Chapter 5
Hippocampal Sequences and the Cognitive Map

Andrew M. Wikenheiser and A. David Redish

Abstract Ensemble activity in the hippocampus is often arranged in temporal sequences of spiking. Early theoretical and experimental work strongly suggested that hippocampal sequences functioned as a neural mechanism for memory consolidation, and recent experiments suggest a causal link between sequences during sleep and mnemonic processing. However, in addition to sleep, the hippocampus expresses sequences during active behavior and moments of waking rest; recent data suggest that sequences outside of sleep might fulfill functions other than memory consolidation. These findings suggest a model in which sequence function varies depending on the neurophysiological and behavioral context in which they occur. In this chapter, we argue that hippocampal sequences are well suited to play roles in the formation, augmentation, and maintenance of a cognitive map. Specifically, we consider three postulated cognitive map functions (memory, construction of representations, and planning) and review data implicating hippocampal sequences in these processes. We conclude with a discussion of unanswered questions related to sequences and cognitive map function and highlight directions for future research.

Keywords Sequence • Cognitive map • Replay • Theta • Hippocampus

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A Taxonomy of Hippocampal Firing Sequences

What Are Sequences?

In this chapter, we discuss the possible functions of temporally coordinated, sequential, firing patterns in hippocampal neurons. First, however, it behooves us to articulate more precisely how we define firing sequences. In our view, sequences are fast, discrete bursts of temporally structured spiking involving numerous hippocampal neurons. Critical to our definition, the temporal structure within the fast timescale sequence reflects or recapitulates important aspects of ensemble firing properties over longer epochs (Fig. 5.1). Spatial tuning is the most obvious slow timescale correlate of many hippocampal pyramidal neurons [1, 2]; consequently, many firing sequences are time-compressed representations of paths through the environment [3–5]. However, sequences should not be thought of as strictly spatial phenomena; neurons with nonspatial firing patterns could also participate in structured sequential representations.

The temporal organization of spiking in sequences exceeds the precision necessary to achieve the canonical tuning properties of hippocampal neurons; place cells could show identical spatial tuning without expressing fast timescale sequences. Sequences thus comprise an additional layer of temporal organization beyond cells' primary tuning properties. Understanding how sequential organization arises, whether it is modulated by behavior, and what functions (if any) it serves is important for better understanding neural representations in the hippocampal network.[1]

Readers may note that we use the term "firing sequence" in place of other descriptors (like "reactivation" or "replay") commonly used to label these events. The term "sequence" captures the unifying property shared by all of these events (temporal organization) while remaining agnostic as to function. This is important, as current understanding of sequence function is incomplete, albeit developing rapidly. Furthermore, as seemingly similar representations might be involved in multiple unique functions during different behavioral or physiological states, a term specifying one particular function seems inappropriately limiting.

Hippocampal Network States

Local field potential (LFP) activity, the low-frequency voltage signal derived from summed electrical activity in the region of tissue surrounding the electrode tip, has a long history of study in the hippocampus [1, 7–10]. Consequently, the behavioral

[1] The hippocampus is divided into multiple anatomical subfields [6], with the majority of place cell recordings deriving from the CA1 and CA3 regions. These regions exhibit interesting differences in both efferent and afferent connectivity [1]. In this chapter, we do not focus on these differences, but instead consider sequences recorded in both regions.

