The hippocampus: a special place for time

Charan Ranganath and Liang-Tien Hsieh

Department of Psychology and Center for Neuroscience, University of California, Davis, California

Address for correspondence: Charan Ranganath, UC Davis Center for Neuroscience, Davis, CA 95618. cranganath@ucdavis.edu

Many findings have demonstrated that memories of past events are temporally organized. It is well known that the hippocampus is critical for such episodic memories, but, until recently, little was known about the temporal organization of mnemonic representations in the hippocampus. Recent developments in human and animal research have revealed important insights into the role of the hippocampus in learning and retrieving sequences of events. Here, we review these findings, including lesion and single-unit recording studies in rodents, functional magnetic resonance imaging studies in humans, and computational models that link findings from these studies to the anatomy of the hippocampal circuit. The findings converge toward the idea that the hippocampus is essential for learning sequences of events, allowing the brain to distinguish between memories for conceptually similar but temporally distinct episodes, and to associate representations of temporally contiguous, but otherwise unrelated experiences.

Keywords: hippocampus; sequence; memory; time; episodic

Each experienced event always occurs at a particular spatial location and in a particular temporal relation to other events that already have occurred… Retrieval of information of this kind from episodic memory is successful if the person can describe the perceptible properties of the event in question and more or less accurately specify its temporal relations to other events.[1] (p.388)

When Endel Tulving defined episodic memory, he proposed that recollection of a past episode includes awareness of *when* the event took place, and, consistent with this view, empirical evidence suggests that our memories of the past are temporally organized.[2,3] This is not to say that memories have an explicit time stamp. People can often remember the date or time of a past event, but these attributions are often based on simple inferences or decision heuristics, rather than explicit retrieval of temporal information.[4] Rather than having a time stamp, evidence suggests that memories are associated with one another according to their temporal context. There is strong evidence to suggest that episodes are encoded as organized sequences of events,[5–7] such that retrieving one event obligatorily triggers recollection,[8,9] or implicit retrieval,[10–12] of the rest of the sequence. In addition to facil-

itating memory for the past, temporal sequence representation allows people to make predictions about the future,[13–16] and it is fundamental for spatial cognition,[17,18] narrative comprehension,[19,20] and imagination and mental simulation.[21,22]

Despite the centrality of time to episodic memory and cognition, until recently little was known about the neural mechanisms that support temporal organization in memory. The hippocampus has long been known to play a central role in episodic memory, but most studies of hippocampal function in rodents have focused on studies of spatial cognition, and human studies have focused on recall or recognition of specific items from a study list. Recent developments in human and animal research, however, have led to a paradigm shift in the field by revealing that the hippocampus might play a critical role in supporting the temporal organization of episodic memory.

In this paper, we review recent advances in the understanding of how the hippocampus encodes temporal sequences and suggest how these findings can help explain the pervasive role of the hippocampus in episodic and spatial memory. We note that focused reviews of relevant research in rodents,[6,23]

research in humans,[24] and computational models[25] have been recently published. Here, we attempt to synthesize results across all of these areas. We also note that our paper will primarily discuss hippocampal representation of sequences. Although our review will allude to findings suggesting that the hippocampus also encodes the duration of temporal intervals between events, MacDonald[26] provides a more detailed treatment of this topic.

Lesion studies demonstrate a role for the hippocampus in temporal memory

Initial evidence for hippocampal involvement in memory for temporal sequences came from Kesner's laboratory,[27] which demonstrated that hippocampal lesions impair retention of a sequence of locations in a radial arm maze. Although the findings from the radial arm maze task could be attributed to hippocampal involvement in spatial memory, Kesner *et al.*[28] and Fortin *et al.*[29] demonstrated that hippocampal lesions impair memory for sequences in a task that did not require spatial memory. In their paradigm, rats were trained to dig in scented sand for a reward across several trials. On probe trials, the rats were presented with two of the previously exposed digging cups, and they were rewarded for choosing the odor that was encountered earlier in the sequence. Both studies found that hippocampal lesions severely impaired performance on this temporal order task, whereas performance on equally difficult odor recognition tasks was spared. These findings revealed a critical role for the hippocampus in sequence learning, over and above its role for recognition of individual odors.

More recently, Kesner and colleagues investigated the effects of lesions to specific hippocampal subfields on learning and retention of temporal sequences. Their findings revealed consistent deficits in temporal sequence memory following lesions in CA1.[30–33] More specifically, they found that lesions of dorsal CA1 disrupt retention of the temporal order of recently explored spatial locations, and lesions of ventral CA1 disrupt retention of temporal sequences of odors.[34]

Computational models of hippocampal sequence representation

Computational models have long suggested that the hippocampus might be uniquely specialized to associate a sequence of temporally discontiguous inputs.[25,35] Most of these models have focused on subfield CA3 (DG/CA3)[36–38] and suggest that sequence learning and retrieval in CA3 could emerge from simple constraints.[25] Specifically, the recurrent collaterals (i.e., extensive excitatory connections between CA3 cells) are central to the functioning of these models, and it is assumed that connectivity within CA3 is sparse and asymmetric. As a result, the network generates *context cells* that exhibit intrinsic persistent activity. Because different context cells are activated at different time points in the sequence, they can become associated with cells that respond to stimulus-driven inputs via the entorhinal cortex (through Hebbian plasticity), thereby linking successive inputs in a sequence during learning. Across learning trials, the strength of the asymmetric connections between neural ensembles increases, which in turn strengthens the tendency for an item input to trigger predictive activation of subsequent items in the sequence (pattern completion).[36] These models predict that the hippocampus should be able to disambiguate overlapping sequences (i.e., it should assign largely distinct representations to different sequences that consist of the same or similar items). As we will describe below, this prediction has been substantiated in both single-unit recording studies in rats and functional magnetic resonance imaging (fMRI) studies in humans.

Although the models described above were designed to account for the role of CA3 in learning tasks performed by rats, they parallel a class of mathematical models designed to account for temporal structure in human memory.[39] In these temporal context models, context is operationalized as a set of elements that randomly fluctuate over time,[40] and items are actively represented for some time after they are processed.[2,9,41,42] Temporal context models can be differentiated from simpler models that assume items are directly linked with one another (or "chained") because in context models temporal associations are mediated by context representations that are associated with, but distinct from, item representations. This distinction is important because, as described below, hippocampal coding appears to be more consistent with a temporal context-based mechanism.

Rather than focusing on CA3, Kesner and Rolls[43] have emphasized the importance of CA1. In their model, CA1 receives inputs about single "items" from CA3, and this information is associated with

temporal information conveyed via direct projections from the entorhinal cortex. Subsequently, presentation of an item in the sequence can elicit reactivation of the CA1 representation that associates the current item with subsequent items in the sequence. To our knowledge, this model has not yet been used to generate detailed simulations of temporal sequence tasks, but its emphasis on CA1 accords with the finding that CA1 lesions impair temporal sequence memory and with studies of "time cells" in CA1 that will be described in the next section.

Single-unit recording studies

Most single-unit recording studies of hippocampal function have focused on recordings of place cells in rodents, and some of these studies have investigated place cell activity during navigation on a linear track or through a directional maze. In these situations, hippocampal place cells appear to encode spatial locations as steps in a sequence, rather than as points in a coordinate space. One salient example comes from recordings of place cells during performance of a delayed alternation task in a T-maze.[44] In this task, an animal must walk through the long arm (i.e., the stem) of a maze until it reaches a junction and must decide to turn left or right; the animal is rewarded only if it turns in the opposite direction on successive trials. Wood et al.[44] demonstrated that different populations of hippocampal place cells code for locations on the stem depending on whether an animal's eventual goal is to make a left or right turn. Because each successive journey through the stem can be thought of as steps toward a particular goal (either the right or the left arm), the journey-selective coding of place cells is often interpreted to reflect encoding of spatial locations as points along a sequence.[45–47]

More direct evidence for temporal coding in the hippocampus has come from studies showing that hippocampal neurons encode temporal intervals in a memory task even when the animal remains in the same place. For instance, Pastalkova et al.[48] used a novel variant of the T-maze task in which the animal had to run on a wheel during a delay period between runs through the maze. Despite the fact that the animal remained in the same place (i.e., on the wheel), different cells in subfield CA1 fired during different points in time during the delay (see Fig. 1). Building on these findings, MacDonald et al.[49] examined temporal patterns of hippocampal firing during a
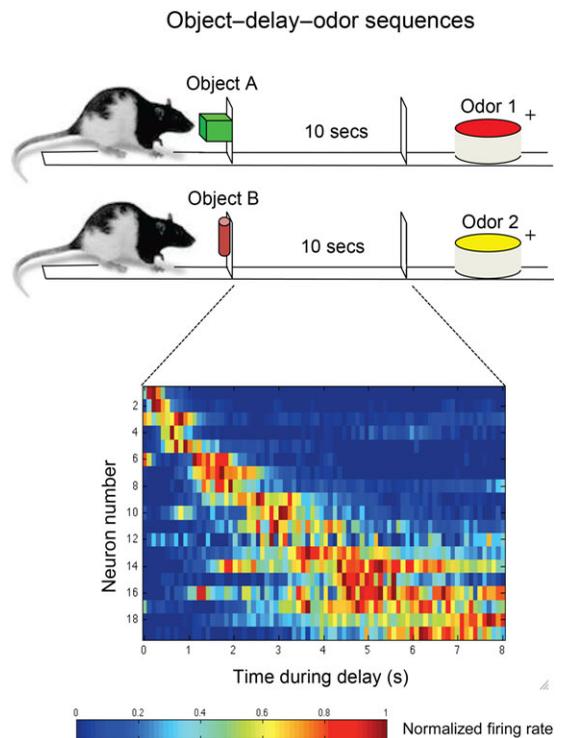

