Representing episodes in the mammalian brain

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Memory lets the past inform the present so that we can attain future goals. In many species, these abilities require the hippocampus. Recent experiments, in which memory demand was varied while overt behavior and the environment were kept constant, have revealed firing patterns of hippocampal neurons that corresponded with memory demands and predicted performance. Although the active population appeared to be 'place cells' that signalled location, it actually included cells the activity patterns of which distinguished the recent or pending history of behavior during identical actions that occurred in the same place. Different populations of hippocampal cells fired as a rat walked along the same spatial path on the way to different goals, and coded past, present and pending events. Other experiments provide converging data that neuronal activity is modulated by goal-directed behavioral episodes. Together, these firing patterns suggest a testable mechanism of episodic memory coding: that hippocampal dynamics encode a temporally extended, hierarchically organized representation of goal-directed behavior.

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Introduction

The purpose of memory is informed action. Human memory encodes new facts and even the briefest events instantly, and can recall them years later to accomplish specific goals. Psychologists describe this declarative memory (see Glossary) [1] as including semantic and episodic features, in that we store both the facts that we learn about the world and the autobiographical information that we remember within a temporal and personal context, respectively [2]. Together, these features let any aspect of past experience be used to anticipate the probable outcome of familiar situations, and thereby inform adaptive behavior. Vastly different situations can evoke similar memories as psychological commonalities are recognized, and conversely, identical physical stimuli can convey diverse meanings at different times. We, thus, recognize both the similarities and the differences of situations, and act by retrieving selectively from memory the relevant features for attaining current goals.

The human hippocampus is crucial for the rapid acquisition and persistence of new episodic [3] and new semantic memories [1,4]. The comparative neuroanatomy and physiology of the hippocampus suggest a memory machine — a network designed to rapidly encode arbitrary coincidences of highly processed cortical information along with key motivational signals. Non-verbal animals appear to possess both 'episodic-like' and 'semantic like' memory, episodic-like memory defined operationally in tasks that require knowing what, when and where [5], semantic-like memory in tasks that require flexible use of established memories to guide behavior. Hippocampal lesions in rats cause enduring deficits in a wide variety of tasks that include such memory demands (reviewed in [6,7]).

In this review, we focus on recent cognitive physiology experiments that have begun to reveal how these memory functions could be coded in part by hippocampal neurons. In the experiments, neuronal activity is recorded while animals perform hippocampus-dependent tasks that explicitly and selectively vary memory demands. The results show that the firing patterns of hippocampal neurons reflect the goal-directed structure of experience and reveal a temporally organized and extended code that predicts memory performance. Such coding by the hippocampus dovetails with requirements for remembering the facts and events that define behavioral episodes.

Memory, goal-directed action, and the hippocampus

Memory guides behavioral episodes that are initiated by appetitive and ended by consummatory behaviors. Such episodes are goal-directed and temporally extended (see Glossary), so that memory enables varied adaptive responses at different times across similar situations. For example, the radial maze tests recent spatial memory by training rats to find food at the end of each of eight arms [8]. The arms are baited only at the start of a daily trial, so to forage optimally, the rat must enter each arm once and not re-enter arms visited previously that day. The arms are distinguished only by their spatial location, and no stimuli signal whether or not an arm has been visited. Although normal rats choose arms in

Glossary

+ (plus) maze: A maze shaped like a plus sign (see Figure 1).

Allocentric and egocentric space: These two terms denote environment-centered and body-centered frames of reference.

Declarative memory: Memory in the everyday sense of the word, it includes both memory for facts and events (semantic memory), and memory for the events one has experienced in one's own past (episodic memory). Declarative memory is formed rapidly expressed flexibly, and is dependent on the intact function of the hippocampus. These cognitive and neuronal features distinguish declarative from other types of memory, such as memory for motor sequences.

Fornix lesions: The fornix is a major fiber bundle that connects the hippocampal system with subcortical structures. Fornix lesions cut that bundle and alter the neurochemistry and physiology of the hippocampus, but hippocampal neurons remain alive. The memory impairments following fornix lesions are typically equivalent to those caused by complete hippocampal lesions.

Place field: The location in an environment where the firing rate of a single hippocampal neuron significantly exceeds its mean or baseline firing rate. Hippocampal CA1 neurons typically fire in one or two local patches in a given environment and are silent elsewhere; the patches associated with high activity comprise the place field of the cell.

Prospective coding: A neuronal signal related to expected events. In the context of this review, prospective coding refers to place fields that are influenced by the goal of the journey and, thus, by pending events.

