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BRIDGING THE GAP BETWEEN BRAIN AND BEHAVIOR: COGNITIVE AND NEURAL MECHANISMS OF EPISODIC MEMORY

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The notion that non-human animals are capable of episodic memory is highly controversial. Here, we review recent behavioral work from our laboratory showing that the fundamental features of episodic memory can be observed in rats and that, as in humans, this capacity relies on the hippocampus. We also discuss electrophysiological evidence, from our laboratory and that of others, pointing to associative and sequential coding in hippocampal cells as potential neural mechanisms underlying episodic memory.

Key words: episodic memory, hippocampus, recollection, associations, odor discrimination, digging, rat

A consideration of neural mechanisms that mediate complex behavior in animals can be traced back at least to Small's use of the maze to study learning in rats more than a century ago (Small, 1901). The design of the maze was complex, inspired by the famous maze at Hampton Court in London. Small's aim was to document in detail the course of acquisition of conditioned responses during repetitions of the turns taken as the rat navigated the maze. He observed, as many have since, that rats reduce the number of their errors gradually over many trials. However, occasionally his rats jumped above the walls of the maze and found that they could ''cheat'' by taking a short cut across the maze alleys directly to the goal. Indeed, after as little as a single such experience, rats preferred to take the short cut rather than the route that had been reinforced on many previous trials. This observation led Small to conclude that the gradual conditioning of responses is not sufficient to account for learned behavior and that future experiments should investigate the ''biological character'' of the animal if one is to be able to interpret the findings. We suspect Small was referring primarily to a consideration of the animal's ethology, but a full biological characterization surely extends also to identification of the underlying neuroanatomical pathways and neurophysiological mechanisms.

Here we will focus on Small's striking observation that rats appear to recall specific prior experiences and use this recollection to guide intelligent choices. In current terminology, Small was suggesting that rats have a capacity for episodic recollection. We will also review efforts in our laboratory to understand the cognitive and neurobiological bases for this important and impressive memory capacity.

IS EPISODIC MEMORY A CAPACITY UNIQUE TO HUMANS?

The notion that non-human animals experience episodic recollection has met stiff resistance from the time of Aristotle to the current success of cognitive neuroscience. Aristotle (1931) contended that ''other animals (as well as man) have *memory*, but, of all that we are acquainted with, none, we venture to say, except man, shares in the faculty of *recollection*'' (p. 453; italics added). By ''memory'' Aristotle referred to an elementary matching of current sensations to impressions from prior experience, today called ''familiarity'', as distinguished from recollection of the event in which the information was obtained. Recently, Tulving (2002) maintained this view in his characterizations of episodic memory, claiming that episodic recollection ''. . . has evolved only once, in only one species, although other species would presumably

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benefit from it as much as do humans'' (p. 7). Neither Aristotle nor Tulving provided evidence in support of their contentions.

A recent study, however, challenged this anthropocentric view. Clayton and Dickinson (1998) argued that scrub jays could remember where and when they had stored particular types of food; they referred to this type of memory as episodic-like because this ability reflects Tulving's (1972) original description of episodic memory as oriented to the time and place of the experience. However, there are alternative explanations of the observations on scrub jays. In particular, as noted by Roberts (2002), the scrub jays might base their performance on a sense of differences in the amount of time passed since exposure to the different types of food, or they might be able to perceive the strength of a memory trace or the amount of time that has passed since the experience, and use these signals to make judgments about ''when'' events occurred (see Eichenbaum & Fortin, 2003, for more details on this issue).

Here we will consider two distinguishing features of episodic recollection that offer alternative approaches to exploring the episodic memory capacities of animals. We will focus on the distinction between episodic recollection of specific past experiences, versus a sense of familiarity for past-experienced stimuli independent of recollection—the distinction highlighted in Aristotle's proposal. First, episodic recall is characterized by an all-or-none retrieval of items along with the circumstances of prior experience, whereas familiarity is characterized by a continuous incremental retrieval depending on the strength of memory. Second, vivid recollective experiences are characterized by the ability to replay the flow of events as they occurred in the experience, whereas familiarity supports only judgments about what stimuli were experienced and offers no information about the order of events in the experience.

In the next sections we will consider these distinguishing features of episodic recollection, determine the extent to which animals exhibit these characteristics, and establish the contribution of the hippocampus. This will be followed by a consideration of the neural representations in the hippocampus that may underlie these properties of episodic memory.

DISTINGUISHING THRESHOLD VERSUS CONTINUOUS RETRIEVAL DYNAMICS IN ANIMALS

Over the last 30 years, efforts to characterize recognition memory have led to dual-process theories that distinguish our capacity to recollect prior experiences from a sense of familiarity of stimuli insufficient for recall of the circumstances of prior experiences (for a review, see Yonelinas, 2002). These theories have dissociated recollection from familiarity by taking advantage of their differences in retrieval dynamics. The fundamental distinction lies in the fact that familiarity grows incrementally, depending on the amount of prior exposure and the degree of perceptual match between a current stimulus and stored stimulus representations. In contrast, recollection occurs at a threshold before which no information is recovered, and after which the item to be remembered plus its associations and context are re-experienced.