Figure 1. Hippocampal time cells. Neurons from CA1 were recorded while rats performed an object-cued odor discrimination task. A heat map shows firing of time cells during the delay period between object and odor presentation. Single neuron firing patterns are illustrated on each row, with neurons sorted by peak firing latency during the delay period. As is evident from the figure, neurons showed peak firing during specific points in the delay (time fields), such that the entire delay was spanned by the population of time cells. Figure adapted with permission from MacDonald et al.[49]

nonspatial object–odor associative memory task. In this task, the animal was exposed to an object and, after a delay, was allowed to approach a digging cup to decide whether to dig for a food reward, depending on the odor of the sand in the cup. MacDonald et al. determined that CA1 time cells fired at specific intervals during the delay between the object and odor presentation. Critically, the animal remained stationary during the delay, so the firing of time cells could not be attributed to active movement on a running wheel. MacDonald et al.[50] replicated these findings in a go/no-go odor–odor association task that required animals to remain immobilized, further ruling out the possibility that the firing of time cells is driven by movement. Both studies[49,50] found that different ensembles of time cells fire during trials that involved different

odor combinations, strongly paralleling findings showing that hippocampal place cells exhibit different firing fields in different spatial contexts.[51]

In addition to carrying information about the temporal structure of events, time cells appear to play a role in successful learning. For instance, MacDonald et al.[50] examined the similarity of activity in hippocampal neurons during an odor-delayed matching-to-sample task. They found that time cell activity patterns were highly correlated during the retention of the same odor across pairs of correct trials, but correlations were significantly lower between correct and incorrect trials corresponding to the same odor. Thus, the population-level activity of time cells depended on accurate learning and retention of the odor sequence. In a similar vein, Modi et al.[52] used calcium imaging to examine population-level activity in CA1 neurons before and after trace eyeblink conditioning. Before learning, the timing of peak activity in CA1 neurons was not reliable across trials. After learning, however, CA1 cell activity peaked at fixed time-points relative to tone onset, consistent with previous descriptions of time cells. However, this effect was only evident in mice that successfully learned the association. These findings indicate the stability of time fields (i.e., reliability of the peak time window for firing of a time cell) is dependent on learning.

Given the parallels between spatial and temporal coding in the hippocampus, Kraus et al.[53] investigated the relationship between the two factors by examining neural firing as rats ran on a treadmill. Whereas rats on a running wheel could independently vary their running speed, the speed of the treadmill could be experimentally controlled. By independently varying the speed and time of treadmill running, Kraus et al.[53] could separately investigate neural coding of the distance run on the treadmill and the duration of running time. The results revealed that both of these variables independently contributed to the firing of most CA1 units, suggesting that the hippocampus encodes both spatial and purely temporal information.

In addition to the sequential activity of time cell ensembles, recent studies have reported temporal coding across long timescales in the rat hippocampus. Mankin et al.[54] demonstrated that spatial coding in CA1 drifts over across several days, such that slightly different neural populations encoded the same places on different days. In a subse-

quent paper,[55] they found evidence for even more pronounced drift in spatial representation in area CA2, such that population codes changed progressively over hours. In contrast, spatial coding in CA3 was shown to be highly stable over time,[54,55] suggesting that time-dependent changes in spatial representation might be more prevalent in CA1 and CA2.

Although the studies described above demonstrate that hippocampal time cells are sensitive to temporal information, no published studies (to our knowledge) have investigated the role of time cells in paradigms that required memory for temporal sequences. Nonetheless, researchers have investigated the activity of broader populations of hippocampal neurons in temporal sequence paradigms. Manns et al.[56] examined population-level hippocampal activity patterns as rats performed a task modeled after an experiment by Fortin et al.[29] On each trial, the rats sampled a sequence of odors. Next, two of the odors were presented and the rats were rewarded for choosing the odor that was presented earlier in the sequence. The results showed that population-level activity patterns elicited by each odor differed according to the time lag between each odor in the sequence. Furthermore, the lag-sensitive differences in hippocampal activity patterns were only seen on correct trials, whereas on incorrect trials there was no effect on temporal lag (see Fig. 2A). The results of Manns et al.,[56] along with results from human fMRI studies that will be described below,[57,58] suggest that hippocampal ensembles encode representations that change over time, and that these changes are related to accurate temporal memory.

Another study[59] used a similar paradigm in which rats were exposed to sequences of odors across successive nose pokes into an odor delivery port. The study tested a critical prediction from the computational models described above by investigating neuronal activity during sampling of odors that were included in two (overlapping) sequences. The results showed that a large proportion of sampled hippocampal neurons showed sequence-specific activity prior to, and during, presentation of the overlapping odors. In other words, consistent with computational model predictions,[25,36,38] the results indicated that hippocampal neurons differentiated between the same odors as a function of the sequence context.
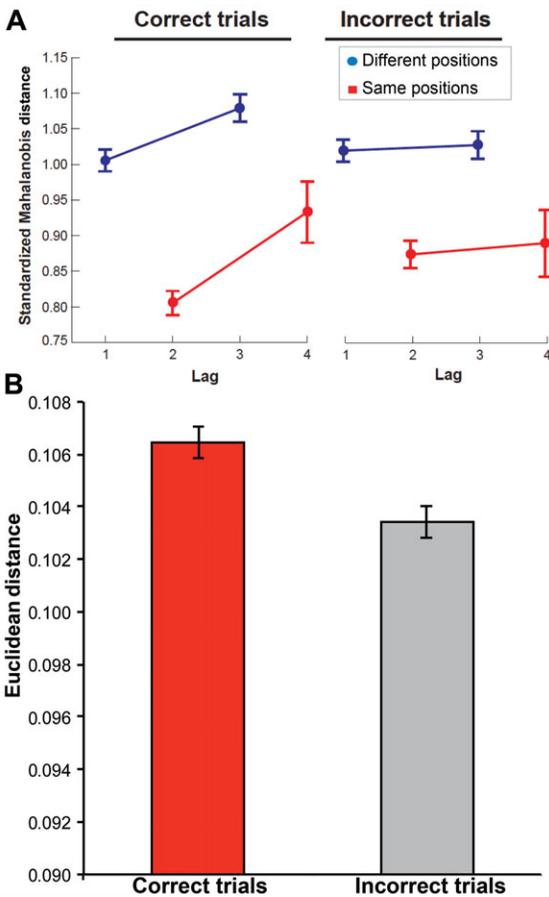
Figure 2. Time-dependent changes in hippocampal activity patterns predict successful temporal order memory. (A) Manns *et al.*[56] examined hippocampal ensemble activity patterns during performance of a temporal order memory task. Animals had to differentiate between odors that were presented 1, 2, 3, or 4 trials apart from one another. Population activity pattern correlations during test trials assessed neural similarity between odors that were studied at lags of 1–4 trials apart. Each line depicts the difference in ensemble activity patterns (Mahalanobis distance) elicited by tested odors as a function of the lag between the items at study. Blue lines illustrate results for odors that had been sampled at different spatial positions, and red lines illustrate results for odors that had been sampled at the same spatial position. For correct trials (left graph), the neural patterns were more distinct for objects as a function of how far they were presented apart at study, but for incorrect trials (right graph), there were no lag-dependent changes in activity patterns. Notably, differences in spatial position affected neural similarity for odors on both correct and incorrect trials. These results suggest that the distinctiveness of hippocampal activity pattern changes across successive events is associated with the degree to which the temporal context of these events can be discriminated. (B) Jenkins and Ranganath[64] used functional magnetic resonance imaging (fMRI) to examine whether the distinctiveness of hippocampal

Allen *et al.*[60] also examined hippocampal activity during a task that required learning of a sequence of odors. After learning, the rats were tested on the ability to discriminate odors that were presented in order from odors that were presented in the wrong position of the sequence. Memory was tested by requiring the rats to make nosepoke responses for odors that were in sequence and to withdraw from the port for odors that were out of sequence. Hippocampal neurons responded differently to odors that were in sequence compared to those that were out of sequence, suggesting a role for the hippocampus in representing sequence information and/or signaling violations of sequence-based predictions. Collectively, these data align well with human neuroimaging data that will be described in the next section.

Although most of the work on temporal coding in the hippocampus has been done in rats, Suzuki and colleagues have also demonstrated neural correlates of temporal coding in recordings from the monkey hippocampus.[61,62] In one study, Naya and Suzuki[62] recorded hippocampal activity during a task that required short-term memory for the temporal order of pairs of objects. Hippocampal neurons fired at specific time points during the delay between each object, which they termed an incremental timing signal. The temporal patterns of activity in these cell populations resembled those seen in time cells, but unlike time cells, the hippocampal incremental timing signal did not differ across different sequence contexts (i.e., the same timing signal was seen for different two-object

---

activity patterns during different events is related to the ability to remember the temporal order of those events. Participants were scanned during learning of a stream of objects, and they were subsequently tested on memory for the temporal order of pairs of objects during the learning phase. fMRI data were used to estimate activity patterns during encoding of each object, and the difference in activity patterns across pairs of tested objects (measured as Euclidean distance) was separately estimated for objects that were associated with correct temporal order decisions and objects that were associated with incorrect decisions (error bars measure the standard error of the mean difference between the two trial types). Consistent with the findings of Manns *et al.*,[56] results showed that pattern distinctiveness was larger between pairs of objects whose temporal context could be correctly discriminated than between pairs of objects whose temporal context could not be discriminated.

sequences). Thus, hippocampal neurons encoded the temporal structure of trial events, irrespective of the currently relevant object sequence.

