Recall of memory sequences by interaction of the dentate and CA3: A revised model of the phase precession

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Abstract

Behavioral and electrophysiological evidence indicates that the hippocampus has a special role in the encoding and recall of memory sequences. Importantly, the hippocampal phase precession, a phenomenon recorded as a rat moves through place fields, can be interpreted as cued recall of the sequence of upcoming places. The phase precession can be recorded in all hippocampal regions, but the role of each region has been unclear. Here, we suggest how the dentate and CA3 regions can work together to learn sequences, recall sequences, and generate the phase precession. Our proposal is constrained by information regarding synaptic plasticity rules, network connectivity, timing delays and theta/gamma oscillations.

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The study of hippocampal function is now reaching the state where the field is a relatively mature one. There is general agreement that the main function of the hippocampus is the storage and recall of memories. Moreover, the underlying circuitry, the properties of individual cells and the rules of synaptic plasticity have all been extensively studied with considerable success. The hippocampus is thus a test-bed for one of the grandest efforts of neuroscience: to understand a behaviorally relevant brain function in a reductionist way, spanning levels from the molecular, to the cellular, to the network. Towards that end, we have previously proposed that major properties of the dentate/CA3 circuitry can be understood as specialized for the storage and recall of memory sequences. This paper will review that work and outline a revision of our thinking regarding which synapses store sequence information. This work is part of a larger effort by many laboratories to understand the theoretical basis of sequence storage in the hippocampus (Levy, 1996; Samsonovich & McNaughton, 1997; Sohal & Hasselmo, 1998; Wu & Yamaguchi, 2004).

1. Behavioral evidence that the hippocampus is involved in memory of sequences

Sequences evolve over time and it should therefore not be surprising that special network and synaptic processes are needed to deal with the temporal issues posed by the storage and retrieval of sequences. There is now a substantial body of data indicating that the hippocampus is required to memorize the sequences of events that make up an ‘episode’. For instance, Honey and Good (Honey, Watt, & Good, 1998) trained rats on tone-light sequences and then measured the rat’s orienting to changes in the order of these sequences. Rats increased their orienting response about two-fold to sequence alterations, but only if their hippocampus was intact (Fig. 1). In more specific tests of order memory (Fortin, Agster, & Eichenbaum, 2002), rats were presented with a series of odors; when presented with a pair of these odors, normal rats could reliably pick the one presented earlier, whereas rats with hippocampal lesions could not. In contrast, if the rat was merely required to recognize whether a test item had been previously presented (regardless of order), the hippocampus was not required.

It should perhaps be emphasized that while this paper focuses on sequence memory, we do not mean to imply that...
this is the only function of the hippocampus. Indeed other functions include the formation of new associations as a result of combining lateral and medial perforant path inputs (Talamini, Meeter, Elvevag, Murre, & Goldberg, 2005), the associations of items with context (Lisman, 1999), and novelty detection (Meeter, Murre, & Talamini, 2004; see review in Lisman & Grace, 2005).

2. Electrophysiological evidence for the involvement of the hippocampus in sequence replay during sleep

Several laboratories (Lee & Wilson, 2002; Nadasdy, Hirase, Czurko, Csicsvari, & Buzsaki, 1999; Skaggs, McNaughton, Wilson, & Barnes, 1996) have observed that sequences of CA1 cell firing that occurred during the awake theta state were seen again during the sharp waves of slow wave sleep (SWS). This ‘replay’ during SWS is about 20 times faster than the sequence observed during awake theta (Lee & Wilson, 2002). In contrast, similar replay during REM sleep appears to be in real-time and involves temporal segments on the time scale of minutes. This dream-related process involves preservation of both the sequence of firing of different cells, and the time course of theta modulation that occurred during the waking state (Louie & Wilson, 2001). It is suspected that these forms of repetition during sleep are important for memory consolidation.

Such sequence replay, in the absence of environmental input, strongly suggests that sequences can be retrieved in the hippocampus. Moreover, since it is known that sharp waves originate in CA3 (Buzsaki, 1986), it seems that the information necessary for retrieval must be stored in the hippocampus itself and is not simply passed on to the hippocampus from connected structures.