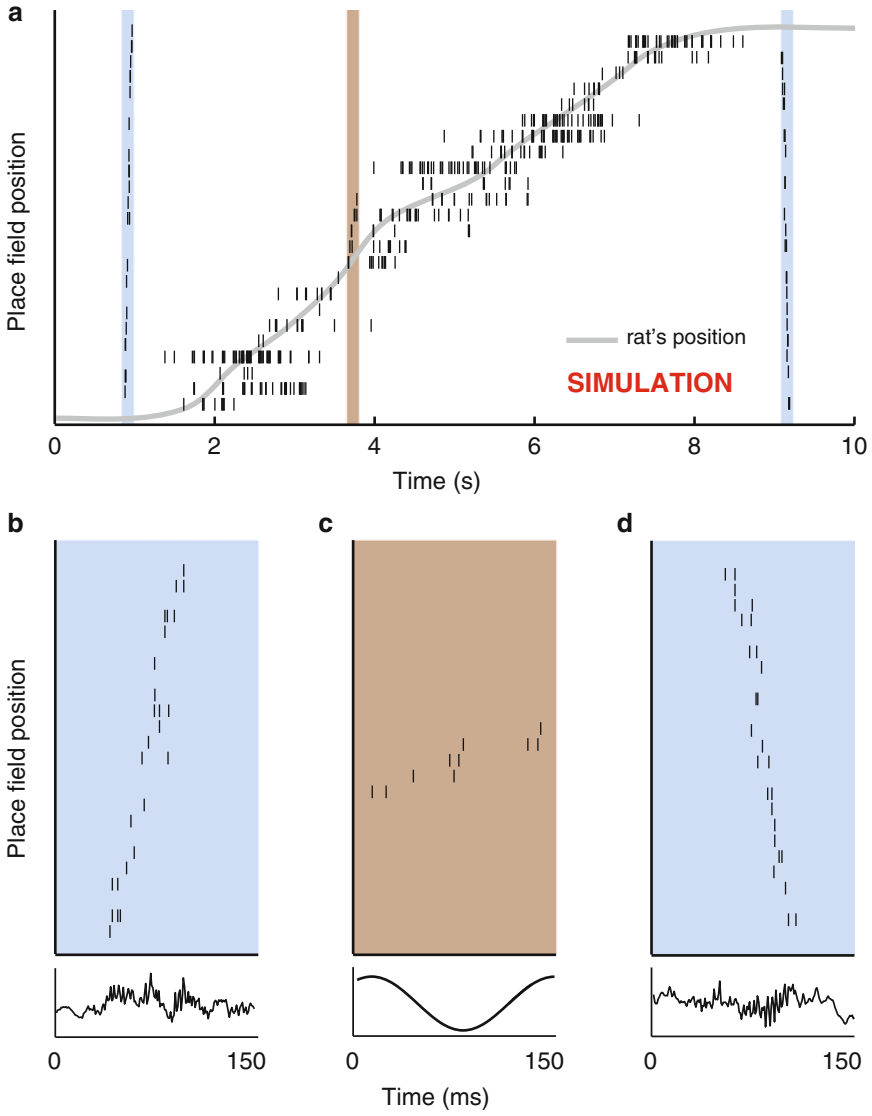

Fig. 5.1 Simulated activity in an ensemble of place cells is plotted as a rat runs through an environment (**a**). Each row represents the activity of a single neuron, and cells are sorted based on where their fields occurred in space. Sequences are reproduced (with the accompanying LFP activity) on an expanded timescale in the lower portion of the figure. Sequences before and after the animal's trajectory (during the LIA network state), occur with both forward (**b**) and backward (**d**) ordering. During active behavior, when the hippocampus is in the theta network state, place cells spiking is organized into sequences bounded by theta oscillations (**c**)

correlates and underlying single-cell activity associated with different hippocampal LFP patterns are well established. Because hippocampal firing sequences often co-occur with characteristic LFP signatures [11, 12], LFP recordings provide both a useful readout of hippocampal network state and a convenient means of detecting candidate firing sequences.

Theta State

Hippocampal LFP patterns are typically divided into theta and non-theta states. During the theta state, the LFP is dominated by strong, theta frequency (5–12 Hz) oscillations [1, 8, 9, 13]. Two distinct forms of theta oscillation (type I and type II) have been described. Type I theta occurs during "voluntary," primarily movement-related behaviors and occupies the upper portion (7–12 Hz) of the theta frequency band. Type II theta occurs when animals are stationary, but in some way alert or attending to their surroundings (e.g., during presentation of conditioned stimuli, preparation of a motor response, fearful freezing). The frequency of type II theta tends toward the lower regions (5–7 Hz) of the theta band. In addition to differences in behavioral correlates and dominant frequencies, types I and II theta are further distinguishable by pharmacology and the brain structures responsible for generating each [14]. The theta network state is also prominent during rapid eye movement (REM) sleep [1].

Theta Sequences

The discovery of phase precession in hippocampal place cells [15] demonstrated that spike timing could carry information along with the cell's firing rate. As noted by Skaggs and colleagues [16], phase precession implies that the relative timing of different place cells' spikes within a theta cycle should reflect the order in which the cells' place fields are arranged in space, giving rise to orderly sequences of place cell spiking. It is now well established that such sequences do exist [12, 17, 18]. Subsequent work suggests that theta sequences occur during both type I and type II theta states and can include both spatial and nonspatial information [18–22].

Large, Irregular Activity (LIA) State

During non-theta states, the hippocampal LFP exhibits broad-spectrum voltage fluctuations, often referred to as large, irregular activity (LIA; [1, 8]). Behavioral correlates of the LIA network state include inattentive wakefulness, consummatory behaviors, and grooming. Slow-wave sleep is also accompanied by LIA [1, 8, 23, 24].

The disorganized voltage fluctuations characteristic of LIA are punctuated by transient, population bursts of spiking that engage large numbers of neurons in the hippocampus. These short bursts of heightened synchrony are called sharp wave-ripple (SWR) complexes because of the distinctive LFP oscillation associated with them [1, 9, 24].

LIA Sequences

Evidence for sequential firing patterns in the hippocampus was first observed during SWRs in slow-wave sleep. Early work showed that correlations between pairs of place cells coactive during behavior were enhanced during post-behavior sleep [25]. It has since been established that place cell spiking in and around SWRs during sleep represents extended, temporally precise spatial trajectories through previously visited environments [11, 26–28]. Additionally, similar sequence representations occur within SWRs during awake LIA [29–32].

Cognitive Maps and the Hippocampus

Tolman proposed the idea of a cognitive map based on behavioral studies of rats, envisioning a proactive, predictive learning system that could flexibly manipulate and retrieve information to guide surprisingly complex behaviors [33–36]. Tolman's conception of the cognitive map was an internal representation of the environment, constructed by animals in the absence of explicit reward or punishment, and used to generate expectancies or predictions about the cause and effect structure of the world [37, 38]. The cognitive map theory ascribed unprecedented mental abilities to rats; needless to say, these ideas were not without controversy [39–41]. Nevertheless, subsequent work has many of Tolman's conjectures, and his cognitive map framework is increasingly accepted. O'Keefe and Nadel [1], based on behavioral and neurophysiological studies in rats, presciently postulated the hippocampus as the neural instantiation of the cognitive map. Recent research on hippocampal function in both humans [42, 43] and increasingly nonhuman species [44, 45] has converged on a theory of hippocampal computation close to Tolman's cognitive map, including prospective processes like mental time travel [46, 47], prediction [48, 49], and imagination [50–53]. There is now growing consensus that the hippocampus is essential for these sorts of future-oriented, synthetic, cognitive processes.

In this chapter, we argue that spiking sequences in the hippocampus play an important role in the development, maintenance, and modification of a Tolmanian cognitive map that learns to predict reliable environmental features and can aid decision-making by allowing subjects to project themselves in both time and space. Functional roles previously attributed to the hippocampus mesh well with the cognitive map theory. We review three processes associated with the hippocampus

(memory, construction of novel representations, and planning), discuss their place within the cognitive map framework, and consider evidence that computations involving hippocampal sequences could underlie these forms of information processing.

Memory: Storing Environmental Features to Develop Expectancies

The hippocampus has long been connected with mnemonic processes due to a consilience of neuropsychological, behavioral, and electrophysiological data [1, 2, 54]. It is not surprising then that many models of hippocampal function link sequences with memory-related computations [1, 3, 4, 24, 54–59]. Memory processes have a place in Tolman's cognitive map framework; he theorized that behavior such as "searching for the stimulus," in which animals actively investigate their surroundings, apparently in search of stimuli that caused noteworthy outcomes, is important for learning about the consequences of behavior [37]. Memory representations could function in linking the current state of the environment with the past, aiding the development of predictive associations and allowing animals to learn the "causal texture" of their surroundings [37, 38].