Whereas the studies of time cells in rodents investigated learning of a small set of consistent associations, Naya and Suzuki[62] used a pool of eight objects to generate different two-object sequences on each trial. It is therefore possible that high trial-to-trial variability in temporal order relationships and stimulus overlap across trials created conditions of high interference that, in turn, prevented reliable encoding of object sequences. Consequently, hippocampal neurons might have encoded the overall temporal structure of each trial as the context. If this is the case, one would expect that the timing signal of hippocampal neurons should carry sequence-specific information under conditions that encourage learning of consistent associations. Sakon et al.[61] tested this prediction in an analysis of hippocampal activity during a test of memory for object–place associations. They found that a subset of hippocampal neurons signaled temporal intervals that were specific to particular object–place associations. These findings suggest that consistency of sequences across learning events is critical for the establishment of stable hippocampal sequence representations.

fMRI studies of hippocampal representation of temporal order information

Functional imaging studies of humans have led to widespread agreement that hippocampal activity is enhanced during successful encoding or retrieval of information related to successful memory for contextual information associated with a study item. Although most studies have focused on memory for task context or for associated items that were encountered in the same context, recent studies have shown that hippocampal activity is especially sensitive to successful encoding of temporal context information. For instance, Tubridy and Davachi[63] found that hippocampal activity during learning of word triplets was associated with subsequent memory for the order in which those words had been shown at study. Jenkins and Ranganath[64] further demonstrated that hippocampal encoding activity was predictive of temporal memory on a coarse timescale. Participants were scanned during processing of objects in a working memory paradigm. After the scan session, temporal memory was probed

by comparing the participant's estimate of the time at which an object was studied (on a timeline) against the actual time of encoding. Study items that subsequently elicited accurate temporal estimates were associated with greater hippocampal activation than items with inaccurate temporal estimates.[64]

In addition to encoding processes, several studies have also shown hippocampal involvement during retrieval of temporal context information. Ekstrom and Bookheimer[65] used a spatial navigation paradigm in which participants freely searched for passengers and delivered them to specific landmark stores. Successful retrieval of the delivery order of passengers, in addition to retrieval of landmarks and spatial associations, was associated with enhanced hippocampal activation. Ekstrom et al.[66] further showed that hippocampal activation was enhanced during retrieval of the temporal order of delivery stores. Using a naturalistic paradigm in which participants viewed a novel movie clip and were later asked to replay/reconstruct the temporal order of the scenes from the movie, Lehn et al.[67] found that right hippocampal activation was enhanced during recall of the temporal order of scenes in the movie clip relative to a control condition in which the participant logically inferred the order of scenes from the same movie. Moreover, Lehn et al.[67] reported that only clusters in the hippocampus exhibited activity that was positively correlated with the accuracy of sequence recall.

Context models of hippocampal function emphasize a critical role of the hippocampus in disambiguating sequences of events that comprise distinct memories.[7,38] Consistent with these models, several neuroimaging studies using virtual spatial navigation,[68] temporal sequence learning,[69,70] or serial reaction time[71] paradigms have reported disproportionate hippocampal involvement during learning and retrieval of event sequences that share overlapping elements.

Another experimental approach has been to examine responses to violations in sequences, under the assumption that an area that is sensitive to sequence representation should show enhanced activation following events that violate predictions derived from a learned sequence. For instance, Kumaran and Maguire[72] scanned participants while they viewed sequences of objects, and each sequence was immediately repeated in either exactly the same order or a completely different order, or the

sequence was such that the first half of the sequence was repeated but the second half was reordered (a "half trial"). The authors predicted that repetition of the first two objects in a sequence context would drive the hippocampus to predict the remaining two objects. If so, then violations of the sequence-based predictions during half trials would elicit increased hippocampal activation. Consistent with a role for the hippocampus in sequence-based prediction, Kumaran and Maguire found that hippocampal activity was significantly higher during half trials than during the other two repetition conditions. Using high-resolution imaging, Chen et al.[73] found that the CA1 subfield of the hippocampus was maximally sensitive to sequence violations, whereas Azab et al.[74] found enhanced activity in CA3/DG and CA1 during sequence violations.

In the above studies, measures of overall hippocampal activity were correlated with successful memory for temporal information. More recently, researchers have investigated the degree to which temporal information can be read out from hippocampal voxel activation patterns. Voxel pattern analysis[75] is analogous to neural population vector analysis in single-unit recording studies[76] in that both assess the similarity in population-level activity patterns across different experimental conditions. The underlying assumption of both methods is that the relative pattern of activation among voxels or neurons in a given region is informative with regard to the kind of information that is processed by that brain region. For instance, if a brain region encodes information about objects, one would expect that hippocampal activity patterns should be more similar during multiple encounters with the same object than during successive encounters with different objects. Hsieh et al.[58] used this approach to investigate hippocampal activation patterns during a sequence retrieval task. Prior to scanning, participants learned sequences of five successively presented objects (Fig. 3). Five sequences were consistent, meaning that the order of objects did not change across repetitions, whereas during the random sequence, the temporal positions associated with each object changed on each repetition. Participants were then scanned while performing semantic decisions on a continuous stream of consistent and random sequences. Notably, the tasks (e.g., "Does this item generate heat?" "Does it use electricity?") were varied across sequence rep-

etitions in order to discourage learning of simple stimulus–response associations. Semantic decisions were faster and more accurate for objects in learned sequences, relative to random sequences (Fig. 3B), demonstrating that they used sequence knowledge to optimize task performance, even though they were not required to do so. Voxel pattern similarity analyses revealed that hippocampal activity during retrieval of learned object sequences reflected both the identity and temporal position of each object. Voxel patterns were correlated across repetitions of the same object in learned sequences (Fig. 3D), and participants who showed larger hippocampal sequence representation effects were better able to use sequence knowledge to optimize decisions (Fig. 3E). Critically, these effects were specific to the hippocampus: the perirhinal and parahippocampal cortices exhibited activity patterns consistent with coding of object and position information, respectively (Fig. 3F). Finally, consistent with computational models of hippocampal sequence disambiguation, voxel patterns differentiated between repetitions of the same object in distinct but overlapping sequences (Fig. 3G). These findings validate one of the strongest predictions of context-based models of sequence representation by showing that the hippocampus assigns distinct representations to successive encounters with the same item in different sequence contexts.