3. Electrophysiological evidence for cued sequence recall during the awake theta state: properties of the ‘phase precession’

If memory sequences are stored in the hippocampus they should be accessible during the awake state in order to guide behavior. Consistent with this assumption, the phase precession (Fig. 2) of hippocampal place cells (O’Keefe & Recce, 1993) can be interpreted as cued sequence recall (Jensen & Lisman, 1996; Skaggs et al., 1996; Tsodyks, Skaggs, Sejnowski, & McNaughton, 1996). For instance, the recall of a stored sequence of positions along a track can be initiated by an environmental cue (the current position), as illustrated in Fig. 3. During each theta cycle, the cue initiates the sequential recall of 5–6 upcoming positions along the track. What drives the precession is that on each successive theta cycle, the current place cue has progressed along the path due to the rat’s movement. Consistent with such a space-driven process, the velocity of the phase precession (phase change per unit time) is proportional to the velocity of the rat (Skaggs et al., 1996). Moreover, when the rat’s movement in space is decoupled from the movement of its legs by placing the rat on a running wheel, no phase precession occurs (Hirase, Czurko, Csicsvari, & Buzsaki, 1999). This finding is particularly telling, but it does not occur under all conditions: if the animal runs rapidly on the running wheel, some phase precession can still be observed (Harris et al., 2002). One resolution of this apparently contradictory data may be that a weak form of phase precession can occur independent of spatial cueing, simply as a result of the interaction of theta-frequency inhibition with a slowly ramping excitation (Kamondi, Acsady, Wang, & Buzsaki, 1998; Magee, 2001).

If, indeed, the phase precession reflects a recall process, it should not be evident before learning occurs. Thus, when an animal is first exposed to a new environment, its movement should not produce phase precession. Since hippocampal

![Fig. 1. Behavioral evidence for sequence storage by the hippocampus. Sham operated rats orient to a change in the sequence of known stimuli (left). In the absence of the hippocampus (right), there is little orienting. Adapted from Fig. 2c of Honey et al. (1998).](image)

![Fig. 2. The phase precession. This is a plot of every spike of a place cell in CA1, as the animal repeatedly runs through the cell’s place field, from left to right. Each spike is assigned a phase relative to ongoing theta oscillation, as observed in the hippocampal field potential. Adapted from Fig. 2A of Mehta et al. (2002). Note that other studies have found somewhat less phase variation in the right half of the place field (e.g. Huxter, Burgess, & O’Keefe, 2003).](image)
function is characterized by fast learning, only a single exposure to the track may lead to the phase precession. Consistent with this scenario, Mehta (Mehta, Lee, & Wilson, 2002) found that the phase precession was not evident on the first passage of a rat around track (Fig. 4), but rapidly developed on subsequent runs. These results suggest that the phase precession is indeed a result of learning. A further test of this hypothesis would be to block the synaptic plasticity that is thought to underlie learning; in this case, development of the phase precession should also be blocked. Many hippocampal synapses display an NMDAR-dependent form of plasticity and it thus will be important to determine whether the development of the phase precession can be blocked by interfering with this plasticity mechanism. However, it is important to recall that the LTP at some important synapses in the hippocampus (perforant path input to CA1 (Golding, Staff, & Spruston, 2002); mossy fiber inputs to CA3 (Zalutsky & Nicoll, 1990)) do not require NMDAR. Furthermore, even the ‘classic’ NMDAR-dependent synapse, the Schaffer collateral input to CA1, can exhibit NMDAR-independent LTP when stimulated at very high frequency (Morgan & Teyler, 1999). The testing of the dependence of the phase precession on learning will have to take into consideration these complexities.

We hope the reader can now see the importance of the phase precession. If it indeed reflects cued sequence recall, it provides experimenters with a window onto a crucial hippocampal memory function. The ability to deal with sequences allows the animal to store causal relations and use them to predict the future. For instance, if a rat’s position predicts an upcoming position where a cat resides, it would be adaptive for the rat to stop before it gets there.