Sequences During Sleep LIA

A popular idea, dating back at least to theoretical work by Marr [55], is that memories are initially encoded in the hippocampus, but are eventually transferred to neocortical sites for long-term storage in a process known as consolidation [3, 60]. Related theories [24] have suggested consolidation entails an intrahippocampal transfer of information (between, e.g., CA3 and CA1 regions). Identifying the brain locus of a particular type of memory's final resting place remains an area of active research [54, 61]; nevertheless, models of consolidation generally require some mechanism for inducing long-term changes in synapse function to store memories.

In many ways, LIA-associated hippocampal sequences are well suited to mediating memory consolidation in neural systems. Sequences were first documented during sleep [25, 26], long known to be important for learning and memory improvement, when the reduction of incoming sensory signals allows internal brain dynamics to dominate information processing. Because sequence representations are temporally compressed, spiking occurs on a timescale fast enough to induce long-lasting changes in synaptic strength, and patterns of spiking experienced during behavior are repeated multiple times during LIA sequences, further increasing the odds of activating plasticity mechanisms [3, 4, 62, 63].

The content of sleep LIA sequences reflects previous behavioral experience, consistent with a role for LIA sequences in memory consolidation. Cells active during behavior fire at a higher rate during sleep [64], and correlations between pairs of place cells coactive during exploration are enhanced during post-behavior sleep [25]. The enhancement of post-behavior correlation strength reflects the order in which cells were activated during behavior [26], suggesting ensemble-level coordination of place cell "reactivation" during sleep. In aged animals, the temporal patterning of LIA sequences is altered, and the extent of sequence alteration predicts spatial memory impairment [65].

In addition to this large body of correlational evidence, recent experiments have causally linked SWR events during sleep and memory consolidation. Real-time detection of SWRs allows researchers to deliver precisely timed electrical stimulation to the hippocampus, disrupting spiking sequences often present during SWRs, but otherwise sparing normal ensemble activity. Using this technique, two groups have found that stimulation contingent on SWRs during post-behavior sleep impairs learning, providing strong evidence in favor of a causal role for SWRs in consolidation [66, 67]. It is important to note that because the electrical stimulation used in these experiments is a fairly nonspecific manipulation that has the potential to simultaneously affect multiple processes in the hippocampus (e.g., spiking, LFP activity, synaptic plasticity), SWR disruption does not uniquely identify a single process that is critical for memory consolidation. Additionally, as discussed above, sequences are less tightly correlated with SWR occurrence than previously thought, raising the possibility that some non-sequence process disrupted by stimulation causes the memory impairment. Nevertheless, these experiments provide some of the strongest evidence to date that a SWR-associated hippocampal process plays an important role in memory consolidation during sleep.

Construction: Building a Cognitive Map with Hippocampal Sequences

A key point of the cognitive map theory is that learning is an active process, which can disassemble and rebuild stored information to generate de novo representations [37, 38]. A classic illustration of such behavior is latent learning, the discovery that animals can extract and integrate information about an environment in the absence of reinforcement or motivated information seeking. Latent learning implies that animals build structured representations of their surroundings without any obvious need to do so and that this might occur without any measurable change in behavior.

Hippocampal sequences (during both LIA and theta states) could participate in the construction of flexible, behaviorally relevant representations of the world. We propose that the hippocampus initially parses experience (potentially both spatial and nonspatial aspects, as discussed below) in theta sequences, enhancing connections between sequence items close to each other in representational space,

creating representational "chunks." During LIA-associated sequences (in both online and off-line states), the hippocampus strings together information acquired in theta sequences, forming integrative representations that capture relationships between distant portions of the environment. By recombining information in configurations that differ from actual experience (e.g., backward sequences), the hippocampus can generate representations of never-experienced paths, which can then be integrated with the rest of the cognitive map, providing animals access to representations necessary for planning flexible behavior.

From Phase Precession to Theta Sequences

As discussed earlier, it was initially proposed that the phase precession [15] of individual place cells might be a mechanism for preserving the correct ordering of place cell spiking within each theta cycle [12, 16, 17, 68, 69], resulting in the formation of theta sequences. However, recent findings suggest instead that theta sequences are the primary organizing principle of spiking within theta cycles and that phase precession is an epiphenomenon resulting from sequence readout as rats move forward [48, 69]. For instance, spike time correlations between pairs of place cells are more reliable than the correlation between spike phase and position that results from phase precession [17]. Similarly, theta sequences are more precisely patterned than would be expected if phase precession alone organized place cell spike timing [12].

When estimated across many cycles, the average theta sequence representation begins slightly behind the rat's current location and extends forward in the direction of motion [12, 16, 70]. Closer examination of theta sequences has revealed greater variability than was previously appreciated. Gupta and colleagues [18] examined theta sequence representations on a cycle-by-cycle basis as rats performed a spatial decision-making task. They found that while theta sequences generally represented a region of space around the rat, the beginning and ending points of these representations varied considerably. Some sequences began behind the rat and ended at its current location, other representations were centered around the rat, and still others began near the rat and swept forward to varying extents. The expression of these different types of theta sequences was modulated in a manner consistent with a role in actively parsing the environment; as rats approached turns, food delivery sites, and other areas of the maze that might plausibly have gained motivational or informational salience, theta sequences shifted from starting near the rat and projecting forward to starting behind the rat and projecting up to its actual position. Thus, as a rat approached a prominent landmark, the hippocampal representation coursing over the rat's location in each theta cycle shifted from predictive and forward-directed to more retrospective or backward-looking (Fig. 5.2). This shift in sequence content around landmarks imposed a distinctive organization on the hippocampal representation of space, in which semi-discrete, landmark-bounded "chunks" of the environment emerged [18]. A recent study of rats performing a linear track task reported a similar result, with CA1 place cell activity appearing more