One of the most compelling methods for distinguishing recollection and familiarity is the analysis of receiver-operating-characteristic (ROC) functions of recognition memory (Yonelinas, 2001). In a typical experiment, human subjects initially study a list of words and then are tested for their capacity to identify those words plus additional new words as *old* or *new*. The resulting ROC analysis plots *hits* (correct identifications of old items) against *false alarms* (incorrect identifications of new items as if they were old) across a range of confidence levels or response bias. The data points are then curve fitted by a model with two parameters (Y intercept and d′) using a least-squares method (see Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998, for details). ROC analysis of human verbal recognition typically reveals an asymmetric function characterized by an above-zero threshold of recognition at the most conservative criterion (zero false alarm rate) and thereafter a curvilinear performance function (Yonelinas, 2001; see Figure 1a). The positive Y intercept is viewed as an index of recollection, whereas the degree of curvature reflects the contribution of familiarity to recognition performance. With appropriate experimental manipulations (see Yonelinas, 2001), the overall ROC curve can be decomposed into separate functions for recollection and familiarity: the recollection ROC

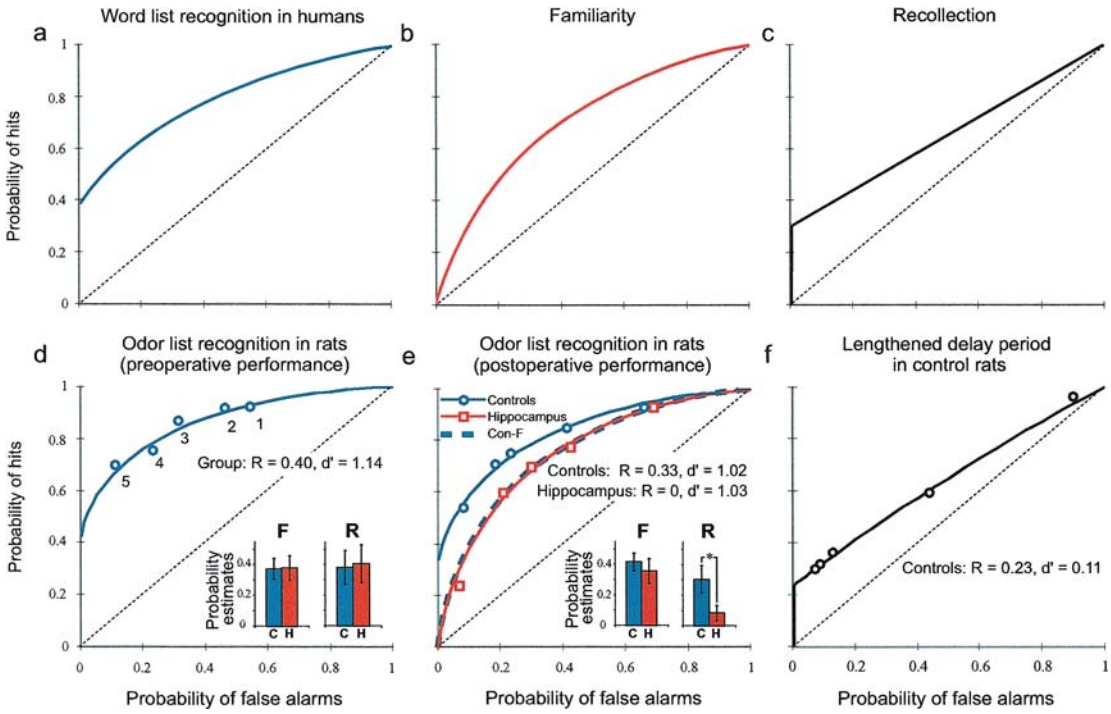

Fig. 1. Receiver operating characteristics (ROCs) for recognition performance in humans and rats. (a–c) Performance of humans in verbal recognition memory. (d–f) Performance of rats on odor recognition memory. (d) Normal rats tested at a 30-min memory delay. Insets show recollection estimates (R), which correspond to the mean Y intercept obtained from the ROC of individual subjects, and familiarity estimates (F) which correspond to the mean degree of curvature (d') of individual ROCs (transformed into a probability in order to facilitate comparisons with R). (e) Control rats and rats with selective hippocampal lesions at 30-min delay; also shown is the ROC curve for Controls with the estimated recollection component (cf. Figure 1c) algebraically removed (Con-F). (f) Control rats tested at a 75-min memory delay. C, control animals; H, animals with lesions to the hippocampus; *, $p < .05$.

curve contains the threshold component of recognition with performance thereafter characterized by a linear function (Figure 1c), whereas the familiarity ROC curve is symmetrical and characterized by a curvilinear function (Figure 1b).