Retrospective coding: A neuronal signal related to past events. In the context of this review, retrospective coding refers to firing fields that are influenced by the journey taken prior to entering the place field.

Retrospective coding fields: Place fields that are selective to the origin of a journey and thereby show retrospective coding.

Spatial behavior: In the context of this review, spatial behavior describes the movements of an animal through the environment, and are measured by the location, direction, and velocity of those movements.

Temporal asymmetry: Like a narrative structure, a temporally directed sequence with a beginning, middle and end that cannot be interchanged without distorting its meaning.

Temporally extended: Events can be momentary, but episodes are typically prolonged and include a linked series of events that continue through time. The duration of an episode defines its temporal extent.

Workspace: In computational and cognitive science, a substrate for representing and manipulating items of information, especially their systematic inter-relationships.

The following terms all refer to task contingencies:

Matching-to-place: A win-stay task in which reward is obtained repeatedly by returning to the same location (e.g. entering the East arm in a + maze).

Serial reversals: Tasks in which consistent stimulus–response contingencies are switched repeatedly but only after criterion performance is reached for a given discrimination.

Spatial alternation: A win-shift (see Glossary) task in which reward location is switched from one trial to the next (e.g. left, right, left, right...).

Spatial delayed non-matching to sample (DNMS): A win-shift task given in trial pairs in which an animal is allowed to go one place to get reward (the sample location), but must go to another location (a non-match) to get a second reward.

Vicarious trial and error: When rats reached the choice point of the maze, they often look back and forth as though considering which choice to make. This was first described as 'vicarious trial and error' by Evelyn Gentry in an unpublished Masters thesis supervised by Karl Muenzinger (1938, Vicarious trial and error at the point of choice: I. A general survey of its relation to learning efficiency).

Win-stay: Consistent contingencies, so that same behavior is rewarded from trial to trial (e.g., turning right at a choice point).

Win-shift: The counterpart of the above — behavior has to change from one trial to the other. For instance, to rapidly retrieve food placed at the ends of a radial 8 arm maze, a rat has to avoid entering the same arm twice.

unpredictable sequences, they almost never err, whereas rats with hippocampal damage perform at chance. The task exemplifies 'episodic-like' memory because the rat has to remember 'where' and 'when', the spatial and temporal contexts of behavior [5]. In this case, the significance of a given arm changes on the basis of remembered events, which in turn define the goal of imminent actions. Just as our cognition is formed retrospectively on the basis of the past and directed prospectively toward a future goal, rats minimize the number of items in memory by switching from a retrospective (arms already visited) to a prospective (arms yet to be visited) memory strategy after half the arms have been visited [9]. In other words, after the rat learns the rules and cognitive structure of the task, he can use memory both to keep track of the arms he's visited and to anticipate which arms still contain reward on a given day. Thus, goal-directed appetitive behavior is guided by previous experience that provides prospective information, and the events surrounding consummatory behavior are informed retrospectively by the history of actions that led to reinforcement.

Memory demand, task performance and hippocampal coding

Spatial memory and place fields

If hippocampal neurons are required for coding remembered episodes, then their activity should reflect memory demands. Normal rats learn spatial memory tasks rapidly, and hippocampal neurons rapidly acquire striking spatial firing correlates. As a rat moves through a familiar environment, the firing rate of hippocampal pyramidal cells varies with the current location of the animal: each active cell fires rapidly in localized patches, or place fields (see Glossary) [10]. Place fields form rapidly and stabilize within minutes as a normal rat explores previously unfamiliar places [11]. Continued plasticity is revealed daily as the centers of CA1 fields shift toward the start of repeated trajectories [12,13]. Beyond such behavioral correlates, place field instability predicts spatial learning and memory deficits.Place field reliability and selectivity correlate with overall performance levels in the radial maze task [14,15]. Unlike normal rats, mice that forage randomly have place fields that are relatively unstable across repeated recording sessions in the same environment. After training in a goal-directed navigation task, however, the mice that learned the task developed stable hippocampal place fields, whereas the others neither learn nor develop stable fields [16]. Treatments that block the establishment of stable place fields also impair spatial learning [17,18,19•]. Just as some people become forgetful in old age, spatial learning is likewise impaired in some aged rats. The age-related deficit is correlated with reduced hippocampal synaptic plasticity and place fields that are both unresponsive to environmental changes and unstable in repeated explorations of the same environment [20,21]. These place field abnormalities are observed most often in CA3 cells [22], in which

age-related synaptic plasticity mechanisms are most compromised [23]. Together, the correspondence between learning and place field formation and the covariance of memory performance with place field stability suggest that hippocampal cells acquire task-related firing patterns during learning episodes, and that these firing patterns encode key information for performing memory tasks. If hippocampal cells contribute to memory by encoding spatial representations through stable place fields, then other coding mechanisms must distinguish different episodes that occur in the same places. Such coding mechanisms have now been observed in the hippocampus.