Other studies have used voxel pattern similarity analysis to examine the emergence of hippocampal representations over the course of learning. For instance, Schapiro et al.[77] examined changes in hippocampal voxel pattern similarity following learning of sequentially presented object pairs in a statistical learning paradigm. They found that hippocampal voxel pattern similarity was enhanced for statistically associated object pairs after learning, compared with before learning. Although Schapiro et al. did not specifically investigate sequential learning, this topic was addressed by a study by Kalm et al.[78] Participants were scanned while learning different auditory letter sequences, each of which consisted of the same common set of letters. The results showed that hippocampal activity patterns became increasingly similar across repetitions of the same sequence over the course of learning, whereas pattern similarity across different sequences decreased over the course of learning. Because items in the sequences were identical and sequences only
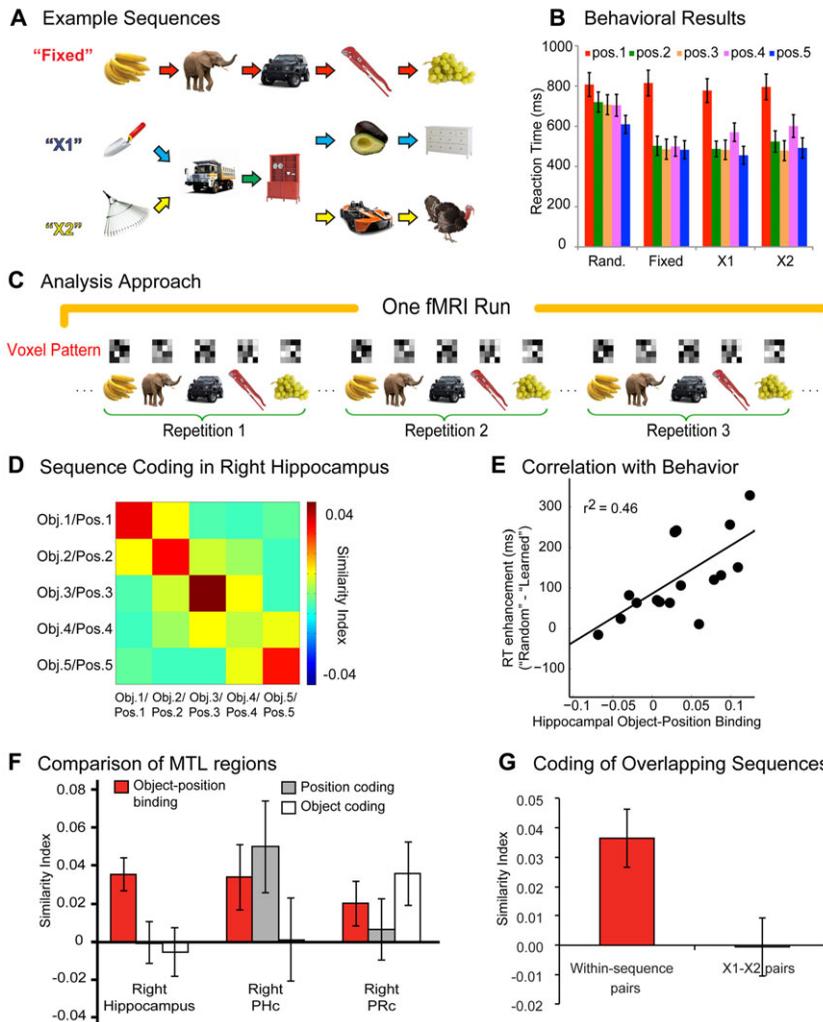
Figure 3. Hippocampal activity patterns carry information about objects in sequences. (A) In this fMRI study, participants learned sequences of objects. Two of these were overlapping sequences (X1 and X2), in that the same objects were used in positions 2 and 3 of these sequences. (B) During the scan session, participants made semantic decisions on a continuous stream of object sequences. Mean reaction times for semantic decisions are plotted as a function of serial position in the sequences. Note that RTs for positions 2–5 are significantly faster for learned sequences than random sequences, and that RTs are slightly elevated for position 4 in the X1 and X2 sequences due to competition induced by the overlapping objects. (C) Voxel activity patterns in the hippocampus (symbolized by grayscale matrices) were extracted for every trial and then correlated across sequence repetitions. (D) A correlation matrix depicts pattern similarity values for repetitions of objects in learned sequences based on data from the right hippocampus. Hotter colors denote higher voxel pattern similarity values. Note that the correlations are strong across repetitions of the same object, dropping off across adjacent objects in a sequence, and they become low for objects that are two or more positions apart. (E) A scatterplot depicts the correlation between hippocampal object–position binding (defined here as the pattern similarity difference between repetitions of the same object in learned sequences and repetitions of the same object in random sequences). (F) A bar graph compares voxel pattern similarity indices of object–position binding, serial position coding, and object coding for right hippocampus, parahippocampal cortex, and perirhinal cortex. The results revealed a statistically reliable region × information type interaction. Whereas hippocampal pattern similarity was sensitive only to repetitions of objects in learned sequences, parahippocampal pattern similarity was enhanced across any trials corresponding to the same temporal position in a learned sequence, and perirhinal pattern similarity was enhanced across any repetitions of the same object, irrespective of sequence context. (G) Bar graphs show right hippocampal pattern similarity values for repetitions of overlapping objects (i.e., in positions 2 and 3) in the X sequences. Note that hippocampal pattern similarity is significantly higher for trial pairs corresponding to repetitions of the same sequence (X1–X1, X2–X2 correlations) than for across-sequence trial pairs (X1–X2 correlations), for which pattern similarity values are close to zero.

differed in terms of the order, this result indicates that learning led to the emergence of sequence-specific representations in the hippocampus.[78]

Although hippocampal activity is sensitive to temporal order, this does not necessarily mean that hippocampal coding is purely temporal, because shifts in situational or mental context can abruptly change hippocampal representations. Many studies have investigated this issue by examining hippocampal activity following transitions between discrete events in narrative text or film clips (i.e., event boundaries). One study[79] examined activation during recognition of an object that either was part of the current event or in a previous event. Despite the fact that the temporal distance between the test item and initial presentation was always fixed at 5 s, hippocampal activation was enhanced when retrieving information that preceded an event boundary.[79] Paralleling this univariate fMRI result, the studies by Hsieh *et al.*[58] found that left hippocampal pattern similarity significantly increased following transitions between object sequences relative to pattern changes observed between adjacent trials that belonged to the same object sequence. Given that temporal distance was matched between conditions, the findings suggest that the hippocampal pattern change reflected a change in the current sequence context, rather than the passing of time.[58]

Several findings suggest that such hippocampal pattern changes predict subjective perception of temporal distance. For instance, Jenkins and Ranganath[57] demonstrated that hippocampal pattern change between encoding of objects was predictive of subsequent memory for temporal order (see Fig. 2B). In this study, participants encoded a series of objects, and after each run they were shown pairs of objects and asked to make recency judgments. Based on the multiunit recording study by Manns *et al.*,[56] the authors hypothesized that it should be easier to make temporal discriminations between objects if they are associated with more distinct temporal context representations. If hippocampal activity patterns contribute to temporal context representation, then one would expect that the distinctiveness of hippocampal activity patterns during encoding of two different objects should be correlated with accurate judgments of relative recency for these objects. Consistent with the results of Manns *et al.*,[56] Jenkins and Ranganath showed that hippocampal pattern change predicted

participants' ability to discriminate which item was presented first in the list, such that pattern change differences were larger during encoding of items that were associated with correct recency decisions than during encoding of items that were associated with incorrect decisions.

Using a paradigm similar to the study of Jenkins and Ranganath,[57] DuBrow and Davachi[80] obtained the opposite result, with increased pattern similarity between pairs of trials associated with correct recency decisions (relative to incorrect decisions). Although the findings from the two studies seem to be contradictory, the studies collectively show that hippocampal representations can be used in different ways to support decisions about temporal context. In DuBrow and Davachi's study, sequences of famous faces were interspersed with pictures of objects. Behavioral evidence suggested that participants tended to associate the temporally contiguous faces as elements of a sequence. Accordingly, when tested, participants probably recalled the sequences in order to identify the face that was presented most recently. In contrast, in the study of Jenkins and Ranganath,[57] a continuous stream of objects was presented, forcing participants to use the distinctiveness of the recalled contexts in order to make recency decisions. Collectively, the results of both studies indicate that hippocampal activity patterns are sensitive to shifts in external and internal context, rather than solely reflecting the passage of time.

Consistent with this idea, Ezzyat and Davachi[81] demonstrated how context changes can influence hippocampal context representation. Participants were scanned while viewing faces and objects that were associated with a scene context. Later, they were shown two objects that were either associated with the same context or with different scene contexts. Hippocampal pattern similarity between pairs of objects that had been associated with distinct contexts was predictive of retrospective temporal distance judgments. Although temporal distance was matched across all test trials, pattern changes were significantly larger for object pairs that were subsequently judged to be far apart than for object pairs that were judged to be close together in time.[81] Interestingly, no effect was seen when the objects were associated with the same context information. The results suggest that, if a change in external context is associated with a large change in

hippocampal representations, then subjective perception of elapsed time will be exaggerated.

Because of the well-known role of the hippocampus in spatial memory, fMRI has been used to investigate the relationship between hippocampal representations of spatial and temporal context. In one study, participants performed a virtual reality task that required participants to successively navigate to different landmarks.[82] During a subsequent memory test, they were shown landmarks and asked to retrieve information about the relative spatial or temporal distances between the landmarks. The authors next compared the pattern similarity between spatial and temporal discrimination trials. Separate correlations were computed for pairs of trials for which the spatial and temporal decisions were correct and pairs in which one decision was correct and another was incorrect. Surprisingly, in CA2/3/DG, pattern similarity was significantly lower between trials that were associated with correct retrieval of both spatial and temporal information than between pairs of discriminations in which only the spatial or temporal decision was correct. Their results indicate that the hippocampus might retrieve separable representations of spatial and temporal context, even when referencing information from the same episode. The results also accord with findings from a study of activity patterns during recall of real-life events.[83] This study showed that anterior hippocampal activity pattern similarity across pairs of recalled events was predictive of how far apart in time and space the two events took place, along with a combined metric of spatial and temporal distance. Thus, available evidence indicates that the hippocampus encodes spatial and temporal contexts separately, and also may encode a combined spatiotemporal representation of past events.

How well do the empirical data conform to computational model predictions?

The results reviewed above reveal significant evidence for temporal coding in the hippocampus and accord with certain predictions that emerge from computational models of sequence representations. For instance, models by Levy[36] and Hasselmo[25,38] propose a central role for hippocampal "context units" that encode temporal intervals within a sequence.[36–38] Despite the fact that these models were proposed several years before time cells

were identified in the hippocampus, the properties of hippocampal time cells closely parallel context units introduced in the models. Another prediction to emerge from the models is that the hippocampus should form different representations for the same item in different sequence contexts. Lesion,[84] single-unit recording,[59] and fMRI[58,70] studies have confirmed that the hippocampus forms sequence-specific object representations, and that it is necessary for disambiguation of overlapping sequences.

One area of inconsistency between models and the data has concerned the roles of different hippocampal subfields. Most computational models have assumed a special role for subfield CA3 in sequence representation, whereas most of the available evidence has linked CA1 to sequence representation.[43] This could simply reflect the fact that most single-unit recording studies record from CA1 and not from CA3, although subfield-specific lesion studies also indicate that CA1 might play a more critical role than CA3.[30,33,34] Recent unpublished fMRI results from Zucker, Ritchey, Ekstrom, Yonelinas, and Ranganath are also consistent with the idea that representation of temporal context is stronger in CA1 than in CA3. Further work is needed to determine whether neural correlates of sequence processing in CA1 are driven by inputs from CA3, or whether the entorhinal-CA1 (temporoammonic) pathway or the entorhinal-CA2-CA1 pathway is sufficient to support sequence learning and retrieval independent of CA3.[55,85] Although the extant evidence is insufficient to rule out an important role for CA3 in sequence learning, it does suggest that models should assign an important role to CA1. Furthermore, the results call into question whether the recurrent collaterals in CA3 are needed for sequence representation, given that CA1 might be sufficient to perform the necessary computations.