4. Where is the phase precession generated?

The phase precession has been recorded in all hippocampal subfields. It remains possible that the phase precession is already present in the entorhinal cortex layer 2/3 cells and is simply passed on to the hippocampus. Now that methods are available to record with certainty from this class of cells (Brun et al., 2002), it will be important to test this possibility directly. However, given the generation of sharp wave replay activity in CA3 (see earlier comments about sharp waves) and the necessity of the hippocampus proper for behavioral sequence memory, it seems likely that the hippocampus is directly involved in sequence generation during theta. Since there are no connections from CA1 back to the dentate or CA3, the phase precession cannot be generated exclusively in CA1. Since the precession is observed in the dentate, it could be generated there and passed forward to CA3 and CA1. Alternatively, since CA3 and the dentate are reciprocally connected, the phase precession could occur through the interaction of these two networks. This idea will be developed in the next sections.

5. Requirements for accurate sequence recall; the roles of autoassociation and heteroassociation

In early ideas about sequence recall, it was thought that learning occurred exclusively by increasing ‘heteroassociative’ weights, i.e. the weights of the synapses between groups of cells encoding sequential memories. The overall sequence is
thus encoded by connecting cells that represent memory A to cells that represent memory B, which then connect to memory C, etc.; see Fig. 5 inset). The recall process can then be triggered by the presentation of A, which acts as a memory cue to evoke the rest of the sequence; specifically, the firing of A cells would excite B cells which excite C cells, and so on. However, this kind of simple chaining process has a major problem: the noise in neuronal recruitment can give rise to errors in the excitation of B, such that some cells that are part of B will not fire, whereas others that are not part of B will. This corruption can be signified as \( B^0 \). In the next step of the recall process, the \( B^0 \) cells will excite the C cells. However, because of the corruption of B and because of additional errors produced in this chaining step, C cells will be more corrupted than \( B^0 \), signified as \( C^0 \). Thus, as chaining proceeds, memories will become progressively more corrupted. This is termed the concatenation of error.

Two papers have suggested similar, theoretical solutions to the concatenation of error problem (Kleinfeld, 1986; Sompolinsky & Kanter, 1986); both are based on the error correction properties of autoassociative networks. Here, autoassociation refers to the strengthening of synaptic connections between cells encoding the same memory (e.g. B). Through such connections, a corrupted memory, \( B' \), may be transformed to the correct form, B (Fig. 5 inset). It was, thus, proposed that the concatenation of error could be avoided if each heteroassociative step in a recall chain (e.g. A to \( B' \)) was followed by an autoassociative step (\( B' \) to B). This would then provide an accurate starting point for the next heteroassociative step in the chaining process. In this way, the entire sequence could be accurately recalled (Fig. 5 inset).

Several critical questions about such interplay of associative processes were left unexplored by early models. In particular, it was unclear what type of network architecture would support such a process and how autoassociative and heteroassociative weights could be selectively stored by different synapses. Moreover, no attempt was made to relate this idea to actual memory circuits. We have sought to map this dual function onto the hippocampal memory networks and to provide a physiologically plausible basis for the selective storage of different types of weights at different synapses. An initial attempt was made in (Lisman, 1999) which we now revise here.

6. The dentate and CA3 networks are reciprocally connected

Several anatomical and electrophysiological observations provided the starting point for our thinking about the operations...
of the dentate and CA3 in the storage and recall of sequences. Dentate granule cells have axons called mossy fibers, which powerfully excite CA3 cells. What is less well appreciated is that there is also a pathway for flow of information back from CA3 to the dentate (reviewed in Lisman, 1999). CA3 axons, in addition to exciting other CA3 cells and providing Schaffer collateral input to CA1, also send collaterals back to the hilus of the dentate (Fig. 5). These collaterals most likely target ‘mossy cells’, which, in turn, provide massive numbers of excitatory synapses to granule cells, forming the principal input in the inner third of the molecular layer (Jackson & Scharfman, 1996; Scharfman, 1994). In the ventral hippocampus, CA3 axons also synapse onto dentate granule cells directly (Li, Somogyi, Ylinen, & Buzsaki, 1994).