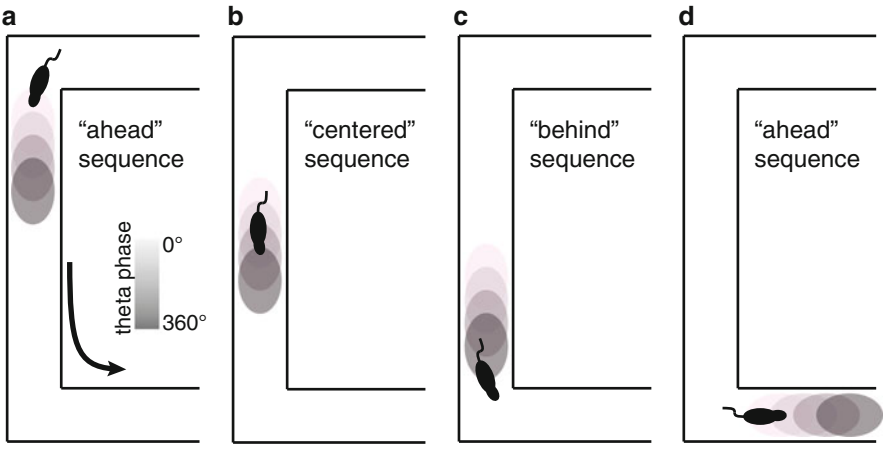

Fig. 5.2 The content of theta sequences is modulated by salient features of the environment in a manner that gives rise to a distinctive "chunked" representation of space [18]. In this example, the landmarks are two turns on a maze. Immediately after rounding the first corner (**a**), sequences begin at the rat's current location and extend asymmetrically, such that a greater portion of space in front of the rat is represented. Midway between turns (**b**), sequences tend to be more centered on the rat (although still forward shifted). As the rat nears the second turn (**c**), sequences shift backward, beginning some distance behind the rat and extending up to its current position. Finally, once past the final turn (**d**), representations are again largely ahead of the animal. Note that this leads to an increased density of representations covering the regions between landmarks and well-defined boundary regions near landmarks that representations tend not to cross

forward-directed as subjects left feeder sites at the ends of the track and more backward-looking on approach to feeders [71]. Interestingly, forward representations were associated with greater LFP power in the low gamma frequency (25–55 Hz) range, suggesting coupling between CA1 and CA3. In contrast, backward-lagging spikes occurred when fast frequency gamma (60–100 Hz) was prominent, suggesting strong entorhinal cortex drive [72].

These results suggest that, rather than passively coding features of the environment as they exist, representations within theta cycles can actively segment space, effectively performing a sort of information compression that could be useful behaviorally.

Awake LIA Sequences Construct Adaptive Representations

In addition to LIA sequences during sleep, sequences also occur during LIA, when animals are quiescent but awake [29, 31, 32, 73]. In contrast to sleep LIA sequences, which possess many properties suggestive of a memory consolidation function, the content and ordering of representations within awake LIA sequences are consistent

with a role in manipulating portions of previous experience to construct novel, i.e., never-experienced, representations.

The content of awake sequences and actual behavior can diverge substantially, both on a moment-by-moment basis and when considered over longer timescales. For instance, sequence representations do not necessarily begin near the animal, nor are they bound to cross through the position the rat currently occupies [74–76]. In fact, sequences representing previously experienced environments (which recruit place cells that are not active in the current location) have been described, intermingled with "local" sequences representing paths through the animal's current surroundings [31, 74]. Neither does cumulative behavioral experience have a strong influence on the frequency with which portions of the environment are included in sequences. For instance, in rats performing a multiple-T decision-making task, the probability of a location being included within awake LIA sequences was sometimes inversely related to how often that area was visited [76]. In a session where only left-side laps were rewarded (and rats consequently made few visits to the right loop of the maze), sequence representations to the unrewarded side were actually more frequent than those representing the path the rat traveled more often that day [76].

Cognitive factors seem to have a strong influence over the content of awake LIA sequences. When animals encounter new environments for the first time, awake LIA sequence content is biased toward representing recently explored portions of space [77]. This suggests that novel experience might be prioritized for incorporation into existing representations via expression in awake LIA sequences. Similarly, reinforcement seems to sculpt awake LIA sequence content. Sequences are more likely to occur during quiescence following reward delivery, and the resulting representations preferentially include regions of space associated with reward delivery [78]. The enhanced sequence representation of rewarded locations follows the time course of task learning, suggesting that LIA sequences construct an adaptive representation used to guide behavior [78]. These results are all consistent with the idea that new experience is integrated with previous learned cognitive components of the cognitive map by coordinated representation during awake LIA sequences.

Sequences during awake LIA can occur in the opposite order of experience (backward sequences; [29, 32, 75, 76]). From a consolidation perspective, this seems problematic, as it could lead to the storage of a memory with the wrong serial ordering. Because awake LIA sequences occur both forward and backward, consolidation during awake LIA would be vulnerable to memory interference, as forward and reverse trajectories represent equally plausible experiences, but the rat may have traveled in only one direction.[2] On the other hand, from a construction perspective, backward sequences could be a key building block for assembling never-experienced trajectories.

[2] Recent evidence [73] suggests that backward LIA-associated sequences are present during sleep as well (albeit to a lesser extent than forward-ordered representations), suggesting that in some cases a similar problem with directional ambiguity could occur during off-line consolidation. Alternatively, this might suggest that both consolidation and constructive processes coexist during slow-wave sleep [79, 80].