In order to examine the retrieval dynamics of recognition memory in rats, we developed a recognition task that exploits rats' superb memory capacities with odors (Fortin, Wright, & Eichenbaum, 2004). On each daily test session, rats initially sampled 10 common household scents mixed with playground sand in a plastic cup containing a cereal reward. Following a 30-min memory delay, the same odors plus 10 additional odors were presented in random order, and animals were required to identify each odor as *old* or *new* (see Figure 2). In order to plot ROC curves, we needed to compare the hit and false alarm rates under a range of response criteria (from conservative to liberal). To achieve this, different response criteria were encouraged for each daily session using a combination of variations in the height of the test cup (making it more or less difficult to respond to that cup), and manipulations of the reward magnitudes associated with correct responses to the test and the unscented cup (see Fortin et al., 2004).

The ROC curve of intact rats was asymmetric (Figure 1d), containing both a threshold component (above-zero Y intercept) and a strong curvilinear component. This pattern is remarkably similar to the ROC of humans in verbal recognition performance (Figure 1a), consistent with a combination of recollection-like and familiarity-based components of recognition in animals (Yonelinas et al., 1998). Subjects were subsequently divided into two groups matched on both performance components, and one group received selective lesions

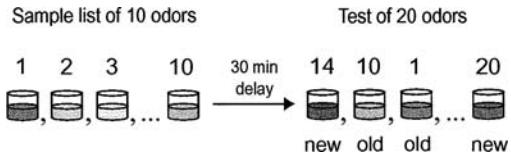

Fig. 2. Odor recognition task for ROC analyses in rats. In each session, rats initially dug for a 1/4 Cheerio reward in each of 10 cups. Each cup was filled with playground sand scented with a distinct odor and presented individually in the front of the home cage. For each of the subsequent 20 test odors, the animal could obtain an additional reward by digging in the test cup if the odor was new (i.e., non-match) or by refraining from digging in the test cup and approaching an alternate empty cup at the back of the cage if the odor was old (i.e., match). We recorded correct responses (hits) and incorrect responses (false alarms) at the alternate cup.

of the hippocampus whereas the other group received sham-control operations. After recovery, we again tested recognition performance at each response criterion. The ROC of control rats continued to reflect both recollection-like and familiarity components. However, the ROC of animals with selective hippocampal lesions was fully symmetrical and curvilinear (Figure 1e), characteristic of recognition memory performance based solely on familiarity (see Figure 1b). To describe these patterns quantitatively, we calculated indices of recollection and familiarity (Figure 1d and 1e insets). Whereas familiarity remained normal in rats with hippocampal lesions, recollection was severely impaired. Furthermore, if the recollective component was algebraically subtracted from the ROC of control animals, the resulting curve superimposed on the ROC of rats with hippocampal lesions (*Con-F*; Figure 1e) provides further evidence that recollection was selectively impaired in the hippocampal group and that their performance relied on familiarity processes.

The overall level of performance (averaged across bias levels) on the task was slightly worse in the hippocampal group (66%, compared to 73% in controls). Given that any performance deficit would be expected to result in an ROC closer to the diagonal (chance performance), it is possible that the ROC of hippocampal animals reflects a generalized decline in memory instead of a deficit selective for recollection. In order to compare their ROC with the pattern of forgetting in normal animals, we challenged the memory of control rats by increasing the memory delay to 75 min. This manipulation succeeded in reducing the overall level of performance of control animals to 64%, equivalent to that of the hippocampal rats. Yet, further testing of the controls showed that their ROC continued to have an asymmetrical threshold component, as indicated by an above-zero Y intercept (Figure 1f—compare with Figure 1c). Notably, the controls' ROC was distinctly more linear than that of both the hippocampal rats and the controls when tested at the shorter memory delay. This pattern of performance suggests that, in normal rats, familiarity fades more quickly than recollection, a result similar to observations on humans (Yonelinas, 2002). Moreover, comparison of the ROC curves in normal rats at a 75 min delay and rats with hippocampal damage at 30 min delay emphasizes the distinction between these two groups in their differential emphasis on recollection and familiarity respectively, even when the overall levels of recognition success are equivalent.

This pattern of findings strongly suggests that rats, and presumably other animals as well, exhibit two distinct processes in recognition: one that is marked by a threshold retrieval dynamic characteristic of episodic recollection in humans; and another that follows a symmetrical and curvilinear processing function characteristic of familiarity in humans. Moreover, these findings show that the hippocampus appears to be critical for this episodic recollective process, whereas familiarity can be sustained by extra-hippocampal areas. These observations match recent findings that distinguish impaired recollection from intact familiarity in humans with putative damage to the hippocampus (Yonelinas et al., 2002).