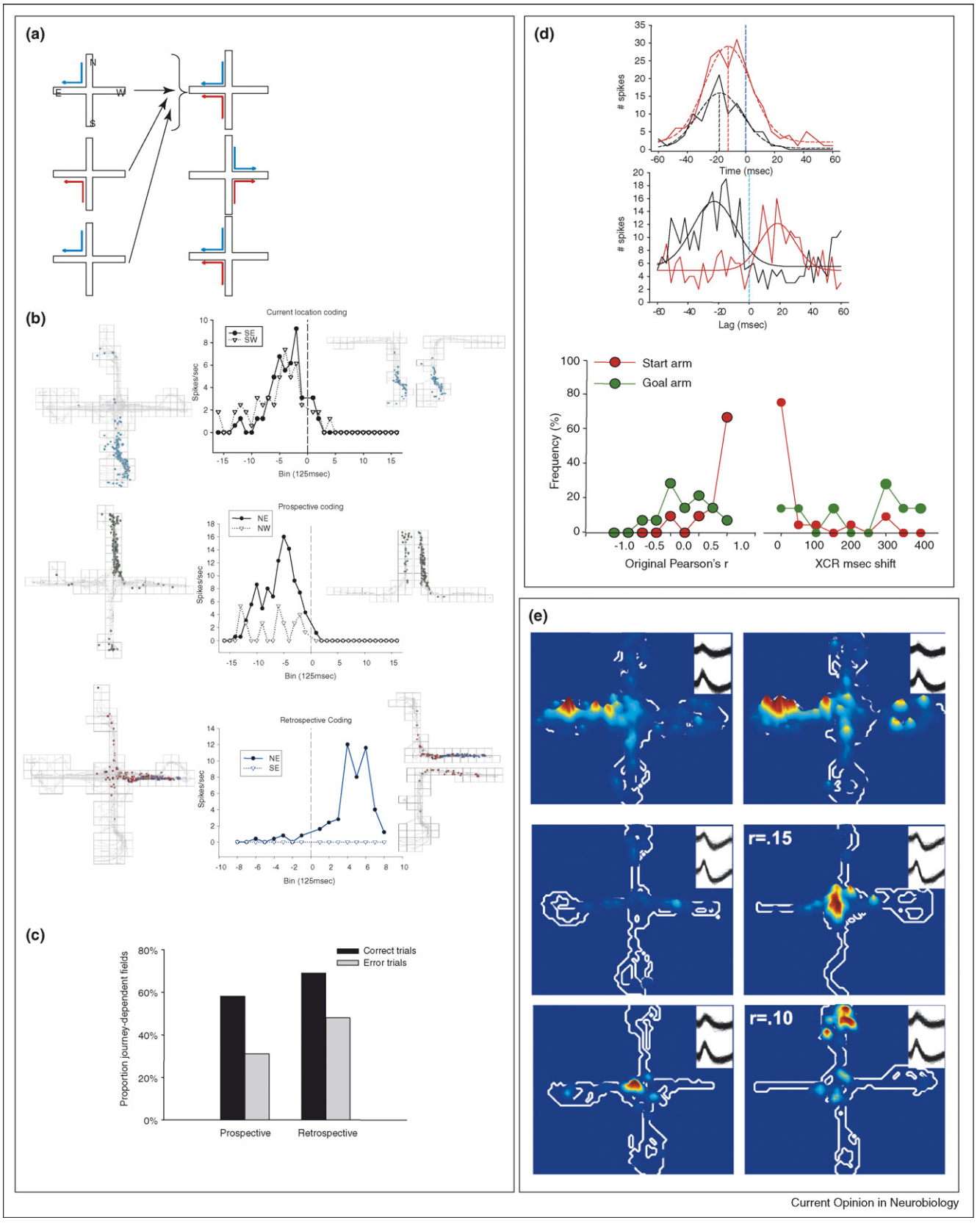
Coding behavioral episodes

Episodic coding was first suggested by two important studies that revealed that behavioral context influences hippocampal representations even when motivation, overt behavior and spatial location are the same [24,25]. In both experiments, rats were trained in spatial alternation (see Glossary) tasks that required them to move along a common spatial path toward a choice point that led to one of two different spatial goals. In both experiments, it was revealed that ongoing hippocampal activity was modulated by recent or pending events — the temporal context of behaviour. One study used a modified T-maze and trained rats to walk from the start of the stem to a choice point at which the rat could turn into either the left or the right goal arm to get food. Each goal arm had a return arm that led back to the start of the stem. The rat was trained to return to the start of the stem and enter alternating left and right goal arms, following a 'figure 8' trajectory. Note that in the stem, spatial location and behavior were identical, but the recent past and the imminent future of the behavior differed during the left- versus right- going trials. About 34% of the cells with fields on the central stem fired equivalently during both left- and right- going trials, demonstrating normal place fields. But even when all other aspects of behavior and location were identical, ~66% of the CA1 cells with place fields in the stem fired significantly differently during left- and right- going trials [25]. Some of these cells fired exclusively during (for example) left going trials and never fired during right going trials; other cells were rate modulated, so they fired at significantly higher rates in the stem during one trial type; others fired in different locations along the stem. More recent data shows that the differential firing appeared as rapidly as the rats acquired the alternation task, during the first day of training [26••]. The influence of the goal on ongoing behavior was revealed as place fields shifted towards the goal across repeated trials within the same recording session [26••]. In a different experiment using the same modified T-maze, cells in the dorsocaudal medial entorhinal cortex (the same region containing 'spatial grid cells' [27]) showed even more robust trajectory dependence than those in CA1 (Lipton PA, White JA, Eichenbaum H. Abstract number 66.6/Z23. Society for Neuroscience Meeting, Atlanta, Georgia, 2006). The entorhinal 'grid' could thereby contribute to coding a memory 'workspace' (see Glossary), as suggested by researchers of neuropsychology [28]. In another study, rats were trained to make alternating paths to and from a central start arm to one of two different goals in a W-shaped track [24]. Because the rat exited and then re-entered the common arm in each trial, firing related to either the pending (prospective coding; see Glossary) or the recently chosen goal arm (retrospective coding; see Glossary) could be distinguished. In this case, only a few CA1 place fields showed retrospective coding and even fewer showed prospective coding; both types were more common in lateral entorhinal cortex [24]. In the same task, preliminary data suggest that subicular cells also show prospective and retrospective coding (L Frank, personal communication). By selectively varying the recent history and pending goal of behavior, these experiments demonstrated that each examined component of the hippocampal system is sensitive to behavioral context. The results imply that memory signals — information about the recent past and indication for the imminent future — are coded by the hippocampal network.