The feedback pathways from CA3 to dentate have received relatively little investigation and warrant further study. Although there is suggestive evidence for the connection of CA3 cells to mossy cells, this needs to be confirmed by paired recordings of identified cells. The fact that sharp waves, generated in CA3, are propagated back to the dentate, provides the strongest evidence to date that feedback is indeed operative (Buzsaki, 1986; Penttonen, Kamondi, Sik, Acsady, & Buzsaki, 1997).

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7. A revised model: network delay determines why autoassociation occurs in CA3, whereas heteroassociation occurs in the dentate

The reciprocally connected dentate and CA3 networks could provide the kind of interaction between an autoassociative and a heteroassociative network needed for accurate sequence recall. A previous model (Lisman, 1999) proposed that the autoassociative step might occur first, and thus in the dentate, and that the heteroassociative step might therefore occur in CA3. The arguments for this assignment were not very strong, and our view of this matter has now changed to the reverse, in line with some recently reported experiments. Specifically, genetic disruption of synaptic plasticity in CA3 has been shown to block pattern completion, the hallmark of autoassociative function (Nakazawa et al., 2002). There is thus good reason to believe that the recurrent collaterals of CA3 cells form an autoassociative network. Moreover, we have developed new ideas about the fundamental importance of network delays in determining how specific synapses can selectively encode heteroassociative weights. As the reader will see, these ideas provide a principled argument that heteroassociation should occur in the dentate.

Before describing these ideas, it is necessary to state the following premises (for more detailed review of these ideas see Jensen & Lisman, 2005; Lisman, 2005).

(1) We assume that each ‘item’ in a sequence is already ‘chunked’, meaning that even though an item, such as a spoken word, has temporal aspects, at the level of the medial temporal lobe it has come to be represented by a purely spatial code.

(2) Sequential items are assumed to arrive at the hippocampus with a temporal separation of about 20 ms. This time corresponds to the period of gamma frequency (~40 Hz) oscillatory population dynamics observed in (para)hippocampal circuits. The importance of such gamma oscillations relates to ideas about a role of a multi-item working
memory buffer that may provide input to the hippocampus (reviewed in Jensen & Lisman, 2005). The need for such a buffer follows from the following consideration. Most models of hippocampal learning have assumed that sequence learning is driven by hippocampal inputs that directly reflect the timing of sensory input. In this case, however, learning can only occur between items that arrive within less than 50 ms because this is the duration of the LTP window (see definition below); the broad class of situations where items arrive at longer temporal separation could thus not be handled by this class of models. A solution to this problem may be that the cortex contains a multi-item buffer in which sequential items that are presented at long temporal separations, become active with a short temporal separation within the buffer. A specific model of such a buffer has been developed based on the theta (5–10 Hz) and gamma frequency (30–100 Hz) oscillations observed in the medial temporal lobe (Lisman & Idiart, 1995). According to this model, successively presented items become active in the buffer in successive gamma subcycles of theta oscillations (irrespective of the actual interval at which they were presented to the organism), and this pattern is repeated on each theta cycle. Successive gamma cycles occur at an interval of 10–30 ms. As we will see, this interval roughly matches the delay produced by transmission from dentate to CA3 and back to the dentate. This, in turn, has important consequences for how heteroassociative weights may be stored.

(3) A final assumption is that heteroassociation is encoded by an LTP-like process and should therefore be consistent with what is known about this process. LTP requires that postsynaptic depolarization occur after the presynaptic spike. There can, however, be some delay; plots of LTP vs. delay decay with a time constant of about 50 ms, defining what is termed the ‘LTP window’.