DISTINGUISHING MEMORY FOR THE TEMPORAL ORGANIZATION OF EVENTS FROM FAMILIARITY FOR THE ITEMS IN UNIQUE EXPERIENCES

Both Aristotle and Tulving characterized episodic recollection as involving temporal organization. Aristotle (1931) emphasized the nature of recollection as involving a sequential recall of serial events in experience. Tulving (1983) contrasted the temporal organization of episodic memory with the conceptual organization of semantic memory. Both characterizations emphasized that vivid episodic

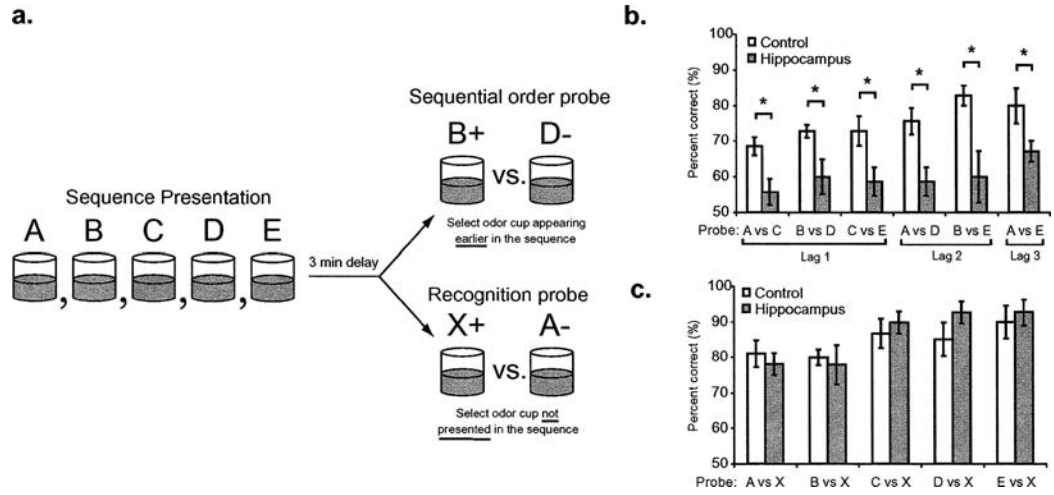

Fig. 3. Sequential order and recognition tasks. (a) *Left*: presentation of sample sequence. Letters A–E designate the five randomly selected odors presented in a particular series. *Right*: examples of the sequential order and recognition probe for that series. + = reinforced odor; − = nonreinforced odor. (b) Performance on the sequential order probe types, grouped according to the lag (number of intervening elements) between items in the probe test. (c) Performance on the recognition probes. X designates a randomly selected odor that was not presented in the series and used as the alternative choice. *Hippocampus* refers to animals with hippocampal damage. *, $p < .05$.

memories are constituted as sequences of events that unfold over time and space. Similarly, recent computational and behavioral analyses also emphasize the temporal organization of behavior in episodic memory (Levy, 1989; Lisman, 1999; Wallenstein, Eichenbaum, & Hasselmo, 1998; Whishaw & Wallace, 2003), indicating that consideration of memory for the orderliness of events in unique experiences may provide another fruitful avenue for exploring the existence of episodic memory in animals.

To investigate the specific role of the hippocampus in remembering the order of events in unique experiences, we developed a behavioral protocol that assesses memory for episodes composed of a unique sequence of olfactory stimuli (Fortin, Agster, & Eichenbaum, 2002; see also Kesner, Gilbert, & Barua, 2002). In addition, our design allowed us to compare directly memory for the sequential order of odor events with recognition of the odors in the list (independent of memory for their order; see Figure 3a). On each trial, rats were presented with a series of five odors, selected randomly from a large pool of common household scents. Memory for the order of each series subsequently was probed using a choice test where the animal received reinforcement for selecting the earlier of two of the odors that had appeared in the series. For example, the rat initially might be presented with odors A then B then C then D then E. Following the delay, two non-adjacent odors (e.g., B and D) would be presented and the animal would receive reinforcement for selecting the odor that appeared earlier (in this case, B). Animals were tested with six different types of probes that assessed memory for different separations (lags) between odor presentations in the series. On each trial, any pair of non-adjacent odors might be presented as the probe, so the animal had to remember the entire sequence in order to perform well throughout the testing session.

Normal rats performed sequential order judgments across all probes, and performance on probes was dependent on the lag, or number of intervening items, indicating that order judgments were easier for more widely separated items. Following assessment of the performance of normal rats, subjects were divided into two groups matched for performance; animals in one group were given selective hippocampal lesions whereas those in the other group received sham operations. After recovery, all animals were tested again on memory for the order of odors in unique odor sequences (see Figure 3b). Normal rats continued to perform well, whereas rats with

hippocampal lesions judged the order of odors at near-chance levels and were impaired at all lags.