Goal-directed episodic coding

Coding by hippocampal neurons has been more strongly linked to memory by extending this experimental strategy to hippocampus-dependent tasks that explicitly vary memory demand. One experiment described retrospective and prospective activity by recording neural activity in rats performing a spatial win-stay task with serial reversals in a + maze (see Glossary; Figure 1a; [29]). Rats were trained to go from either a North or South start arm to find food at the end of the East or West goal arm. The start arm varied from trial to trial, whereas the rewarded arm was kept the same within each block of ~10 trials until the rat responded reliably, at which point the goal was switched. The rats were kept on a platform for 30–60 s between trials, so that the beginning and end of each behavioral episode was distinct. To find food efficiently, the rat had to remember the current goal location, which varied with the trial block — the 'where' and 'when' of episodic-like memory. The rats moved along common spatial paths during different goal-directed journeys guided by identifiable and dissociable memory demands. In each start arm, memory for the current goal guided the imminent behavioral discrimination; in each goal arm, memory of the most recently exited start arm provided additional information. Fornix lesions (see Glossary) impaired choice accuracy, so that although the rats entered the goal arms readily, they only entered the one containing food by chance, proving the hippocampal system was necessary for successful memory performance. NMDA lesions of the hippocampus proper caused similar deficits (ML Shapiro and J Ferbinteanu, unpublished), proving that hippocampal neuronal activity was crucial. Memory coding by hippocampal neurons was

Figure 1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(b)
Current location coding
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Spikes/sec
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Bin (125msec)
Retrospective Coding
NE
SE
Spikes/sec
Bin (125msec)
(c)
Correct trials
Error trials
Proportion journey-dependent fields
80%
60%
40%
20%
0%
Prospective
Retrospective
(d)
spikes
Time (msec)
spikes
Lag (msec)
Start arm
Goal arm
Frequency (%)
Original Pearson's r
XCR msec shift
(e)
r=.15
r=.10
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revealed by differential place field activity in the same locations during different journeys, for example, in the N start arm during NE versus NW journeys, or in the W goal arm during NW versus SW journeys (Figure 1b). Standard place fields were similar during both types of journeys and showed current location coding. Fields in a goal arm that had varied activity depending upon where the animal started the trial defined retrospective coding; fields in a start arm that had varied activity depending on the location of the current goal defined prospective coding. Most fields showed either prospective (58% of the fields in the start arms) or retrospective (69% of the fields in the goal arms) coding. Analogous coding features have also been observed in the human and nonhuman primate hippocampus. Monkeys trained to associate specific spatial targets in different visual scenes develop hippocampal codes that predict correct responses [30]. Hippocampal neurons recorded from people trained to perform a virtual navigation 'taxi driver' task were described as having place fields, but an even larger proportion were modulated by the goal of the virtual journey (see supplementary material table 2 in [31]).