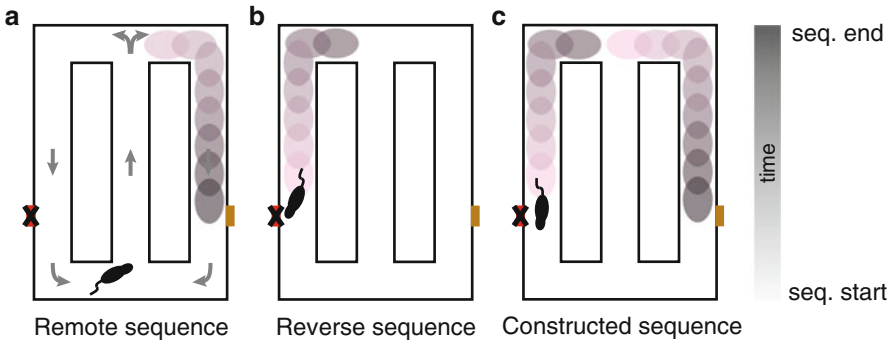

Fig. 5.3 Combinatorial expression of sequences can generate trajectory representations never directly experienced by the subject. In this example (modeled after the results in [76]), a rat is performing a T-maze decision-making task. Food delivery sites are marked with *rectangles*; in this example, only the right-side feeder is rewarded. *Arrows* in (**a**) indicate the possible directions the rat is allowed to travel at each location on the maze. A forward sequence spanning the region between the choice point and the right feeder (**a**), preceded by a backward sequence originating at the left feeder and ending at the choice point, could be used to represent the unexperienced trajectory from left-side feeder to right-side feeder (**c**), a shortcut between potential reinforcers. Gupta and colleagues [76] observed constructive sequences like this more frequently than would be expected due solely to chance, sequential expression of the sequences in (**a**) and (**b**)

Gupta and colleagues [76] observed novel trajectories represented within awake LIA sequences. During the performance of a spatial decision-making task, the authors discovered sequences connecting spatially contiguous portions of the maze that the rat had never traversed. Forward- and backward-ordered sequences occurred in equal proportion during the performance of this task; never-experienced trajectories were constructed via linking backward and forward representations of neighboring maze segments (Fig. 5.3). Representations that synthesize novel trajectories by linking chunks of previous experience are an important idea within Tolman's cognitive map theory [36] and could subserve shortcut behavior or other cognitive processes requiring extrapolation beyond actual, physical experience [50, 76, 81].

Together, the findings reviewed here suggest online LIA sequences, in conjunction with theta sequences, are involved in synthesizing representations of the world by assembling bits of previous experience and connecting them together in a novel fashion. It is interesting to note that the data discussed here concerning construction within awake LIA sequences [76] and chunking within theta sequences [18] derive from the same set of neural recordings. While theta sequences show clear evidence of spatial segmentation [18], awake LIA sequences were not constrained in this respect, representing trajectories that crossed landmarks in a way that theta sequences did not [76]. This is further suggestive of a more integrative function for awake LIA sequences in linking information, in contrast to the parsing and compression function evidenced by theta sequences.

Planning Function in Hippocampal Sequences

Tolman suggested that an important function of the cognitive map was to allow animals to mentally explore the outcomes of possible courses of action before committing to one [37]. Behaviors like "vicarious trial and error" (VTE), in which animals pause before making difficult decisions and alternately orient toward possible options, support this proposal [34, 35, 37]. In more modern parlance, we might call Tolman's VTE concept mental time travel [47], episodic future thinking [82], or imagination [53], all of which seem to involve hippocampal function in humans. Representations that could be used to perform mental simulations over possible actions coupled with valuation signals that balanced the costs and benefits associated with each would be powerful tools in a decision-making arsenal [83, 84].

Sequence representations in the hippocampus could play an important role in computing predictions about future states of the world. As discussed previously, theta sequences often contain a predictive component near the end of each theta cycle [48]. Maurer and colleagues [70] demonstrated that the look-ahead representation late in the theta cycle is modulated by behavior in a manner consistent with predictive function. By carefully examining average ensemble representations across the theta cycle, they found that the extent of space represented within a cycle scaled with running speed. This scaling resulted in representations that extended farther forward as animals moved more quickly and were arguably in greater need of predictive representations extending farther along their immediate future path [70].

Similar theta sequence representations could play a role in planning as animals pause before making a difficult choice. Johnson and Redish [85] analyzed ensembles of CA3 hippocampal neurons recorded as rats performed a multiple-T decision-making task. While pondering high-cost decisions, rats paused at the choice point and engaged in VTE, one of Tolman's cognitive map hallmarks [34, 35, 37]. Coincident with VTE, decoded hippocampal representations became nonlocal, projecting forward along the maze ahead of the rat's current location, tracing out trajectories along possible future paths (Fig. 5.4). Analysis of the LFP recorded during these nonlocal events revealed clear theta oscillation and the absence of LIA-associated LFP signatures, suggesting that theta sequences underpinned the decoded representations [85] (also see Chap. 14). Evidence in support of this idea can also be seen in Gupta and colleagues' [18] explicit analysis of theta sequences, which revealed two populations of events—one during active locomotion and another during periods of immobility. These results suggest a model in which sequences during type I theta represent an information gathering and processing stage, while sequences during type II theta are a planning process [56, 57]. The timing of types I and II theta sequences is consistent with this idea (type I sequences during active exploration and type II sequences during pauses, when animals might be planning future actions).