The same rats then were tested on their ability to recognize the odors that were presented in the series (see Figure 3a). On each trial, a series of five odors was presented in a format identical to that used in the sequential order task. Then recognition was probed using a choice test in which the animal was presented with one of the odors from the series and another odor from the pool that was not in the series. Reinforcement was given for selecting the odor not presented in the series. For example, the rat might be presented with the series A through E then, following a delay, an odor selected randomly from those initially sampled and an odor not presented in the sequence (e.g., A and X) were presented (with X being rewarded).

Both control rats and rats with selective hippocampal damage acquired the simple recognition task rapidly, and there was no overall performance difference between the groups in acquisition rate. Subsequent analyses of the performance on the different types of probes showed that rats with hippocampal lesions performed as well as normal rats in recognition throughout the series (see Figure 3c). Furthermore, in both groups, recognition scores were consistently superior on probes involving odors that appeared later in the series, suggesting some forgetting of items that had to be remembered for a longer period and through more intervening items.

A potential confound in any study that employs time as a critical dimension in episodic memory is that memories obtained at different times are likely to differ in the strength of their memory traces, due to the inherent decremental nature of memory traces. To what extent could normal animals be using differences in the relative strengths of memory traces for the odors to judge their sequential order? The observation of a temporal gradient in recognition performance by normal animals suggests that memories were, in fact, stronger for the more recently presented items in each sequence (performance on E vs X was better than performance on A vs X; see Figure 3c). These differences in trace strength potentially provide sufficient signals for the animals to judge the order of their presentation. However, the observation of the same temporal gradient of recognition performance in rats with hippocampal damage indicates that they had normal access to the differences in trace strengths for the odors. Yet these intact trace-strength differences were not sufficient to support above-chance discrimination on any sequential order probe (with the exception of deficient but above-chance performance on the furthest separated items; see A vs. E in Figure 3b). These considerations strongly suggest that normal rats also could not utilize the relative strengths of memories for the recently experienced odors, and instead based their sequential order judgments directly on remembering the odor sequence. Our observations suggest that animals have the capacity to recollect the flow of events in unique episodic memories and that the hippocampus plays a critical role in this capacity.

NEURONAL MECHANISMS OF THE HIPPOCAMPUS UNDERLYING EPISODIC MEMORY

In addition to the behavioral and neuropsychological findings described above, characterizations of the firing patterns of hippocampal neurons in animals performing memory tasks have helped clarify the nature of representations within the hippocampus that support episodic memory. Observations from rats, monkeys, and humans, and across many different behavioral protocols, show that hippocampal neuronal activity reflects two of the fundamental features of episodic memory discussed above: the strongly associative nature of the contents of threshold recall, and the temporal organization of episodic memories.

Associative representations. A large body of evidence shows that hippocampal neurons encode an animal's location within its environment. Many studies also have shown that hippocampal neurons fire in association with the ongoing behavior and the context of events as well as with the animal's location. The combination of spatial and non-spatial features of events captured by hippocampal neuronal activity is consistent with the view that the hippocampus encodes many features of events and the places where they occur (for a review, see Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999).

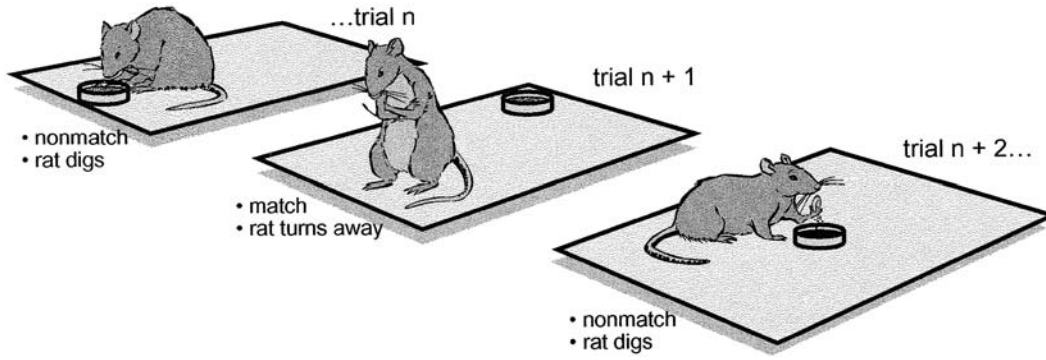

Fig. 4. Odor guided, continuous non-matching-to-sample task. Trial *n* represents a non-match trial where the odor differs from that presented on the previous trial, and the rat digs to find a buried reward. On the next trial (*n* + *1*), the same scent is repeated, but in a different location. As no reward was available, animals quickly learned not to dig on these match trials and to turn away from the cup. On the subsequent trial (*n* + *2*), the odor again differs from that of the previous trial, and the animal digs for a buried reward. Note that the position of the cup is independent of the match/non-match contingency.

