel, 1978; Wiebe and

Staubli, 1999; Moita et al., 2003; Leutgeb et al., 2005). How do these two types of information reach the hippocampus? The EC is divided into two regions that differ markedly in terms of their cytoarchitecture, connections, and electrophysiology (Ramon Y Cajal, 1911; Witter and Amaral, 2004). It has long been known that medial EC contains neurons with some degree of spatially specific firing (Barnes et al., 1990; Quirk et al., 1992; Mizumori et al., 1992). Recent results have demonstrated that these MEC neurons actually encode an exquisite, grid-like map of the environment (Fyhn et al., 2004; Hafting et al., 2005). MEC neurons that are connected with the most septal (dorsal) hippocampus fire at each vertex of a crystalline grid that tessellates the environment into a repeating pattern of equilateral triangles (or hexagons). Cells that project to more temporal (ventral) locations display this same grid pattern at a larger spatial scale. In different environments, each cell displays the same grid pattern. Thus, this pattern is a universal representation that probably performs path integration computations in all environments. The ensemble firing of these grid cells can encode the rat's current location with precision; thus, the MEC is the input to the hippocampus that presumably endows place fields with their spatial specificity.

If spatial information derives from the MEC, do similar properties exist in the lateral EC (LEC)? Hargreaves et al. (2005) recorded from LEC and MEC in regions that project to the dorsal half of the hippocampus (Fig. 3). In that study, spatially selective neurons in the MEC (including two grid cells in a region near the MEC-parasubiculum-retrosplenial border) were recorded as rats foraged for food in a simple square chamber, but little spatial tuning was apparent in LEC neurons. The only two examples of spatially biased firing were from a cell that fired at the edge of the single cue card and a cell that fired at the location where the food pellets dropped from the ceiling. Thus, these cells fired at the locations of salient, local cues. Pilot studies suggested that LEC neurons may also respond to specific objects placed in an environment (Hargreaves, Lee, and Knierim, unpublished). Thus, nonspatial information about specific objects or cues in an environment may be conveyed to the hippocampus through the LEC, which is part of the ventral (what) processing stream of primates, and spatial information may be conveyed to the hippocampus through the MEC, which is part of the dorsal (where) processing stream of primates

(Ungerleider and Haxby, 1994). The hippocampus appears to perform two important computations on these inputs: (1) in contrast to the MEC (Quirk et al., 1992), the place cells of the hippocampus can change their spatial firing properties ("remap") in different environments, either as a result of changing inputs or as the result of pattern separation of similar inputs (Muller and Kubie, 1987; Anderson and Jeffery, 2003; Knierim, 2003). This remapping allows the hippocampus to create context-specific representations of different environments (or even the same environment), which can be used to disambiguate the behavioral contingencies of similar stimuli that can occur in different spatial or behavioral contexts (Nadel et al., 1985); (2) the hippocampus may create configural object + place representations by combining the object-related information from the LEC and the spatial information from MEC. Thus, each context-specific, hippocampal map can become associated with the individual items that occupy locations in the map and events that occur in that environment (O'Keefe and Nadel, 1978; Nadel et al., 1985; Gilbert and Kesner, 2004; Janzen and van Turennout, 2004; Rivard et al., 2004). This binding may also allow the hippocampus to activate the same representation each time the rat enters a familiar environment (Touretzky and Redish, 1996; Redish and Touretzky, 1997; Kentros et al., 1998). These object + place representations may be the rodent analog of event + context or item + source representations that presumably are necessary to support episodic memory in humans (Suzuki et al., 1997; Gaffan, 1998; Davachi et al., 2003; Rolls et al., 2005).

Figure 4 presents a summary diagram of the parallel processing streams through the medial temporal lobe (Burwell, 2000; Witter et al., 2000; Witter and Amaral, 2004). One stream arises from the perirhinal cortex and projects in order to the superficial layers of LEC, distal CA1, proximal subiculum, and back out to the deep layers of LEC. Input into this stream comes from areas thought to be homologous to the object-related, ventral pathway of primates. The other stream arises from the postrhinal cortex [the rodent homologue of primate parahippocampal cortex (Burwell et al., 1995)] and projects in order to the superficial layers of the MEC, proximal CA1, distal subiculum, and deep layers of MEC. Input into this stream comes from areas thought to be homologous to the space-related, dorsal pathway of primates. Although there is crosstalk between these pathways, they are relatively segregated. Notice that the place-related pathway remains relatively segregated from the object-related pathway even in CA1. The two streams become fully integrated only in their projections to the DG and CA3, as LEC and MEC projections converge on the same regions in both of these areas. The output of CA3 is then projected onto the anatomically segregated processing streams in CA1. This anatomy suggests a way of looking at hippocampal processing that is very different from the classic notion of the trisynaptic loop. In this alternative view, direct projections from the MEC to CA1 and subiculum and from the LEC to CA1 and subiculum form two primary, parallel streams that process spatial and object-related information in the temporal lobe. The projections to the DG and CA3 can be considered a side-
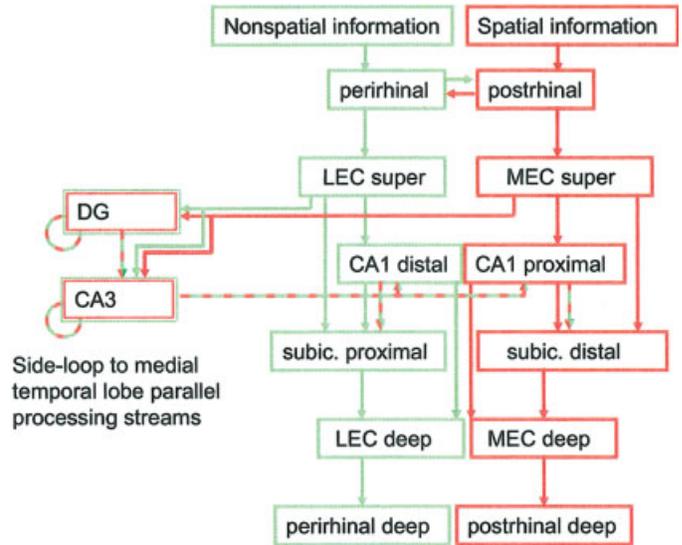