Goal-directed memory demand, rather than incidental aspects of behavioral history (e.g. different spatial paths), determines the extent to which hippocampal neurons distinguish among different memory episodes that overlap in the same places.

In each experiment that has reported memory coding, the rats were trained to distinguish different journeys — behavioral episodes that included overlapping trajectories that were directed to distinct goals. For example, a recent experiment recorded hippocampal activity while rats searched for food in a + maze (Figure 1e). In different tests, the food was either placed randomly, so the rat could not use a goal-directed strategy, or placed repeatedly and predictably in one arm so that the rat performed a matching-to-place (see Glossary) memory task. After 15 trials, the goal was switched to the opposite arm for another block of 15 trials. Differential firing patterns analogous to the prospective and retrospective coding just described emerged during the goal-directed, but not during the random foraging tasks [32••]. By comparison, in an entirely different procedure rats were trained to move across an open field through a sequence of different linear paths that overlapped in one common segment [33•]. If the rat was rewarded at the end of the common segment, so that the goal of the behavior in that segment was identical even if the preceding paths were different, no differential activity was observed in the place fields in the common segment. If, however, training included stimuli that distinguished the different paths to or from the common segment, or if reward was given only after the choice point so that distinct paths led through the common segment on the way to different goals, then hippocampal neurons fired differently in the common segment [33•].

Nonspatial goals can also define episodes that are coded by distinct patterns of neuronal activity in the hippocampus. Rats were trained to use their deprivation state (hunger or thirst) to select among three visually distinct and movable goal boxes to obtain reward [7]. Each goal box was mounted at the end of an arm of a 4 arm radial maze. As in the experiments described above, the rat had to walk through a start arm along a common path to a choice point to access to the goal boxes. For each rat, one goal box was paired with powdered rat chow, another with water drops, and a third had no reward; the specific box and reward pairings were consistent for each rat and counterbalanced among rats. Rats were food or water restricted on alternate days, and given six trials to find the appropriate reward. Only the goal box designated to contain the reward appropriate to the deprivation state was baited. The goal boxes were moved pseudorandomly among three locations at the start of each trial, so neither an egocentric nor an allocentric (see Glossary) spatial strategy could be used to find the reward. Normal rats entered the correct goal box reliably, but rats given hippocampal lesions entered the two rewarded boxes randomly [7]. Preliminary results show that hippocampal neurons with fields on the common path are modulated by the motivation-defined goal, so that different populations

(Figure Legend 1) Goal-directed episodic coding by place fields. **(a)** The spatial win-stay task with serial reversals. Individual trials are shown on the left by colored arrows drawn next to overhead views of the + maze (trials starting from the North in blue, trial starting from the South in red), and blocks of goal-directed trials are illustrated on the right. **(b)** Spatial firing is shown by overhead views of the + maze; **(i)** firing during the entire recording session is **(ii)** divided into corresponding journeys. Each square shows a location the rat visited, gray lines show the path followed by the rat during a given trial, and dots indicate the firing of single units identified by color. The graphs in the middle show the trial averaged firing rate (vertical axis) in peri-event time histograms centered around the choice point (125 ms bins along the horizontal axis). Examples show current place (top), prospective (middle), and retrospective (bottom) coding. Note that two simultaneously recorded cells are shown in the bottom firing plots, one in red, the firing rate of which is modulated but fires in both SE and SW journeys, and the other in blue, which fires exclusively during NW journeys. **(c)** The proportion of fields showing journey-dependent activity during correct (black) and error (gray) trials in the start (prospective) and goal (retrospective) arms. **(d)** Spike timing in overlapping pairs of place fields were consistent across corresponding journeys (red and black lines) in the start (top) but not the goal arms (middle). The graphs show the probability (vertical axis, in spikes) of one cell spiking in the $\pm$60 ms interval from its pair (horizontal axis). The bottom graph shows that the overall distribution of cross-correlations among cell pairs was more variable across journeys at the end (green) compared with that at the start (red) of trials (adapted from [37]). **(e)** Fields were consistent across journeys during random foraging (top) but new patterns emerged during different goal-directed journeys (middle, bottom). Firing rate is shown by color intensity from blue (lowest) to red (highest); the white traces indicate locations entered by the animal that were not associated with neuronal activity (adapted from [39]).

of cells fire depending upon whether the rat is hungry or thirsty, despite the fact that identical behaviors are performed in the same environment (PJ Kennedy, ML Shapiro, unpublished). The differential activity is not affected by the location of the goal box, nor is it simply a consequence of internal context: the same population of neurons recorded on the same day had identical place fields during random foraging in an open field in the same two deprivation states.