Two recent studies highlight the conjunctive coding of events and places by hippocampal neurons. In one study rats were trained on an auditory fear conditioning task (Moita, Rosis, Zhou, LeDoux, & Blair, 2003). Prior to fear conditioning, few hippocampal cells were activated by an auditory stimulus. Following pairings of tone presentations and shocks, many cells fired briskly to the tone when the animal was in its particular *place field*, a location in an environment where a given hippocampal cell increases its firing rate above baseline. The other study examined the firing properties of hippocampal neurons in monkeys performing a task where they rapidly learned new scene-location associations (Wirth, Yanike, Frank, Smith, Brown, & Suzuki, 2003). Just as the monkeys acquired a new response to a location in the scene, neurons in the hippocampus changed their firing patterns to become selective to particular scenes. These scene-location associations persist even long after learning is completed (Yanike, Wirth, & Suzuki, 2004).

Wood, Dudchenko, and Eichenbaum (1999) directly examined the associative coding of hippocampal neurons by having animals perform the same behavioral judgments at many locations in the same environment. Rats were trained to perform a recognition memory task in which cups with scented sand, placed in any of nine locations, were the relevant cues (see Figure 4). On each trial the rats approached the cup and sniffed the odor, and then dug for a reward if the odor was different from the odor presented on the preceding trial (non-match), or turned away if it was the same (match). Because the location of the discriminative stimuli was varied systematically, cellular activity related to the stimuli and behavior could be dissociated from that related to the animal's location. In addition, the stimuli were small cups of scented sand, not enclosed chambers, and the cups were placed on the platform while the rat was present, emphasizing interactions with them as episodes occurring within a single spatial reference frame.

Different hippocampal neurons encoded each element of task events, including both non-spatial and spatial features of the events, and many cells encoded combinations of these features (see Table 1). Some cells fired in association with a feature of the task independent of other features. Many of the cells fired during a particular phase of the approach toward any stimulus cup, whereas others fired differentially as the rat sampled a particular odor, regardless of its location or match/non-match status. Other cells fired when the rat sampled odors at a particular place, regardless of the odor or its status. Yet other cells fired differentially, associated with the match and non-match status of the odor, regardless of the odor or where it was sampled.

Other cells' firing was associated with combinations of events and the context in which they occurred. Some cells fired only if

Table 1

Number of hippocampal neurons with task-related firing correlates (n = 96 of 127 cells).

Nonspatial 50		Spatial 46	
Approach	19	Position	19
Odor	15	Position and odor	5
M/NM[a]	15	Position and M/NM	21
Odor and M/NM	1	Position and odor and M/NM	1

[a] M/NM = match/nonmatch.

the animal began the approach from a particular location, or fired only if the odor was a particular conjunction of the odor, the place where it was sampled, and the match/nonmatch status of the odor. Some of these cells encoded an odor and the location where it was sampled, the odor and its match or non-match status, or a combination of odor, match/nonmatch status, and location. These firing patterns are consistent with the representation of the associations among features of events that are unique to particular episodes.

A recent study reported very similar results in humans (Ekstrom et al., 2003). They recorded the activity of hippocampal neurons as subjects played a taxi driver game, searching for passengers picked up and dropped off at various locations in a virtual-reality town. Some cells fired when subjects viewed particular scenes, occupied particular locations, or had particular goals in finding passengers or locations for drop off. Many of these cells fired selectively, associated with specific conjunctions of a place and the view of a particular scene or a particular goal. Thus, in rats, monkeys, and humans, a prevalent property of hippocampal firing patterns involves the representation of unique conjunctions of stimuli, their significance, specific behaviors, and the places where these events occur.

Representations of sequences of events. Within the overall hippocampal network, cellular activity can be characterized as a sequence of firings representing the successive events in each behavioral episode. A common observation across species is that different hippocampal neurons become activated during virtually every moment of task performance, including during simple behaviors such as foraging for food as well as learning-related behaviors directed at relevant stimuli that have to be remembered (Eichenbaum et al., 1999). This general pattern is observed across a broad range of learning protocols, from studies that involve classical conditioning, discrimination learning, non-matching or matching-to-sample tasks, and a variety of maze tasks. In each of these paradigms, many hippocampal cells show time-locked activations to specific stimuli, reinforcers, and appropriate cognitive judgments and conditioned behaviors.