Time as the currency of the hippocampus

Based on the evidence reviewed so far, it is clear that: (1) hippocampal damage disrupts memory for sequences, (2) hippocampal neurons in rats and monkeys encode information about event sequences, and (3) patterns of activity in the human hippocampus carry information about items in sequence contexts over and above information about the items themselves. These findings converge

to suggest that time is central to understanding hippocampal function.

The results reviewed earlier do not accord with the idea that the hippocampus plays an equivalent role in all forms of declarative memory, including memory for item information.[86,87] The fMRI and single-unit recording studies described above provide a critical test of this idea by identifying neural activity elicited during retrieval of the same item in different sequence contexts. In fMRI studies, for instance, hippocampal activity differentiated between the same items presented in different sequence contexts,[58,78] and voxel pattern similarity was insensitive to object information.[58] Furthermore, hippocampal lesions in rodents impair temporal order memory while sparing performance on an equally difficult recognition memory task,[29] and single-unit recording results have shown that hippocampal neurons differentially process odors according to their sequence context.[60] These results are in line with the idea that the hippocampus plays a specific role in memory by associating items with an intrinsic representation of temporal context.[6,58]

The results reviewed here are potentially consistent with other theories of hippocampal function in rodents and humans.[88] Most theories of hippocampal function in rodents have focused on spatial navigation,[89,90] but theories of hippocampal function in humans have focused on explaining its role in episodic memory.[91–93] The results reviewed here are consistent with the idea that time is the common currency that could be used by the hippocampus in the service of both episodic memory and spatial navigation.[7,88] Hippocampal representations of time could play a crucial role in episodic memory by allowing one to differentiate between similar events that took place at different times. For instance, in order to find your car in a parking lot, it is necessary to differentiate between the memory of where you parked your car today from memories for other instances in which you parked the car in the same lot. The hippocampus could accomplish this task by assigning distinct representations to each parking event based on its temporal context. Hippocampal encoding of time could also facilitate learning of cognitive maps. As one explores a new spatial context (through eye movements or body movements), the layout could be initially learned by encoding sequences of spatially informative sensory cues.[17,47] Furthermore, distances between landmarks can be estimated by computing velocity over a particular temporal interval.[53]

Complementary roles of hippocampal and extrahippocampal regions in sequence representation

Although the present results strongly implicate the hippocampus in memory for temporal sequences, there is substantial evidence for temporal coding in other brain regions as well. It is clear that extrahippocampal areas are sufficient to support some forms of sequence learning even in the absence of the hippocampus.

One obvious question is whether hippocampal sequence representation can be differentiated from neocortical medial temporal lobe areas, such as the perirhinal and parahippocampal cortices. At present, only a few findings speak to this question. Using fMRI, Hsieh and Ranganath[58,94] found that the hippocampus, the perirhinal cortex, and the parahippocampal cortex carry distinct information about object sequences. Specifically, the perirhinal cortex carries information about objects, regardless of sequence context; the parahippocampal cortex about the current serial position in a sequence, regardless of the object or sequence context; and the hippocampus, uniquely, conjunctive information about the sequence context, temporal position, and identity of each object. Using single-unit recordings in monkeys, Naya and Suzuki[62] compared hippocampal and perirhinal activity during a test of short-term memory for the order of two sequentially presented objects. As noted earlier, hippocampal neurons signaled the temporal structure of each trial, irrespective of the objects to be retained. In contrast, perirhinal neurons were significantly more likely to show phasic responses during object presentation, and these responses often differed as a function of the object's serial position in the sequence. Although the findings from Hsieh *et al.*[58] might seem at odds with those of Naya and Suzuki,[62] they can be explained by a common framework in which the hippocampus and perirhinal cortex play complementary roles in temporal coding (see Fig. 4A).

We speculate that the hippocampus associates objects with an internal representation of temporal position within a particular episode or sequence. Given evidence suggesting that the perirhinal cortex can associate visual, semantic, and auditory
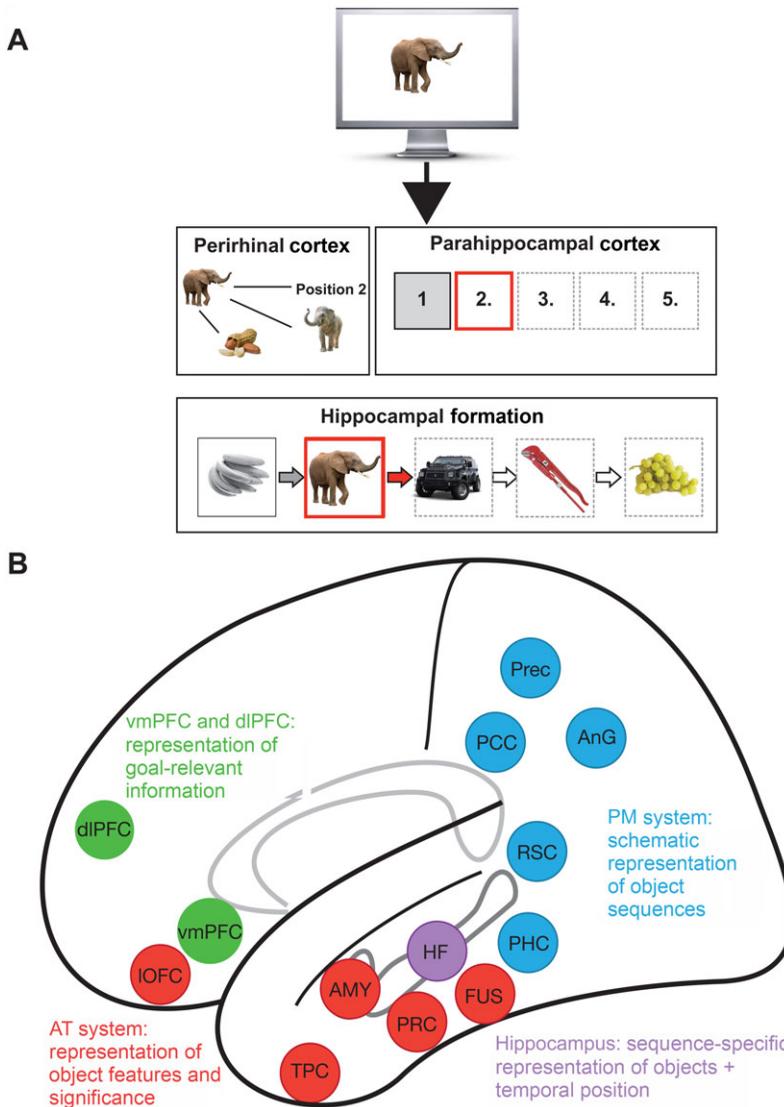
Figure 4. A preliminary model of sequence processing by hippocampal and extrahippocampal regions. (A) Schematic depiction of sequence processing in the medial temporal lobes. As a participant views an object from a learned sequence, we hypothesize that the perirhinal cortex prioritizes the visual and semantic characteristics of the current object, along with its temporal position. The parahippocampal cortex, in turn, is hypothesized to preferentially represent the sequence structure (i.e., five successively presented objects) and the position of the current object in that sequence (indicated by the red box) relative to past (black box) and future (dotted gray box) events. The hippocampus is hypothesized to form a context-specific representation of each item relative to past and future items in the sequence context. It is also expected to generate predictions of upcoming sequence elements, as indicated by the arrows. (B) Speculative model of neocortical involvement in sequence representation. Previous studies have demonstrated that the parahippocampal cortex is part of an extended posterior medial (PM; blue circles) network that includes the retrosplenial and posterior cingulate cortex, precuneus, and angular gyrus.[98,99] This network is hypothesized to encode sequences schematically allowing generalization across episodes that share a common event structure (e.g., the typical sequence of events that one might experience while visiting a restaurant). The perirhinal cortex is a critical component of an anterior temporal (AT; red circles) network[98,99] that also includes the lateral orbitofrontal, temporopolar, and fusiform cortices, along with the amygdala. The AT network is hypothesized to represent the perceptual and semantic features of the currently processed object, along with its salience and motivational significance. The ventromedial and dorsolateral prefrontal cortices (green circles) are hypothesized to preferentially represent information from sequence-based predictions that are relevant to one's current goals or relevant for action selection or decision making.

attributes of an object, we believe that it can come to associate an object representation with a specific temporal position.[95] Naya and Suzuki's study made it difficult for animals to learn and differentiate between different two-object sequences due to the high degree of interference across successive trials. Animals could still perform accurately, however, by associating each object with its serial position (e.g., object 1 = pumpkin, object 2 = bowtie). In contrast, Hsieh *et al.* trained participants in four overlapping sequences, requiring them to learn the object and its temporal position within a specific sequence context. Because Hsieh *at al.*[58,94] trained participants by repeatedly exposing them to each sequence across an entire block of trials, participants could more easily learn and differentiate between each sequence context. Thus, Hsieh *et al.*'s paradigm encouraged learning of objects within a distinct sequence context, whereas Naya and Suzuki's paradigm discouraged long-term sequence learning while encouraging differentiation of each object as a function of its serial position on the current trial. Thus, the results are consistent with the idea that, with training, the perirhinal cortex can encode temporal information if that information is relevant to determining the significance of an object (Fig. 4A). The hippocampus, in contrast, seems to incorporate object information into sequence context representations if the contexts can be adequately learned and differentiated (Fig. 4A).