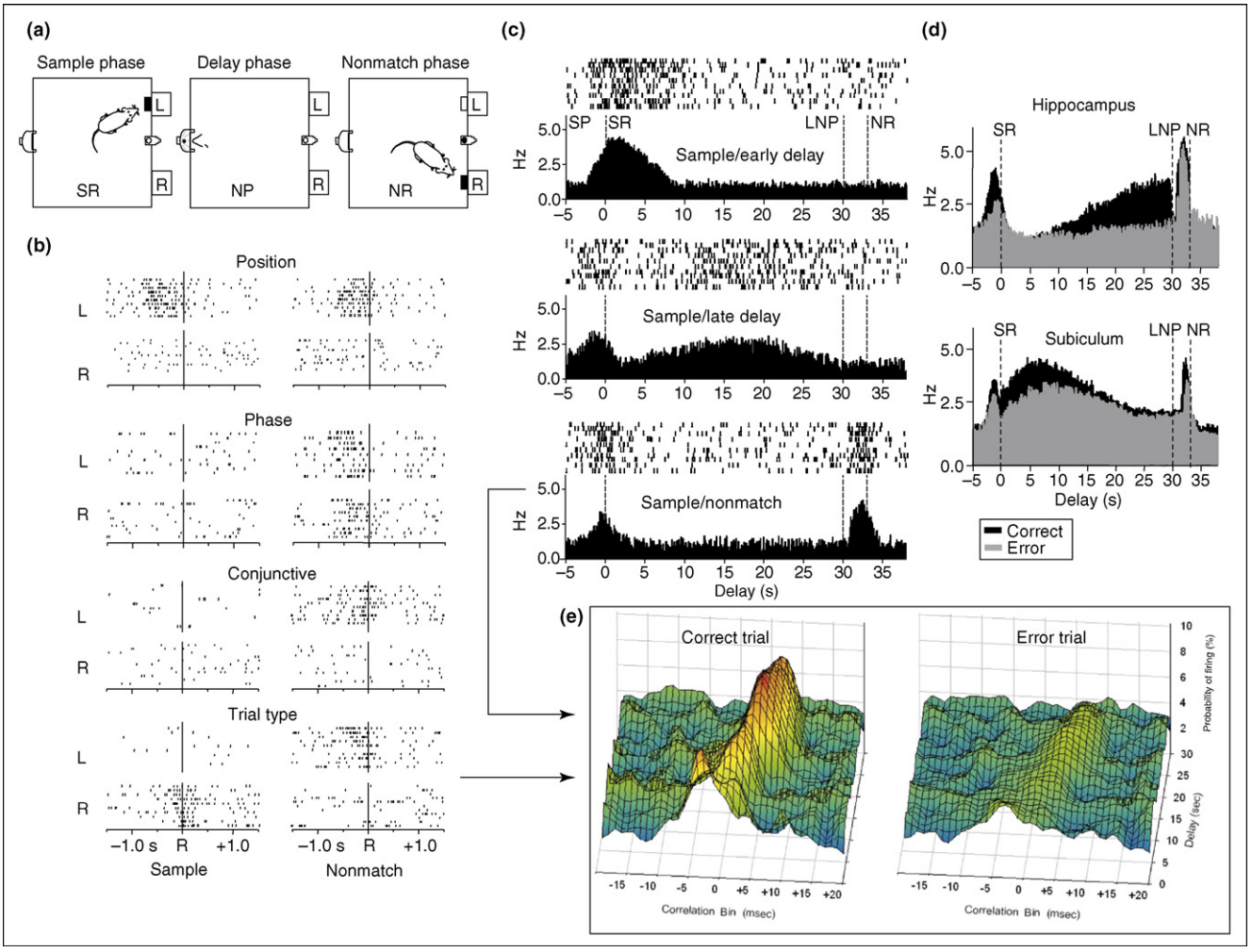
Together, the results suggest that hippocampal neurons distinguish different episodes that occur in the same place only to the extent that the rat discriminates among different goals, so that psychologically distinct behavioral episodes are remembered. This interpretation helps to explain why rats trained to make alternating left and right turns to and from a single goal arm in a Y maze revealed only place fields [34], and indeed, why episodic-like 'journey-dependent' coding was discovered only recently. Distinct behavioral histories or spatial movements *per se* do not entail that psychological episodes will be established. Rather, goals guide appetitive behavior, consummatory behavior marks the end of goal-directed behavioral sequences, and together these factors comprise an 'intention-recollection cycle' that defines episodes psychologically. From this view, appetitive and consummatory signals are crucial for establishing journey-dependent, temporally extended, and temporally asymmetric hippocampal codes (see Glossary). Motivation, such as deprivation state, provides an appetitive context that helps to select, through content addressability, the range of information retrieved from memory. Consummatory behavior not only activates reward systems, but provides information that the goal of a particular behavioral episode has been attained. Hippocampal physiology reflects these motivation derived signals. After rats obtain a reward and enter a quiescent consummatory state, hippocampal neurons with overlapping place fields replayed the same firing sequence but in reverse order, suggesting a mechanism by which reward can be associated with events of the past [35•]. Furthermore, when rats pause at the choice point of a T-maze, the population of hippocampal neurons with place fields in the two goal arms fire in alternating sequences, as though hippocampal 'preplay' is representing pending entries into one and then the other arm, as proposed by Gentry's vicarious trial and error (see Glossary) [36]. The sequential activation of hippocampal neurons provides the temporally extended and asymmetric link between appetitive intention and consummatory recollection. At a finer temporal resolution, the precise spike timing in pairs of co-active cells with overlapping, standard place fields signaled the temporal asymmetry of journeys. In the + maze task described above, cell pairs with overlapping place fields fired in the same theta cycle and were typically separated by a lag of 0–2 gamma cycles (0–60 ms). During different journeys through the start arms, spike timing was consistent and did not distinguish between different pending goals [37], consistent with the just-described 'preplay' of both potential goal arms in the choice point of the T-maze [36]. By contrast, spike timing was modulated strongly during different journeys through the goal arms, revealing a powerful influence of the recent past on when one cell fired with respect to the other (Figure 1d). The journey-related changes in spike timing were not predicted by spatial behavior (see Glossary), place field parameters or different temporal firing patterns by single cells. Rather, spike timing among the cells showing current location coding revealed a mechanism that could distinguish the beginning and end of episodes in memory [37]. This view predicts that prospective coding by hippocampal neurons should distinguish multiple goals, that psychologically differentiated goals determine the neural coding of episodes, and more importantly, that episodic coding should predict memory performance across all hippocampus-dependent tasks.