Furthermore, as described above, many hippocampal neurons show striking specificities corresponding to particular combinations of stimuli, behaviors, and the spatial location of the event. This coding can be envisioned to represent a series of events and their places that compose a meaningful episode, and the information contained in these representations both distinguishes and links related episodes. Recent studies on the spatial firing patterns of hippocampal neurons provide compelling data consistent with this characterization. In one study, rats were trained on the classic spatial alternation task in a modified T-maze (see Figure 5a; Wood, Dudchenko, Robitsek, & Eichenbaum, 2000; see also Ferbinteanu & Shapiro, 2003; Frank, Brown, & Wilson, 2000). Performance on this task requires that the animals distinguish left-turn and right-turn episodes, and remember the immediately preceding episode so as to select the other option on the current trial – task demands similar to that of episodic memory (Olton, 1984, 1986).

The analysis of firing patterns in animals performing this task directly contrasted predictions of the popular cognitive mapping hypothesis of hippocampal function (O'Keefe & Nadel, 1978) with the notion that the hippocampus encodes episodic memories. The key comparison focused on the central ''stem'' of the maze, the portion the rat traversed on both trial types prior to making a left or right choice. According to the cognitive mapping hypothesis, the activity of each cell should identify the location of the rat within its map of the room in which the maze is situated, regardless of the demands of the ongoing alternation task. Therefore, according to this view, each place cell that fired when the rat was on the stem should fire similarly on left-turn and right-turn trials. Alternatively, according to the episodic memory hypothesis, the majority of hippocampal neurons encode an event and its location within one type of

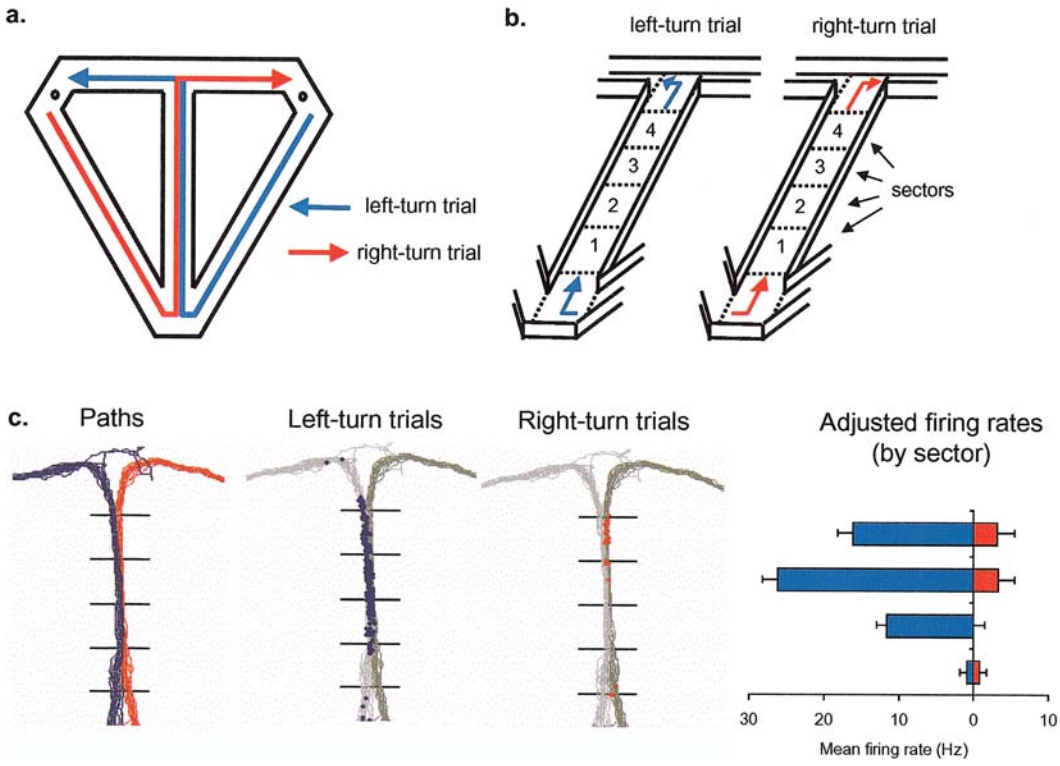

Fig. 5. Hippocampal neuronal activity as rats perform a delayed alternation task. (a) Schematic view of the modified T maze. Rats performed a continuous alternation task in which they traversed the central stem of the apparatus on each trial and then alternated between left and right turns at the T junction. Reinforcement for correct alternations was provided at water ports (small circles) on the end of each choice arm. The rat returned to the base of the stem via connecting arms, and then traversed the central stem again on the next trial. For analysis of neural firing patterns, left-turn (blue arrow) and right-turn (red arrow) trials were distinguished. Only trials that involved correct responses were included in the analyses. (b) Schematic of the stem of the T maze indicating divisions of the central portion of the stem into the four sectors used in the data analyses. (c) Examples of hippocampal cells that are active when the rat is traversing the central stem. These cells fire almost exclusively during either left-turn or right-turn trials. In each example, the paths taken by the animals on the central stem are plotted in the left panel (blue: left-turn trial; red: right-turn trial). In the middle panels, the location of the rat when individual spikes occurred is indicated separately for left-turn trials (blue dots on light grey path), and right-turn trials (red dots on dark grey path). In the right panel, the mean firing rate of the cell for each sector, adjusted for variations in firing associated with covariates (see text), is shown separately for left-turn trials (blue) and right-turn trials (red).

episode, leading to the prediction that most cells should have fired when the rat was on the stem during either the left-turn or right-turn episode, but not both. Notably, the activity of a smaller subset of hippocampal cells was expected to reflect the common features of the two types of episodes to allow the linking of similar episodes, in this case the common locations traversed on both trial types (Eichenbaum et al., 1999).