Going beyond the medial temporal lobes, we recently characterized the roles of several neocortical and striatal regions during retrieval of object sequences.[58,94] Like the perirhinal cortex, several ventral stream neocortical areas carry information about specific objects that generalized across sequence contexts. More striking is that several cortical regions—including the lateral prefrontal cortex and a distributed posterior medial (PM) network consisting of the parahippocampal cortex, retrosplenial cortex, precuneus, angular gyrus, and ventromedial prefrontal cortex—carried information about the serial position of an item in a sequence, regardless of the identity of the object or sequence context.

One might have expected the regions described above to carry information about objects in a particular sequence context, as we found in the hippocampus. Available evidence suggests a critical role for the prefrontal cortex in sequence learning, and recent unpublished evidence suggests that time cells could be identified in the prefrontal cortex (Eichenbaum, Howard, and Shapiro, personal communications). Likewise, regions in the PM network show high functional connectivity with the hippocampus,[96,97] and, like the hippocampus, these regions show robust activation during recollection-based recognition, autobiographical memory retrieval, and virtual spatial navigation.[98,99]

Although further research will be needed to better understand the roles of the prefrontal cortex and PM network in temporal sequence memory, the results allow us to form some hypotheses (Fig. 4B).

We speculate that the prefrontal cortex encodes sequence information only if the information is behaviorally relevant. Several lines of research converge on the idea that prefrontal regions preferentially represent information about behavioral context that is goal relevant in order to guide action selection.[100] In our study,[58] participants were only required to make semantic decisions; during the training phase, however, sequence learning could be facilitated by first learning that each sequence consisted of five objects. We predict that if the serial position of each object informed the participant of the upcoming task or response to be selected, then the prefrontal cortex might carry more detailed, conjunctive information about objects in sequence contexts.

The PM network might play a complementary role in sequence tasks. PM network activity increases during performance of tasks that require one to construct a mental model of abstract relationships.[98,99] Thus, it is possible that, during retrieval of a sequence, pattern completion in the hippocampus triggers predictive activation of item representations in ventral stream regions and of representations of the temporal, spatial, and situational relationships between these items in the PM network.[94] It is possible that the PM network would play a more pronounced role in representations of sequences that have a meaningful and well-learned temporal structure.[99,101] For instance, the sequence of events unfolding during a dinner at a restaurant could be encoded in the context of a mental model of typical event sequences in restaurants (i.e., waiter brings menu → takes order → brings appetizer → brings main course → presents check). In such cases, regions in the PM network could facilitate

retrieval of the event sequence without hippocampal involvement.

To sum up, we expect that the hippocampus makes a unique contribution to sequence learning; but in certain task situations, neocortical areas may also represent sequence information in a manner that could support task performance. Although we have only considered a few neocortical areas (summarized in Fig. 4B), we note that many other regions undoubtedly contribute to representation of certain types of sequences.

Boundary conditions of hippocampal involvement

This review has described how the hippocampus plays a strong role in sequence memory tasks; but there are limits to hippocampal involvement. It is clear that, at least under some conditions, motor sequences can be learned via frontal and striatal regions, independent of the hippocampus.[102–105] One possibility is that frontal and striatal areas can support implicit retrieval of simple sensorimotor sequences, and thus the hippocampus is only needed for conscious retrieval of sequence information. Although more research is needed to test this hypothesis, results from Schendan et al.[71] indicate that the hippocampus contributes to both implicit and explicit expressions of memory for complex motor sequences.[106]

Another nonexclusive possibility is that the extent of hippocampal involvement in sequential learning could depend on how a sequence is learned. Earlier, we speculated that the hippocampus encodes actions and objects according to their temporal position in a sequence context. This leads us to expect that the hippocampus might play an important role when sequence contexts can be clearly identified and differentiated from one another, but it might play a small role in the spaced, incremental learning of sequences amid a backdrop of randomly occurring items. Consistent with this idea, Lungu et al.[107] examined motor sequence learning in two groups. One group learned the sequence incrementally, by first learning different subcomponents ("chunks") of the sequence and then putting them together. Participants in the "global" group, in contrast, were exposed to the entire sequence repeatedly, allowing them to learn the entire set of movements within a single sequence context. The results showed that, across groups, frontal regions

and the putamen exhibited increased activation during learned sequence retrieval, but participants in the global group also showed hippocampal activation during retrieval of sequence elements. Although further research is warranted, these findings indicate that hippocampal involvement in sequence representation might depend on whether the entire sequence can be differentiated from random elements, or whether the sequence is learned by successive acquisition of elemental associations.

Open questions and directions for future research

Our review has highlighted the remarkable progress that has been made in understanding hippocampal sequence representation. These findings, however, raise new and important questions that need to be addressed in future studies. For instance, the discovery of time cells in the rat and monkey hippocampus prompts the question of whether hippocampal time cells are functionally and mechanistically distinct from cells in other brain areas that exhibit sequentially organized activity. Sequential, temporally organized firing has also been observed in the prefrontal cortex, parietal cortex,[108] and the ventral striatum.[109] These findings call into question the assumption that time cell activity must emerge because of anatomical features unique to the hippocampus. A more parsimonious explanation might be that sparse and asymmetric connectivity in any network could give rise to sequentially firing cell assemblies. At the mechanistic level, it is also not clear whether time cell–like activity in extrahippocampal areas contributes to or arises because of hippocampal time cell activity. This question could be addressed by multisite recording and optogenetic or reversible inactivation studies in rodents.

Another outstanding question is whether time cells play a direct role in memory for temporal sequences. Given the strong parallels between time cells and context cells proposed in computational models of sequence representation, it is tempting to assume that there is a direct relationship. However, to our knowledge, sequential firing of time cells has only been linked to successful learning of specific items[50] or simple associations.[52] Thus, further work is needed to determine whether time cell activity is necessary for sequence learning.

The findings from fMRI studies have raised other important questions about temporal context

representation in the human hippocampus. For instance, fMRI studies typically examine arbitrary sequences; but in human experience, sequences often follow a meaningful progression, and prior knowledge can dramatically alter how memories are formed and retained. How does prior knowledge affect hippocampal and extrahippocampal sequence representation? One hypothesis to be tested in future experiments is that, although the hippocampus differentiates between physically and semantically similar objects (i.e., pattern separation), it might generalize across similar objects if they are encountered in conceptually similar event sequences. Additionally, prior knowledge might facilitate consolidation of recently learned sequences.[110]

The neural mechanisms of sequence learning might also depend on the nature of the sequences to be learned. For instance, unlike object sequences, research on learning of motor sequences and phonological sequences has implicated regions in the (pre)motor cortex and ventral prefrontal cortex, respectively, but hippocampal activation in these paradigms is inconsistent. Interestingly, consolidation of motor sequences is associated with hippocampal function,[111] suggesting that the hippocampus might be engaged at different stages depending on the kind of sequence that is learned.

Another unresolved question concerns the potential role of neural oscillations in sequence retrieval. Oscillations are rhythmic, synchronous changes in the excitability of large neural populations, and large oscillations (in theory) can drive sequential activation of different neural ensembles. Lisman and Idiart[112] proposed that cell assemblies that represent particular items are activated during high-frequency gamma oscillations (20–70 Hz), and that gamma oscillations are nested within low-frequency theta oscillations (4–8 Hz). Consequently, cell assemblies corresponding to different items in a sequence could be successively activated at different phases of the theta oscillation. Because the temporal separation of each item is compressed in a theta sequence (i.e., temporal separation of 20–30 ms), this mechanism could allow successive items to be associated in the hippocampus via spike timing–dependent plasticity.[113,114] Although this model is widely cited, its key predictions have not yet been tested empirically. Future studies could assess the prediction by decoding the population-level activity patterns associated with each object in a sequence and then testing whether these activity patterns are sequentially activated during different theta phases.

General conclusions

The author William Gibson wrote, "Time moves in one direction, memory another."[115] Although true, the results reviewed above indicate that the movement of time is a central principle for organizing episodic memories. The hippocampus associates conceptually distinct experiences that occurred in the same temporal episode, and it segregates conceptually similar events that were experienced in different temporal contexts. By capturing the fundamental temporal structure of experience, the hippocampus appears to play a specific role in memory and a pervasive role in virtually every form of high-level cognition.

Acknowledgments

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Tulving, E. 1972. Episodic and semantic memory. In *Organization of Memory*. E. Tulving & W. Donaldson, Eds.: 381–402. New York, NY: Academic Press.
2. Polyn, S.M., K.A. Norman & M.J. Kahana. 2009. A context maintenance and retrieval model of organizational processes in free recall. *Psychol. Rev.* **116:** 129–156.
3. Howard, M.W. *et al.* 2005. The temporal context model in spatial navigation and relational learning: toward a common explanation of medial temporal lobe function across domains. *Psychol. Rev.* **112:** 75–116.
4. Friedman, W.J. 1993. Memory for the time of past events. *Psychol. Bull.* **113:** 44–66.
5. Allen, T.A. *et al.* 2014. A sequence of events model of episodic memory shows parallels in rats and humans. *Hippocampus* **24:** 1178–1188.

6. Eichenbaum, H. 2013. Memory on time. *Trends Cogn. Sci.* **17:** 81–88.

7. Howard, M.W. & H. Eichenbaum. 2015. Time and space in the hippocampus. *Brain Res.* **1621:** 345–354

8. Schwartz, G. *et al.* 2005. Shadows of the past: temporal retrieval effects in recognition memory. *Psychol. Sci.* **16:** 898–904.