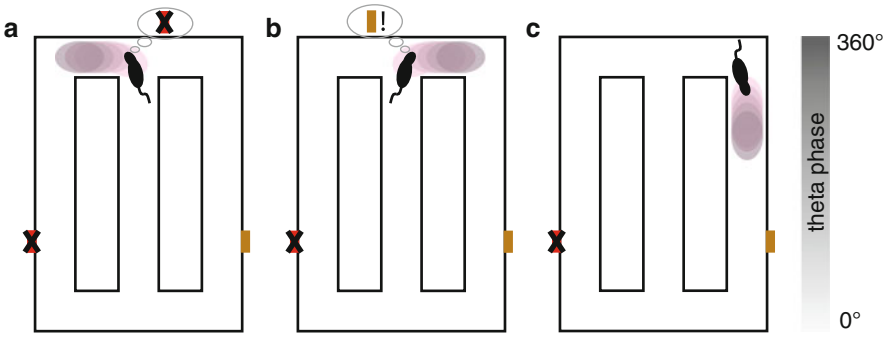

Fig. 5.4 Forward-shifted theta sequences could be a means of mentally investigating potential future options. In rats performing a T-maze decision-making task, Johnson and Redish [85] found that CA3 hippocampal representations projected ahead of animals as they paused at the choice point. These forward-directed, decoded representations typically traversed both the left (**a**) and right (**b**) paths of the maze. Representations like these could be useful for calling up value information associated with each option to adaptively guide behavior (**c**), perhaps via interactions with other brain regions such as the prefrontal cortex [132, 133] or the ventral striatum [134]

Nonspatial Information in Theta Sequences

An important feature of the cognitive map is that nonspatial information can be embedded within the primary spatial tuning of hippocampal neurons, where it could be used in coordinating future behaviors along with spatial representations. Just as spatial phase precession could result from spatial sequence readout during forward movement, phase precession during nonspatial behaviors might be thought of as nonspatial theta sequences expressed during an imagined, mental progression through the representational dimension of the sequence [48]. Representations like these are consistent with processes like mental time travel [46, 47] and imagination [53] and could be useful for mentally exploring the consequences of future actions.

Previous experiments suggest (but do not show explicitly) that nonspatial information represented by the hippocampus is also organized into sequences within theta cycles. Early work established that phase precession can occur even when rats are not actively moving through space [19]. Pastalkova and colleagues [20] furthered this work, providing tantalizing evidence for the existence of theta sequence-like representations of nonspatial information. In their experiments, rats performed a hippocampus-dependent delayed spatial alternation task. During the delay periods punctuating alternation trials, rats were trained to run on a stationary running wheel, which induced strong theta oscillation in the hippocampus. During alternation trials, hippocampal neurons showed typical spatial tuning. However, during wheel-running epochs, hippocampal cells showed strong, reliable tuning to time spent in the running wheel, consistent with previous theoretical work [86]. Different subsets of time-encoding neurons were activated during delays that preceded leftward or rightward alternation trials, and much like place cells, these temporally tuned cells showed clear phase precession [20]. Hippocampal neurons with temporal tuning

have since been found in rats performing other behavioral tasks that require planning [87–89]. Together, these findings are strongly suggestive of coordinated, sequential representations within theta cycles, in this case encoding a temporal, rather than spatial, sequence.

Takahashi et al. [22] recorded hippocampal pyramidal neurons in rats performing a nosepoke-based alternation task. Subjects initiated a trial by maintaining a nosepoke in a central well until the fixation period expired and then alternated nosepokes in wells to the left or right of the fixation port. During fixation, pyramidal neurons showed theta-modulated spiking spanning portions of the delay period. Reminiscent of Pastalkova and colleagues' [20] findings, unique ensembles of neurons were recruited prior to leftward or rightward alternation trials [22]. Fixation period spiking phase precessed relative to LFP theta, consistent with coordinated theta sequences (in preparation).

Lenck-Santini and colleagues [21] recorded hippocampal neurons as rats performed a shock avoidance task. At the beginning of trials, subjects were dropped on to the metal floor of the test arena. The rats then had to jump out of the arena within a particular time window (>2 s but <15 s from trial start) to avoid electric shock. Hippocampal pyramidal neurons discharged around both the beginnings of trials and the self-initiated escape jumps, and these spikes precessed over subsequent theta cycles, suggesting that ensembles of hippocampal neurons may have encoded the temporal intervals around important task-related events. Although executing the jump to safety was, of course, a voluntary movement, jump-responsive neurons began phase precession seconds before the actual jump. Administration of moderate doses of the cholinergic antagonist scopolamine interfered with the reliable generation of type II theta oscillation, and the extent to which normal theta patterns were disrupted was predictive of behavioral errors on a trial-by-trial basis. These findings suggest a behaviorally relevant role for phase precession of nonspatial information during type II theta [21].

A Causal Role for Theta Sequences in Planning

Studies reviewed in this section provide evidence that both spatial and nonspatial features of the environment are encoded within theta sequences, that cells encoding nonspatial information phase precess, and that the behavioral task subjects are performing can influence the content of theta sequences. These data are consistent with a role for theta sequences in planning, but establishing a causal link has proven difficult.

Cannabinoid agonists offer a surprisingly specific manipulation of the precise timing of place cell spikes [90, 91]. Robbe and colleagues [91] administered a cannabinoid agonist to rats trained to perform a delayed spatial alternation task. The drug had a strong behavioral effect, reversibly reducing task performance to chance. Surprisingly, when the authors analyzed recordings of CA1 pyramidal neurons,

normal spatial firing patterns were mostly unaffected by the drug. Temporal coordination between cells, however, was disrupted. Theta phase precession was greatly attenuated following drug administration, and the correlation between place field separation and theta-scale cross-correlogram lag weakened substantially. Thus, a manipulation that disrupted temporal organization (while mostly sparing other place cell properties) had drastic effects on behavior in a hippocampus-dependent task.

Because cannabinoid receptor activation impaired performance of an already-learned task [91], these data support the idea that theta sequences play an important role in online planning processes. Close inspection of position tracking data before and after drug administration ([91]; their Fig. 1) suggests that cannabinoid activation altered behavioral dynamics in an interesting way. When the drug was active, the subject displayed much more pausing on the central stem of the maze and at the choice point. Additionally, the rat appears to have spent more time peering over the edge of the maze and generally scanning his surroundings [91]. This is suggestive of an increase in VTE, a behavior Tolman [34, 35] and others [83, 85, 92] have associated with deliberative decision-making. Usually, however, VTE is a much more transient event [85, 92]. A fascinating possibility is that with dysfunctional sequence expression in the hippocampus, rats remain deliberative and indecisive for much longer periods, lacking sequences for planning a suitable course of action. Because cannabinoid agonism also caused notable motor side effects [91], this hypothesis, although intriguing, remains speculative.