Our analyses separated firing patterns associated with possible differences in the animal's speed of movement as it traversed the maze stem, possible differences in its head direction, and possible differences in lateral position on the stem. Taking into account these potential confounds, we directly compared firing rates during the performance of left-turn and right-turn trials as animals traversed sectors of the stem (see Figure 5b). A typical example is shown in Figure 5c. This cell fired almost exclusively as the animal reached the end of the stem during the performance of left-turn trials, and fired hardly at all on right-turn trials. Importantly, other cells showed similar selectivity as the animal sequentially traversed each part of the stem. Indeed, virtually all cells that fired when the rat was on the maze stem,

and whose differential activity could not be accounted for by differences in running speed, head direction, or location on the two trial types, fired differentially on left-turn versus right-turn trials. The majority of cells showed striking selectivity, firing at over ten times the rate on one trial type, suggesting they were part of the representations of only one type of episode. As predicted, a smaller number of cells fired substantially on both trial types, potentially providing a link between left-turn and right-turn representations for the common places traversed on both trial types.

Taken together, these results suggest that hippocampal neurons represent the series of locations, and the events that occur at those locations, which compose each type of trial episode. Consistent with this notion, recent studies have characterized the off-line memory processing of previous spatial experiences as the sequential activation of places (Lee & Wilson, 2002; Louie & Wilson, 2001; Nadasdy, Hirase, Czurko, Csicsvari, & Buzsaki, 1999). These findings challenge the notion that the hippocampus simply encodes a static map of space (O'Keefe & Nadel, 1978) and support the idea that hippocampal ensembles represent spatially extended experiences as sequences of events and the locations where they occur (Eichenbaum et al., 1999). Such a representation of spatial experiences attests to the ability to retrieve specific spatial memories of previous experiences in the same environment.

CONCLUSIONS

Even with the full emergence of the field of cognitive neuroscience, we are barely beginning to understand the fundamental brain mechanisms of complex behavior and cognition. The findings reviewed here address one important area within that large domain, specifically the cognitive and neural mechanisms of episodic memory. We have envisioned episodic memory as the rapid encoding of episodes as sequences of conjunctive features of events and their places. The hippocampus is critically involved in the encoding and retrieval of episodic memories and, in our view, does so via supporting two information-processing mechanisms: the rapid encoding and threshold retrieval of associations that comprise distinct events, and the temporal organization of event representations into complete replays of experiences.

In behavioral and anatomical studies, we have found that animals demonstrate these features of episodic memory, including threshold retrieval dynamics and memory for sequences of events in unique episodes. Furthermore, these capacities are critically dependent on the hippocampus. Consistent with these observations, hippocampal neuronal representations reflect associations among items that comprise events and these event representations are organized to encode behavioral sequences. The contents of hippocampal neuronal representations can be characterized as a broad range of stimulus and behavioral events and contingencies that characterize the task at hand, and the places where these events occur. In addition, a subset of hippocampal neurons is selectively activated in association with each and every event throughout task performance across a broad range of behavioral protocols. Thus, hippocampal population activity can be viewed as a continuous and automatic recording of attended experiences (Morris & Frey, 1997).

These observations can be incorporated into a model of neural mechanisms that support episodic memory (Eichenbaum et al., 1999). According to this model, the circuitry of the hippocampus is ideally suited to encode events as associations among stimuli, actions, and the surrounding context, and to encode whole experiences as sequences of those contextually defined events. To the extent that the hippocampus represents events as conjunctions of items and their contextual associations, retrieval of an item from the hippocampal network would be expected also to result in retrieval of the associated context of the item—such a representational scheme could underlie the threshold dynamics of memory retrieval supported by the hippocampus. Also, to the extent that hippocampal networks bind representations of events in the order in which they are experienced, when the threshold for recall is reached, then retrieval of a sought item would be expected to result in retrieval of the flow of events that compose the entire experience—such a representational scheme could underlie the ability to remember the order of events in unique experiences. This kind of neural organization can provide the substrate for the phenomenology of features of

episodic memory observed in animals. Furthermore, one may envision that these fundamental information-processing characteristics also may underlie the subjective experience of episodic recollection in humans.

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