Given this as background, we can now put forward our model of sequence learning in dentate–CA3 circuits (illustrated in Fig. 6). It is proposed that encoding of autoassociation and heteroassociation at different synapses results simply from delays in the looping of information between dentate and CA3 circuits. Measurements in rats suggest that the time it takes to go around this loop will be about 20 ms; 7–10 ms for spikes to be evoked in CA3 as a result of firing in dentate granule cells (Henze, Wittner, & Buzsaki, 2002; Yeckel & Berger, 1990), and another 7–10 ms for the activation of granule cells by the firing of CA3 cells (Scharfman, 1994; 1996; Wu, Canning, & Leung, 1998). As a result of these delays, feedback information triggered by a memory A will arrive at synapses on the dentate cells that encode A about 20 ms after they first fired. Such pre after post timing will not evoke LTP; if anything LTD will occur. On the other hand, the same feedback from A will arrive at the dentate at approximately the same time that a pattern representing B is excited by input from cortex. This coincident timing will produce pre- and postsynaptic firing that falls within the LTP window and lead to the strengthening of feedback connections between CA3 pattern A and dentate pattern B. Thus, according to these principles, the feedback synapses in the dentate are well suited to selectively encode the heteroassociative links that underlie sequence memory.

An important remaining question is the identity of the dentate synapses that mediate heteroassociation. One candidate is the set of feedback synapses of CA3 cells onto mossy cells. Since mossy cells also receive feedforward excitatory synapses from dentate granule cells, the coincidence of feedforward and feedback excitation, referred to in the above paragraph, could be occurring at mossy cells. A second possible site for the coincidence is the mossy cell synapse onto dentate granule cells. According to this view, the CA3–mossy cell pathway should be viewed as a conduit of information from CA3 back to the dentate cells; the critical coincidence then occurs at the granule cell dendrites when they receive feedforward input from cortex and feedback information from CA3 via mossy cells. Given the large number of granule cells ($10^6$) compared to mossy cells ($10^5$) and the enormous number of mossy cell synapses onto the granule cell population ($>10^7$), these synapses would seem to be an appropriate site for heteroassociative connections.

8. Understanding additional properties of the phase precession

8.1. The role of gamma in chaining: predicting the magnitude of the phase precession

As we emphasized previously, the recall of sequences is proposed to occur through a cue-initiated chaining process. In principle such chaining could be very rapid, with delays limited only by conduction delays, synaptic delays and postsynaptic integration time. Such delays are short and cumulatively in the range of several milliseconds. Indeed, such rapid chaining is thought to underlie the so-called ‘synfire’ chains in cortex and sharp waves in the hippocampus (Abeles, Hayon, & Lehmann, 2004; Buzsaki, 1986). However, we believe that the chaining process that underlies the phase precession is much slower and that the slowing results from gamma frequency oscillatory population dynamics. Gamma oscillations arise from a negative feedback loop between principle cells and interneurons that provide fast feedback inhibition (Fisahn, Pike, Buhl, & Paulsen, 1998; Mann, Suckling, Hajos, Greenfield, & Paulsen, 2005). Whereas fast feedback is weak during sharp waves, it is very powerful during the awake state, leading to prominent gamma oscillation superimposed on the theta wave (Fig. 3, inset) (Bragin et al., 1995; Buzsaki, Buhl, Harris, Csicsvari, Czeh and Morozov, 2003). The slowing of the chaining process by gamma can be understood as follows: after a group of cells fires (representing a particular place), they excite inhibitory interneurons which shut down all remaining pyramidal cells; these cells are unlikely to fire again until this inhibition has decayed. Thus, the chaining process is turned into a series of discrete epochs by gamma (the utility of this discreteness is that it allows downstream networks to detect groupings using a coincidence detection mechanism).
The presence of strong gamma means that firing may not occur at the moment excitation arrives; rather inhibition has to decay before firing occurs, thereby slowing the chaining process.