LIA Sequences and Planning

Is online planning function in the hippocampus the exclusive domain of theta sequences? Emerging results suggest that LIA sequences might be involved as well. The recent report of "pre-play," LIA sequences that represent trajectories through regions of an environment that subjects can view but not physically enter [93], suggests that the hippocampus is equipped to plan trajectories over regions of space it has not yet encountered. Alternatively, pre-play could be interpreted as a constructive process, involved in allocating representations to nearby, but novel, regions of space. Interestingly, while observation alone is not sufficient for the development of stable place cells covering unvisited portions of the environment [94], the dorsal hippocampus has been implicated in processing visible but inaccessible objects [95]. It is possible, as suggested by Rowland and colleagues [94], that pre-play serves to establish a rough, approximate spatial representation that is subsequently refined and bound to prominent environmental features upon direct physical experience. Although the behavioral implications of pre-play are not yet clear, this sort of representation could be useful in both the planning and constructive cognitive map functions outlined in this chapter.

In rats trained to shuttle back and forth between food delivery sites placed at both ends of a linear track, awake LIA sequences expressed before and after completion of trials contained representations consistent with both planning and memory-like functions [32]. While paused at a feeder site, before initiating a new trial, forward-ordered sequences beginning at the rat's current location and extending to the opposite feeder were detected. Interestingly, after arriving at a feeder, sequences retracing the recently completed journey in reverse were recorded [32]. The sequences preceding trial start might play a role in planning upcoming trajectories. Reverse-ordered sequences occurring after the completion of a trial may have some memory role, perhaps in associating past behavior with reward, in a process reminiscent of Tolman's [37] "searching for the stimulus" or the credit assignment problem of reinforcement learning [29, 96, 97]. Interestingly, forward-ordered sequences occurred more frequently than backward sequences in this study [32], suggesting that whatever function differently ordered sequences may have fulfilled, forward sequences were in greater demand than backward sequences.

The results of a study by Jadhav and colleagues [98] support a causal role for awake LIA sequences in online planning. The authors probed the function of awake SWRs in rats learning to perform a hippocampus-dependent decision-making task [99]. In these experiments [98], electrical stimulation disrupted spiking during SWRs, following the same paradigm used to probe the function of SWR sequences during sleep [66, 67]. In the behavioral task, rats were required to visit the arms of a W-shaped maze in a particular order. Inbound trials required rats to run from an outer arm to the central stem. In contrast, on outbound laps, rats departed the central stem and headed to the outer arm opposite that they had visited most recently. Interestingly, although hippocampal lesions slow the learning of both inbound and outbound trials, real-time disruption of awake SWRs specifically impeded acquisition of outbound trials. Further, in animals pretrained to proficiency on the task, SWR disruption resulted in mildly degraded performance on outbound choices [98]. Although subject to the same caveats discussed above in reference to sleep SWR disruption [66, 67], these data provide strong evidence that awake SWRs play some role in coordinating behavior in real time, in addition to whatever learning function they might fulfill. Consistent with this idea, recent work by Pfeiffer and Foster [100] showed that sequences recorded while rats performed a goal-directed navigation task were biased to end in the spatial location that the rat would next travel to.

Unanswered Questions and Ways Forward

In this chapter, we have described hippocampal firing sequences and reviewed theories relating to the function they might subserve. Although a great deal of progress has been made in this direction, many knowledge gaps remain. Here, we identify pressing unanswered questions concerning sequence function and discuss possible experimental strategies that could be used to approach them.

How Does the Ventral Hippocampus Contribute to the Cognitive Map?

The vast majority of data relating to hippocampal sequences comes from recordings made in the dorsal region of the hippocampus. More ventral regions of the hippocampus receive unique anatomical inputs [101] and exhibit different patterns of gene expression [102]. Additionally, lesions of the dorsal and ventral hippocampus cause distinct changes in behavior [103–108]. This has led to the suggestion that the dorsal and ventral hippocampal regions are distinct functional modules, with the dorsal hippocampus involved in more cognitive operations and the ventral hippocampus playing a greater role in affective processes [109–111]. Although we have focused on the cognitive functions of hippocampal sequences in this chapter, affective information bound to the cognitive map could also aid animals in adaptively selecting behavior.

Only a handful of electrophysiological studies have recorded neural activity in ventral regions of the hippocampus [112–115]. In general, differences between dorsal and ventral hippocampal neural representations seem to be more quantitative than qualitative. The spatial tuning of neurons in the ventral hippocampus tends to be broader and perhaps less organized, with place fields often covering large swaths of a given environment. In addition, ventral hippocampal neurons seem more likely to encode nonspatial aspects of the world (e.g., closed vs. open arms on a radial maze; [115]). Theta modulation (of both the LFP and single-unit spiking) is greatly attenuated in the ventral hippocampus. However, the existence of some phase precessing ventral hippocampal neurons argues that dorsal and ventral hippocampal regions may share at least some information-processing mechanisms [114–116].

Ventral hippocampal representations could provide useful input to many of the cognitive map functions described in this chapter. For instance, the larger field size in ventral neurons would produce an even greater predictive look-ahead component if spiking is indeed organized into theta sequences [116]. However, little is currently known about sequence representations in the ventral hippocampus; establishing whether or not theta and LIA sequences exist in the ventral hippocampus and examining how they differ from sequences in more dorsal regions could reveal how ventral and dorsal hippocampal activity is coordinated. Understanding whether and how ventral hippocampal neurons contribute to cognitive map-like representations might require the development of new behavioral tasks. For instance, if the ventral hippocampus is more involved in affective processes, a task requiring animals to escape from an anxiety-provoking stimulus (e.g., [117, 118]) might reveal how cognitive and affective information are combined to guide behavior.

Why Are Sequences Rare?