9. Howard, M.W. & M.J. Kahana. 1999. Contextual variability and serial position effects in free recall. *J. Exp. Psychol. Learn. Mem. Cogn.* **25:** 923–941.

10. Turk-Browne, N.B. *et al.* 2010. Implicit perceptual anticipation triggered by statistical learning. *J. Neurosci.* **30:** 11177–11187.

11. Turk-Browne, N.B., M.G. Simon & P.B. Sederberg. 2012. Scene representations in parahippocampal cortex depend on temporal context. *J. Neurosci.* **32:** 7202–7207.

12. Swallow, K.M. & J.M. Zacks. 2008. Sequences learned without awareness can orient attention during the perception of human activity. *Psychon. Bull. Rev.* **15:** 116–122.

13. Lisman, J. & A.D. Redish. 2009. Prediction, sequences and the hippocampus. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **364:** 1193–1201.

14. Eichenbaum, H. & N.J. Fortin. 2009. The neurobiology of memory based predictions. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **364:** 1183–1191.

15. Baker, R. *et al.* 2014. Learning to predict: exposure to temporal sequences facilitates prediction of future events. *Vision Res.* **99:** 124–133.

16. Luft, C.D. *et al.* 2015. Decoding the future from past experience: learning shapes predictions in early visual cortex. *J. Neurophysiol.* **113:** 3159–3171.

17. Mehta, M.R. 2015. From synaptic plasticity to spatial maps and sequence learning. *Hippocampus* **25:** 756–762.

18. Lisman, J.E. & N.A. Otmakhova. 2001. Storage, recall, and novelty detection of sequences by the hippocampus: elaborating on the SOCRATIC model to account for normal and aberrant effects of dopamine. *Hippocampus* **11:** 551–568.

19. Zacks, J.M. & B. Tversky. 2001. Event structure in perception and conception. *Psychol. Bull.* **127:** 3–21.

20. Zacks, J.M., B. Tversky & G. Iyer. 2001. Perceiving, remembering, and communicating structure in events. *J. Exp. Psychol. Gen.* **130:** 29–58.

21. Schacter, D.L. & D.R. Addis. 2009. On the nature of medial temporal lobe contributions to the constructive simulation of future events. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **364:** 1245–1253.

22. Schacter, D.L., D.R. Addis & R.L. Buckner. 2007. Remembering the past to imagine the future: the prospective brain. *Nat. Rev. Neurosci.* **8:** 657–661.

23. Eichenbaum, H. 2014. Time cells in the hippocampus: a new dimension for mapping memories. *Nat. Rev. Neurosci.* **15:** 732–744.

24. Davachi, L. & S. DuBrow. 2015. How the hippocampus preserves order: the role of prediction and context. *Trends Cogn. Sci.* **19:** 92–99.

25. Wallenstein, G.V., H. Eichenbaum & M.E. Hasselmo. 1998. The hippocampus as an associator of discontiguous events. *Trends Neurosci.* **21:** 317–323.

26. MacDonald, C.J. 2014. Prospective and retrospective duration memory in the hippocampus: is time in the foreground or background? *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **369:** 20120463.

27. Chiba, A.A., R.P. Kesner & A.M. Reynolds. 1994. Memory for spatial location as a function of temporal lag in rats: role of hippocampus and medial prefrontal cortex. *Behav. Neural. Biol.* **61:** 123–131.

28. Kesner, R.P., P.E. Gilbert & L.A. Barua. 2002. The role of the hippocampus in memory for the temporal order of a sequence of odors. *Behav. Neurosci.* **116:** 286–290.

29. Fortin, N.J., K.L. Agster & H.B. Eichenbaum. 2002. Critical role of the hippocampus in memory for sequences of events. *Nat. Neurosci.* **5:** 458–462.

30. Hoge, J. & R.P. Kesner. 2007. Role of CA3 and CA1 subregions of the dorsal hippocampus on temporal processing of objects. *Neurobiol. Learn. Mem.* **88:** 225–231.

31. Hunsaker, M.R. & R.P. Kesner. 2008. Evaluating the differential roles of the dorsal dentate gyrus, dorsal CA3, and dorsal CA1 during a temporal ordering for spatial locations task. *Hippocampus* **18:** 955–964.

32. Hunsaker, M.R., B. Lee & R.P. Kesner. 2008. Evaluating the temporal context of episodic memory: the role of CA3 and CA1. *Behav. Brain Res.* **188:** 310–315.

33. Kesner, R.P., M.R. Hunsaker & W. Ziegler. 2010. The role of the dorsal CA1 and ventral CA1 in memory for the temporal order of a sequence of odors. *Neurobiol. Learn. Mem.* **93:** 111–116.

34. Hunsaker, M.R. *et al.* 2008. Dissociating the roles of dorsal and ventral CA1 for the temporal processing of spatial locations, visual objects, and odors. *Behav. Neurosci.* **122:** 643–650.

35. Marr, D. 1971. Simple memory: a theory for archicortex. *Phil. Trans. R. Soc. Lond. B Biol. Sci.* **262:** 23–81.

36. Levy, W.B. 1996. A sequence predicting CA3 is a flexible associator that learns and uses context to solve hippocampal-like tasks. *Hippocampus* **6:** 579–590.

37. Hasselmo, M.E. 2005. What is the function of hippocampal theta rhythm?—Linking behavioral data to phasic properties of field potential and unit recording data. *Hippocampus* **15:** 936–949.

38. Hasselmo, M.E. & E. Howard. 2005. Hippocampal mechanisms for the context-dependent retrieval of episodes. *Neural Netw.* **18:** 1172–1190.

39. Burgess, N. & G. Hitch. 2005. Computational models of working memory: putting long-term memory into context. *Trends Cogn. Sci.* **9:** 535–541.

40. Estes, W.K. 1955. Statistical theory of spontaneous recovery and regression. *Psychol. Rev.* **62:** 145–154.

41. Sederberg, P.B., M.W. Howard & M.J. Kahana. 2008. A context-based theory of recency and contiguity in free recall. *Psychol. Rev.* **115:** 893–912.

42. Davelaar, E.J. *et al.* 2005. The demise of short-term memory revisited: empirical and computational investigations of recency effects. *Psychol. Rev.* **112:** 3–42.

43. Kesner, R.P. & E.T. Rolls. 2015. A computational theory of hippocampal function, and tests of the theory: new developments. *Neurosci. Biobehav. Rev.* **48:** 92–147.

44. Wood, E.R. *et al.* 2000. Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* **27:** 623–633.

45. Ferbinteanu, J. & M.L. Shapiro. 2003. Prospective and retrospective memory coding in the hippocampus. *Neuron* **40:** 1227–1239.

46. Ferbinteanu, J., P. Shirvalkar & M.L. Shapiro. 2011. Memory modulates journey-dependent coding in the rat hippocampus. *J. Neurosci.* **31:** 9135–9146.

47. Dabaghian, Y., V.L. Brandt & L.M. Frank. 2014. Reconceiving the hippocampal map as a topological template. *eLife* **3:** e03476.

48. Pastalkova, E. *et al.* 2008. Internally generated cell assembly sequences in the rat hippocampus. *Science* **321:** 1322–1327.

49. MacDonald, C.J. *et al.* 2011. Hippocampal "time cells" bridge the gap in memory for discontiguous events. *Neuron* **71:** 737–749.

50. MacDonald, C.J. *et al.* 2013. Distinct hippocampal time cell sequences represent odor memories in immobilized rats. *J. Neurosci.* **33:** 14607–14616.

51. Colgin, L.L., E.I. Moser & M.B. Moser. 2008. Understanding memory through hippocampal remapping. *Trends Neurosci.* **31:** 469–477.

52. Modi, M.N., A.K. Dhawale & U.S. Bhalla. 2014. CA1 cell activity sequences emerge after reorganization of network correlation structure during associative learning. *eLife* **3:** e01982.

53. Kraus, B.J. *et al.* 2013. Hippocampal "time cells": time versus path integration. *Neuron* **78:** 1090–1101.

54. Mankin, E.A. *et al.* 2012. Neuronal code for extended time in the hippocampus. *Proc. Natl. Acad. Sci. U.S.A.* **109:** 19462–19467.

55. Mankin, E.A. *et al.* 2015. Hippocampal CA2 activity patterns change over time to a larger extent than between spatial contexts. *Neuron* **85:** 190–201.

56. Manns, J.R., M.W. Howard & H. Eichenbaum. 2007. Gradual changes in hippocampal activity support remembering the order of events. *Neuron* **56:** 530–540.

57. Jenkins, L.J. & C. Ranganath. 2016. Distinct neural mechanisms for remembering when an event occurred. *Hippocampus* doi: 10.1002/hipo.22571.

58. Hsieh, L.T. *et al.* 2014. Hippocampal activity patterns carry information about objects in temporal context. *Neuron* **81:** 1165–1178.

59. Ginther, M.R., D.F. Walsh & S.J. Ramus. 2011. Hippocampal neurons encode different episodes in an overlapping sequence of odors task. *J. Neurosci.* **31:** 2706–2711.

60. Allen, T.A. *et al.* 2016. Nonspatial sequence coding in CA1 neurons. *J. Neurosci.* **36:** 1547–1563.

61. Sakon, J.J. *et al.* 2014. Context-dependent incremental timing cells in the primate hippocampus. *Proc. Natl. Acad. Sci. U.S.A.* **111:** 18351–18356.