FIGURE 4. Parallel processing streams through the medial temporal lobe. Nonspatial object- or item-related information and spatial information are proposed to be processed through anatomical pathways that are segregated (at least partially) (Burwell, 2000). The two streams converge in the DG/CA3 regions, which outputs a combined object + place representation back onto the segregated, parallel processing streams. Not all pathways are shown in this simplified wiring diagram, including the pathways that demonstrate degrees of crosstalk between the two streams. For example, there are some connections from the perirhinal cortex to MEC and from the postrhinal cortex to LEC, and there are regions in CA1 between the proximal and distal parts where the inputs from MEC and LEC overlap. See Burwell (2000) for more details. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

loop to these primary processing streams. A side-loop does not imply that these areas are unimportant; indeed, damage to the side loops of the motor system hierarchy (basal ganglia and cerebellum) results in profound motor system dysfunction, just as damage to DG and CA3 produces profound memory dysfunction. Rather, the notion is that the primary streams perform much processing without need of the trisynaptic loop. This independence is dramatically demonstrated by the lack of remapping of spatial representations in the MEC and in the subiculum, under conditions in which CA1 and CA3 place fields readily remap (Quirk et al., 1992; Sharp, 1997, 1999). In addition, CA1 place fields are present even when the DG and CA3 regions are lesioned (McNaughton et al., 1989; Brun et al., 2002). For most tasks, the parallel processing streams can carry out their functions without the hippocampal processing. Under certain conditions, however, the object + place representations in the DG and CA3 presumably become critically important, perhaps under conditions in which episodic-like memory demand is high. Thus, when the pattern completion/pattern separation functions are needed, or when the object and place streams need combined object + place representations to support context-dependent behavior for their respective functions, the DG-CA3 loop may impose these projections onto these streams via the CA1 layer. Although the notion that the EC

and parahippocampal areas perform functions that are dissociable from the hippocampus is not new (e.g., Aggleton and Brown, 1999; Bohbot et al., 2000; Egorov et al., 2002; Remondes and Schuman, 2004; Bussey et al., 2005; Hafting et al., 2005), the conceptualization of the EC-DG-CA3 pathway as a side-loop to the primary medial temporal lobe processing streams emphasizes the hypothesis that online behavior, in the absence of strong memory demands, is supported by the parallel processing streams that maintain anatomical segregation. The classic trisynaptic loop may be less involved in ongoing behavior and instead play a supporting role of memory storage or consolidation, or providing object + place (event + context, item + source) conjunctive representations when required by task demands.

CONCLUSIONS

Rats almost certainly possess some analog of human episodic memory, but this capacity may be a qualitatively different experience for the rat than for the human. Given the difficulties in determining whether rats experience "mental time travel" in the way that humans do, we must look at the functions of the rat hippocampus in terms of the information processing and computations that it performs on its input representations. We have to understand the nature of the input and the output representations, the transformations/computations that occur between the input and output representations, and how these representations/computations change with learning. Moreover, these investigations must be performed from the ethological perspective of the rat—what does the hippocampus do for the rat? As more data come in from monkeys and humans, we will need to understand the same issues from the ethological perspective of these species, and the understanding we gain from the rat will be fundamental in guiding the interpretation of these data. But we should not necessarily expect to see, at the level of rat place cell data, direct neural correlates of what we intuitively think of as "episodic memory" in humans. It is the nature of the computations that the hippocampus performs on its inputs that defines its role in cognition and memory. Perhaps the nature of the inputs in humans gives rise to an output that underlies episodic memory, but the nature of the inputs in the rat may be much simpler and give rise to outputs that underlie a very different experience for the rat. The lack of understanding of entorhinal and parahippocampal cortex and of the input–output relationships of the hippocampus has been the largest impediment to progress along these lines, and once we begin to understand the system better at these levels, a lot of the murkiness surrounding these questions will start to become clearer.

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