Episodic coding predicts memory performance

Beyond differentiating behavioral episodes, journey-dependent signals predict memory performance when tasks require discriminating behavioral episodes in the same situation. In the + maze experiment just described [29], rats that mistakenly entered an empty goal arm were allowed to correct the error and obtain the food through an indirect path. Such errors distinguished goal-directed journeys from spatial trajectories: a 'journey' entails traveling from a starting point to a goal, and can be accomplished by different routes; a 'trajectory' is one particular path of many that can be used to complete a journey. Of the retrospective coding fields that could be assessed during indirect trajectories, ~50% continued firing selectively in the goal arm depending upon the start arm from which the rat began its journey. In the remaining cases, fields that had coded retrospective information during correct trials seemed to code only current location during errors. An even greater proportion (72%) of the prospective fields lost the prospective signal in the start arms during errors and coded only location (Figure 1c). These results are consistent with the hypothesis that journey-dependent coding contributes to choice accuracy [29]. In the modified T-maze task described above [25], place field activity in the return arms predicted performance on the subsequent trial as the rat approached the delay area in a spatial delayed-non-matching-to-sample task (DNMS; see Glossary) [38]. In this case, high firing rates during the approach to the common stem predicted correct responses, and low firing rates in the same location predicted errors.

Goal-directed, temporally extended hippocampal memory coding generalizes beyond classically defined place fields (e.g. [39]). A series of experiments compared task-related neuronal activity in ensembles of CA1 and CA3 neurons as rats performed an operant spatial DNMS task

Figure 2



Goal-directed coding by functional task correlates. **(a)** The DNMS task required rats to depress a lever during the sample phase, poke their nose into the cul-de-sac on the left side during the delay phase, and press the opposite lever to get reward during the non-match phase (top). Raster plots show the functional task correlates of **(b)** hippocampal and **(c)** subicular neurons (see text). **(d)** Peri-event time histograms show the complementary timing of the activity of hippocampal and subicular neuronal populations during correct (black) and error (grey) trials. Firing rate is shown on the vertical axis, the duration of the trial is shown on the horizontal axis. **(e)** The temporal coupling of CA1 'trial type' predicted by subicular 'sample-non-match' neurons is shown in correct (left) and incorrect (right) trials. The three-dimensional plot shows continuous cross correlograms in +/−20 ms bins (each horizontal row) throughout the delay interval (front to back). The height and color represent the probability that the CA1 cell fired in the particular temporal interval after the subicular cell (statistically significant correlations are shown in orange [$P < 0.02$] and red [$P < 0.001$]). Abbreviations: SP, sample presentation; SR, sample response; LNP, last nose poke; NR, non-match response.