62. Naya, Y. & W.A. Suzuki. 2011. Integrating what and when across the primate medial temporal lobe. *Science* **333:** 773–776.

63. Tubridy, S. & L. Davachi. 2011. Medial temporal lobe contributions to episodic sequence encoding. *Cereb. Cortex* **21:** 272–280.

64. Jenkins, L.J. & C. Ranganath. 2010. Prefrontal and medial temporal lobe activity at encoding predicts temporal context memory. *J. Neurosci.* **30:** 15558–15565.

65. Ekstrom, A.D. & S.Y. Bookheimer. 2007. Spatial and temporal episodic memory retrieval recruit dissociable functional networks in the human brain. *Learn. Mem.* **14:** 645–654.

66. Ekstrom, A.D. *et al.* 2011. Dissociable networks involved in spatial and temporal order source retrieval. *Neuroimage* **56:** 1803–1813.

67. Lehn, H. *et al.* 2009. A specific role of the human hippocampus in recall of temporal sequences. *J. Neurosci.* **29:** 3475–3484.

68. Brown, T.I., M.E. Hasselmo & C.E. Stern. 2014. A high-resolution study of hippocampal and medial temporal lobe correlates of spatial context and prospective overlapping route memory. *Hippocampus* **24:** 819–839.

69. Ross, R.S., T.I. Brown & C.E. Stern. 2009. The retrieval of learned sequences engages the hippocampus: evidence from fMRI. *Hippocampus* **19:** 790–799.

70. Kumaran, D. & E.A. Maguire. 2006. The dynamics of hippocampal activation during encoding of overlapping sequences. *Neuron* **49:** 617–629.

71. Schendan, H.E. *et al.* 2003. An FMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. *Neuron* **37:** 1013–1025.

72. Kumaran, D. & E.A. Maguire. 2006. An unexpected sequence of events: mismatch detection in the human hippocampus. *PLoS Biol.* **4:** e424.

73. Chen, J., P.A. Cook & A.D. Wagner. 2015. Prediction strength modulates responses in human area CA1 to sequence violations. *J. Neurophysiol.* **114:** 1227–1238.

74. Azab, M., S.M. Stark & C.E. Stark. 2014. Contributions of human hippocampal subfields to spatial and temporal pattern separation. *Hippocampus* **24:** 293–302.

75. Kriegeskorte, N., M. Mur & P. Bandettini. 2008. Representational similarity analysis—connecting the branches of systems neuroscience. *Front. Syst. Neurosci.* **2:** 4.

76. Quian Quiroga, R. & S. Panzeri. 2009. Extracting information from neuronal populations: information theory and decoding approaches. *Nat. Rev. Neurosci.* **10:** 173–185.

77. Schapiro, A.C., L.V. Kustner & N.B. Turk-Browne. 2012. Shaping of object representations in the human medial temporal lobe based on temporal regularities. *Curr. Biol.* **22:** 1622–1627.

78. Kalm, K., M.H. Davis & D. Norris. 2013. Individual sequence representations in the medial temporal lobe. *J. Cogn. Neurosci.* **25:** 1111–1121.

79. Swallow, K.M. *et al.* 2011. Changes in events alter how people remember recent information. *J. Cogn. Neurosci.* **23:** 1052–1064.

80. DuBrow, S. & L. Davachi. 2014. Temporal memory is shaped by encoding stability and intervening item reactivation. *J. Neurosci.* **34:** 13998–14005.

81. Ezzyat, Y. & L. Davachi. 2014. Similarity breeds proximity: pattern similarity within and across contexts is related to later mnemonic judgments of temporal proximity. *Neuron* **81:** 1179–1189.

82. Copara, M.S. *et al.* 2014. Complementary roles of human hippocampal subregions during retrieval of spatiotemporal context. *J. Neurosci.* **34:** 6834–6842.

83. Nielson, D.M. *et al.* 2015. Human hippocampus represents space and time during retrieval of real-world memories. *Proc. Natl. Acad. Sci. U.S.A.* **112:** 11078–11083.

84. Agster, K.L., N.J. Fortin & H. Eichenbaum. 2002. The hippocampus and disambiguation of overlapping sequences. *J. Neurosci.* **22:** 5760–5768.

85. Suh, J. *et al.* 2011. Entorhinal cortex layer III input to the hippocampus is crucial for temporal association memory. *Science* **334:** 1415–1420.

86. Squire, L.R. 2009. The legacy of patient H.M. for neuroscience. *Neuron* **61:** 6–9.

87. McClelland, J.L., B.L. McNaughton & R.C. O'Reilly. 1995. Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* **102:** 419–457.

88. Zucker, H.R. & C. Ranganath. 2015. Navigating the human hippocampus without a GPS. *Hippocampus* **25:** 697–703.

89. Burgess, N., E.A. Maguire & J. O'Keefe. 2002. The human hippocampus and spatial and episodic memory. *Neuron* **35:** 625–641.

90. O'keefe, J. & L. Nadel. 1978. *The Hippocampus as a Cognitive Map.* London: Oxford University Press.

91. Eichenbaum, H. & N.J. Cohen. 2014. Can we reconcile the declarative memory and spatial navigation views on hippocampal function? *Neuron* **83:** 764–770.

92. Eichenbaum, H., A.P. Yonelinas & C. Ranganath. 2007. The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* **30:** 123–152.

93. Ranganath, C. 2010. A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. *Hippocampus* **20:** 1263–1290.

94. Hsieh, L.T. & C. Ranganath. 2015. Cortical and subcortical contributions to sequence retrieval: schematic coding of temporal context in the neocortical recollection network. *Neuroimage* **121:** 78–90.

95. Inhoff, M.C. & C. Ranganath. 2015. Significance of objects in the perirhinal cortex. *Trends Cogn. Sci.* **19:** 302–303.

96. Libby, L.A. *et al.* 2012. Differential connectivity of perirhinal and parahippocampal cortices within human hippocampal subregions revealed by high-resolution functional imaging. *J. Neurosci.* **32:** 6550–6560.

97. Kahn, I. *et al.* 2008. Distinct cortical anatomy linked to subregions of the medial temporal lobe revealed by intrinsic functional connectivity. *J. Neurophysiol.* **100:** 129–139.

98. Ritchey, M., L.A. Libby & C. Ranganath. 2015. Cortico-hippocampal systems involved in memory and cognition: the PMAT framework. *Prog. Brain Res.* **219:** 45–64.

99. Ranganath, C. & M. Ritchey. 2012. Two cortical systems for memory-guided behaviour. *Nat. Rev. Neurosci.* **13:** 713–726.

100. Ranganath, C. & R.S. Blumenfeld. 2008. "Prefrontal cortex and memory." In *Learning and Memory: A Comprehensive Reference.* Vol. **3.** J.H. Byrne, Ed.: 261–279. Oxford: Academic Press.

101. Hasson, U. *et al.* 2008. A hierarchy of temporal receptive windows in human cortex. *J. Neurosci.* **28:** 2539–2550.

102. Doyon, J. *et al.* 1997. Role of the striatum, cerebellum, and frontal lobes in the learning of a visuomotor sequence. *Brain Cogn.* **34:** 218–245.

103. Shin, J.C. & R.B. Ivry. 2003. Spatial and temporal sequence learning in patients with Parkinson's disease or cerebellar lesions. *J. Cogn. Neurosci.* **15:** 1232–1243.

104. Siegert, R.J. *et al.* 2006. Is implicit sequence learning impaired in Parkinson's disease? A meta-analysis. *Neuropsychology* **20:** 490–495.

105. Vandenbossche, J. *et al.* 2013. Impaired implicit sequence learning in Parkinson's disease patients with freezing of gait. *Neuropsychology* **27:** 28–36.

106. Schendan, H.E. *et al.* 2003. Sequence? What sequence?: the human medial temporal lobe and sequence learning. *Mol. Psychiatry* **8:** 896–897.

107. Lungu, O. *et al.* 2014. Striatal and hippocampal involvement in motor sequence chunking depends on the learning strategy. *PLoS One* **9:** e103885.

108. Harvey, C.D., P. Coen & D.W. Tank. 2012. Choice-specific sequences in parietal cortex during a virtual-navigation decision task. *Nature* **484:** 62–68.

109. Lansink, C.S. *et al.* 2012. Reward cues in space: commonalities and differences in neural coding by hippocampal and ventral striatal ensembles. *J. Neurosci.* **32:** 12444–12459.

110. Tse, D. *et al.* 2007. Schemas and memory consolidation. *Science* **316:** 76–82.

111. Debas, K. *et al.* 2010. Brain plasticity related to the consolidation of motor sequence learning and motor adaptation. *Proc. Natl. Acad. Sci. U.S.A.* **107:** 17839–17844.

112. Lisman, J.E. & M.A. Idiart. 1995. Storage of 7 $+/-$ 2 short-term memories in oscillatory subcycles. *Science* **267:** 1512–1515.

113. Jensen, O. & J.E. Lisman. 2005. Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. *Trends Neurosci.* **28:** 67–72.

114. Jensen, O. & J.E. Lisman. 1996. Hippocampal CA3 region predicts memory sequences: accounting for the phase precession of place cells. *Learn. Mem.* **3:** 279–287.

115. Gibson, W. 2012. *Distrust That Particular Flavor.* New York: G.P. Putnam's Sons.