Hippocampal sequences are striking because they possess structure and informational content that clearly distinguishes them from “spontaneous” (i.e., apparently random) activity in other structures. Nevertheless, many SWRs are accompanied by

spiking that lacks any detectable sequence content. Similarly, in Gupta and colleagues' [18] study of theta sequences, only a fraction of theta cycles were found to contain significant structure. There are several possible explanations for these findings.

One possibility is that methodological or technical issues sometimes prevented the detection of sequences represented by the hippocampus. For instance, ensemble size could profoundly limit sequence detectability. Similarly, the distribution of place fields an ensemble of neurons expresses could limit the number of theta sequences observed. Advances in recording technology and techniques increasingly render these concerns moot, however. As the number of simultaneously recordable neurons increases, it will be possible to examine quantitatively how this variable impacts sequence detection.

Spiking that appears to be nonsequential might simply reflect our ignorance of what the cells are encoding. Detecting sequence activity depends on our ability to compute place fields for hippocampal neurons during active behavior. Using the wrong set of tuning curves to decipher spike sequences might explain why bursts of ensemble spiking sometimes do not seem to form an interpretable representation. For instance, it is known that LIA sequences can represent an entirely different environment than the one a rat currently occupies [31, 74]. Although the typical laboratory rat presumably does not physically explore more than a handful of environments thoroughly enough to establish strong place cell maps, it remains possible that some apparent non-sequences are simply representations of distal locations for which experimenters have no knowledge of the cells' tuning.

Nonspatial tuning could also thwart detection of sequences. Of course, if clear nonspatial firing correlates can be identified, nonspatial sequences could be measured as easily as spatial sequences. An important unanswered question is whether hippocampal neurons with nonspatial tuning are incorporated into sequence representations (during either LIA or theta network states) in the same manner as spatially tuned hippocampal cells.

It is also possible that some ensemble bursts of spiking are simply not self-consistent sequence representations. Random bursts of spiking might be adaptive in some cases, perhaps enabling some sort of homeostatic downscaling of synaptic weights [119]. Another possibility (not mutually exclusive) is that SWRs and theta cycles are times at which the hippocampal network is primed for plasticity [120] and that these network events are essentially "containers" that can be filled with sequence content (or not) depending on the behavioral and cognitive demands faced by the subject at the moment. Consistent with this idea, rabbits being trained on an associative learning task acquire the task more quickly when training trials are initiated contingent on awake hippocampal SWRs [121]. Similarly, electrophysiological evidence shows that presenting behaviorally relevant tone cues to rats during post-behavior sleep biases LIA sequence content toward representing the regions of space that were associated with the tone during behavior [122]. These findings suggest that LIA sequence content can be influenced in real time, even by incidental external stimuli, which effectively hijack whatever representation may have otherwise occurred. This suggests that sequence content ought to reflect the cognitive

demands an animal is faced with during behavior. Relatively simple behaviors would be expected to induce a greater proportion of incoherent bursts of spiking in and around SWRs, as the hippocampus has little need to construct, consolidate, or otherwise operate on experience when behavior does not demand it. More complex tasks might be expected to induce more complicated sequence representations. Although these ideas are speculative, they are testable with today's recording technologies and cleverly designed, well-controlled behavioral tasks.

How and When Do Hippocampal Sequences Interact with Other Brain Regions?

In this chapter, we have argued that hippocampal sequences sharing many similarities actually have unique functional roles, depending on when they occur, what information they represent, the behavioral state of the animal, and the network state of the hippocampus. If this is the case, it seems likely that sequences with different functions would interact with distinct subsets of other brain regions. This raises the question of how information flow out of the hippocampus is routed to the appropriate structure.

One possible mechanism for coordinating information transfer between brain regions is oscillatory interactions. Changes in cross-structural synchrony or other properties of the LFP could transiently link hippocampal activity to certain brain regions while simultaneously disconnecting hippocampal output from other parts of the brain [10, 123–128]. Such a scheme allows rapid reorganization of functional interactions across the brain. If cross-structural coordination were actually achieved in this way, hippocampal sequences involved with particular functions might have unique and consistent LFP correlates that would distinguish them from sequences performing other roles. If such signals could be identified and detected online, SWR disruption techniques and other experimental manipulations could be applied to particular functional classes of hippocampal sequences. Experiments like these could shed light on both the behavioral impact of hippocampal sequences and the neural mechanisms by which sequences achieve their effects. It is already known that hippocampal SWRs during off-line states influence the firing rate of neurons in the ventral striatum [129] and the prefrontal cortex [125] and that neurons in these structures encoding task-relevant rule [125] or reward [130, 131] information are preferentially modulated. Likewise, during active behavior, hippocampal theta oscillations influence the timing of spikes in the prefrontal cortex [132, 133] and ventral striatum [134]; future work aimed at further characterizing the LFP signatures of functional interactions between brain regions seems a promising approach to better understanding sequence function.

A related question is whether and how the brain measures sequence quality. Sequences expressed in the hippocampus range from high-fidelity representations of behavioral patterns to seemingly random bursts of spiking activity. Intuitively, it

seems as though only high-quality representations would be useful for broadcasting to other structures. Carr and colleagues [135] have suggested that slow gamma oscillations in the hippocampal LFP clock activity within LIA sequences. They found that gamma synchrony between CA1 and CA3 hippocampal subregions is predictive of high-quality LIA sequence representations. A signal indicating the self-consistency of a sequence representation could be useful for many of the potential sequence functions described in this chapter. Such a signal (especially one involving changes in network properties) could also play a role in determining where and how the sequence representation is routed to and the extent to which structures downstream of the hippocampus are affected.

Interactions between the hippocampus and other brain regions should also be considered in the opposite direction, that is, rather than being influenced by hippocampal output, other brain areas might influence the content that is included in sequences. As discussed above, sensory input (even during sleep) can affect sequence content [122]; it seems likely that neural input to the hippocampus has a similar effect. Accordingly, examining how inactivation of extra-hippocampal brain regions affects sequence content could elucidate how information processing outside the hippocampus sculpts hippocampal representations.

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