(Figure 2) [40]. Rats were trained to remember which of two levers (left or right) was presented at the start of a trial; after a variable 1–40 s delay, pressing the other (non-match) lever was rewarded (Figure 2a). Each of the ~100 daily trials was separated by 10 s, and memory performance declined with longer delay intervals. The match and non-match contingencies required the same spatial behaviors to accomplish different goal-directed actions. Although some neurons responded in particular locations and, for example, fired at high rates whenever the rat approached one lever, most neurons responded to other memory demands. For example, some cells distinguished the sample and non-match phases and fired when the rat approached either lever during the sample, but did not fire when the rat approached either lever during the non-match phase, despite identical spatial behaviors. Other cells responded to specific conjunctions of place and phase, and fired, for example, only during right-hand samples. Finally, yet other cells responded selectively during specific trial types and fired, for example, during both the sample of the right lever and non-match of the left lever (Figure 2b) [41].

Together, the ensemble of these different 'functional cell types' in the hippocampus predicted memory performance accurately and revealed two sources of memory

errors (Figure 2d, upper right). Miscoding occurred when the hippocampal ensemble signaled the opposite trial type to the one actually presented to the rat during the sample, as though the rat 'thought' it pressed one sample lever when it in fact had pressed the other. Such miscoding predicted an even distribution of errors across different delays. By contrast, code decay occurred when the sample was poorly encoded and firing rates diminished; such code decay predicted errors that correlated with delay duration [42,43]. Temporally organized neuronal activity across anatomically linked hippocampal regions further contributes to coding and maintaining memory across different time spans. Although memory coding and other behavioral correlates were similar in CA1 and CA3, subicular cells strongly differentiated the temporal sequence of events within trials (Figure 2c–e) [40,43]. Subicular activity predicted performance at short (<15 s), but not long delays, hippocampal activity best predicted performance after long delays, and together the two populations accounted for performance with high accuracy[40]. Spike timing among the different groups of cells revealed dynamic shifts in temporal coupling as information was maintained [44••]. In brief, hippocampal ensembles encoded the trial types during the sample presentation and transmitted that information to subicular neurons. During the delay, the information was maintained by subicular ensembles that eventually reactivated hippocampal neurons, the increased firing rates of which ultimately predicted correct responses during long delays (Figure 2e). Indeed, the strong coupling between pairs of subicular and hippocampal neurons predicted correct responses and was dramatically reduced in error trials [44••]. Finally, the different population codes help to explain memory deficits induced pharmacologically or by lesions [40]. Thus, selective excitotoxin lesions of the hippocampus reduced performance at long delays; lesions that included the subiculum further impaired performance at shorter delays. Together, the experiments show that ensemble activity across the hippocampal system provides a temporally extended neuronal representation that connects events in the past to pending actions.

Conclusions

Whether neuronal activity is analyzed spatially to identify place fields or temporally to identify event-related task correlates, hippocampal firing patterns reveal a temporally extended representation of goal-directed behavioral episodes. Individual hippocampal neurons encode the salient features of learned, temporally extended tasks; the overall population represents and predicts goal-directed actions, and both learning and memory impairment are predicted by these functional task correlates. Across hippocampus-dependent learning and memory tasks, firing patterns throughout the hippocampal system encode the key information needed to obtain goals. More specifically, hippocampal cells code temporally defined behavioral episodes, whether those episodes are framed by the sample and non-match phases of a DNMS task or the start and goal of different but overlapping journeys in the + maze. Hippocampal neurons recorded from people performing a virtual navigation task had place fields that were typically modulated by the goal of the virtual journey [31]. Thus, across species, hippocampal cells fire in patterns that reflect the episodic structure of ongoing behavior in general, and goal-directed memory demands in particular. If these observations generalize to other situations and species, then analogous population and spike timing codes should predict memory performance in any goal-directed tasks that require the hippocampus and distinguish the start and end of different episodes. Furthermore, if these coding properties are necessary for memory, then any intervention that selectively disrupts these codes should impair performance.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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