One line of experiments that directly demonstrates the importance of theta phase allowed testing of just how finely theta phase can be meaningfully subdivided. The idea of discrete phase coding predicts that optimal decoding schemes should be dividing theta into a number of phase bins equal to the number of gamma cycles within a theta cycle; yet finer phase bins should provide no additional information. This prediction was tested on a large data set from groups of neurons recorded simultaneously as rats moved along a track (Jensen & Lisman, 2000). Ensemble data sorted by different phase criteria were used to predict the animal’s position along the track. The difference between the predicted and actual position allowed objective comparison of different binning processes. It was found that increasing the number of phase bins within theta cycles increased the accuracy of position prediction up to about five phase bins (Fig. 7). Increasing the number of phase bins further did not produce further improvement and appears to have been deleterious. These results are therefore consistent with the idea that information is parceled out in the different gamma subcycles of a theta cycle.

The clocking of the hippocampus by theta and gamma, during learning and recall, leads to a simple explanation of the magnitude of the phase advance. Consider a rat running at its average velocity during learning (VA_L); the core assumption is that a working memory buffer absorbs information about the rat’s current position at every theta cycle, and compresses the information, so that sequential positions on the rat’s trajectory are placed in sequential gamma bins of one theta cycle. Thus, when the buffer is full (let us say its capacity, as determined by the number of gamma cycles within theta, is \( w \)), it will contain the current position in the last gamma cycle, and the previous six positions in the preceding gamma cycles. This set of information will be repeated for many theta cycles, allowing LTP-like processes to incorporate the information into hippocampal long-term memory. Now, during recall, when the animal enters the initial place in this sequence, the gamma-frequency chaining process leads to the prediction of the upcoming six positions. If the rat is running at its average velocity VA_R during recall, the rat’s position will have moved to the second position by the onset of the next theta cycle and it is this second position that now serves as a cue. As explained previously, it is exactly this updated cueing that leads to the phase precession. However, one can now see an additional

![Diagram showing network delay](image_url)

Fig. 6. Scheme showing how network delay can lead to selective strengthening of heteroassociative linkages in CA3-to-dentate feedback synapses, based on a learning rule (top right) that, at other synapses (e.g. in recurrent collaterals in CA3), leads to autoassociation.
prediction; as the rat is approaching a given position on the familiar trajectory, the firing response of a cell encoding that position will fire predictively during six theta cycles; on the seventh cycle, the rat is at that position, and fires as a response to direct sensory input (presumably from entorhinal cortex). On the eighth cycle, the rat is beyond the place field and the cell is silent. This argument makes it clear that if, during recall, the rat runs through the place field at velocity $V_{A_L}$, the place cell should fire on a number of theta cycles that equals the number of gamma cycles within a theta cycle. To a first approximation this is the case (Skaggs et al., 1996). More rigorous testing of this prediction could be achieved by determining $V_{A_L}$ during learning, correcting phase precession during recall for actual velocity relative to $V_{A_L}$, and determining directly the number of gamma cycles within a theta cycle as the animal moves.

8.2. Bimodality of the phase precession

There are several intriguing properties of the phase precession that should further constrain possible models. As seen in Fig. 2, the phase precession in CA1 begins as the animal enters the place field of the recorded cell from the left. It is in this region of the place field that the phase distribution is relatively narrow and changes systematically as the animal moves (the precession). However, as the rat reaches the end of the place field, the phase distribution becomes wide and is distributed over a range of phases that overlaps little with the phase-range that occurs during the precession (Fig. 2). On the basis of such observations, it has been suggested that the cell’s firing response within the place field is bimodal, with a phase-dependent part and a less phase-dependent part (Yamaguchi, Aota, McNaughton, & Lipa, 2002). Interestingly, the phase-independent firing is not as evident in the dentate; rather granule cells are simply quiet during this period. There are currently no reports about the pattern in CA3.

Fig. 8 shows a potential explanation of the bimodality. The central assumption is that in the first, phase-independent, half of the theta cycle the sensory stimulus representing current position is imposed on CA3/CA1 by layer 2/3 of the entorhinal cortex, while the chaining process is somehow inhibited (e.g. by inhibiting the feedback relay through mossy cells or by inhibiting granule cells). Then, in the next period of theta, the entorhinal input ceases and the intrahippocampal chaining begins. It is this chaining process that gives rise to the phase dependent part of the curve in Fig. 2. The assumption of an oscillatory EC input is in line with observations of theta-frequency population dynamics in this structure (e.g. Kocsis, Bragin, & Buzsaki, 1999). Furthermore, entorhinal excitation to the hippocampus is known to be accompanied by a powerful inhibitory influence, which may contribute to inhibition of the chaining process (Behr, Gloveli, & Heinemann, 1998; Buzsaki, 1984; Empson & Heinemann, 1995). The explanation of bimodality can now be formulated as follows: as the rat enters the place field the neuron fires with late phase as a result of the intrahippocampal chaining; on subsequent theta cycles, it fires with earlier phase and earlier phase because it is earlier in the chaining process (the rat’s movement has updated the cue). Finally, as the rat approaches the end of the place field, the cell is now driven by the entorhinal cortex rather than by intrahippocampal connections. The phase distribution is now broad because the entrohinal cortex drives the hippocampus over a broad phase range (which however overlaps little with the phase range over which the precession occurs).

8.3. Place field expansion and asymmetry

As a rat repeatedly traverses a track, graphs of firing rate vs. position gradually change in several ways: they become asymmetric and they expand to cover a larger area (Mehta, Barnes, & McNaughton, 1997). Place field expansion is blocked by NMDA antagonists, consistent with the idea that the phenomenon arises from an LTP-like process (Ekstrom, Meltzer, McNaughton, & Barnes, 2001). Place field expansion lasts for hours, but appears to decay entirely within a day (Mehta et al., 1997). Several models of how this occurs have been put forward, having in common the idea that asymmetric LTP could allow the network to enhance its predictive
(prospective) ability—i.e. cells further ahead of the current position will become active in the process of expansion (Abbott & Blum, 1996; Mehta, Quirk, & Wilson, 2000). Jensen and Lisman (1996) showed through simulation that gamma frequency is not fixed, but rather arises dynamically through the interplay of excitation and negative feedback inhibition. As the excitation that mediates intrahippocampal chaining becomes stronger through repeated experience, postsynaptic...
cells fire earlier, and lead to an increase in gamma frequency. A consequence is that more gamma cycles can fit within a theta cycle (Fig. 9). Given that more distant positions can be predicted with every additional gamma cycle contained within a theta cycle, the furthest predicted position increases, thereby accounting for the expansion of the place field.

9. Concluding remarks

The current account of phase precession, based on the bidirectional interaction of the dentate and CA3, provides the first explanation of why phase precession should be seen in both these structures. It also assigns a function to the feedback connections from CA3 to dentate, for which no purpose has been previously proposed. It should be emphasized that this bidirectional interaction has not yet been simulated. Such simulation, including the roles of gamma, feedback delays and plasticity rules, would provide an important test of our model and clarify some of the population dynamics underlying the proposed mechanism. The model of sequence memory, as we have developed it here, leads to many further predications that are summarized in Table 1. It is hoped that through an interplay of theory and experimental tests, we will converge upon a well-constrained model of how the hippocampus stores and recalls memories.

Table 1
Testable predictions of the current model

<table>
<thead>
<tr>
<th>Prediction</th>
<th>Description</th>
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<tbody>
<tr>
<td>Generation of phase precession by dentate/CA3 interaction</td>
<td>Predictions: 1. The delay important for heteroassociative learning is not predicted by the current account of phase precession. 2. The relative timing of layers 2 and 3 of the entorhinal cortex is important for phase precession. 3. The firing rate of CA3 cells is important for phase precession.</td>
</tr>
<tr>
<td>Reciprocal interaction between dentate and CA3 on each gamma cycle</td>
<td>Predictions: 1. The delay important for heteroassociative learning is not predicted by the current account of phase precession. 2. The relative timing of layers 2 and 3 of the entorhinal cortex is important for phase precession. 3. The firing rate of CA3 cells is important for phase precession.</td>
</tr>
<tr>
<td>The pathway from CA3 to dentate: role of mossy cells</td>
<td>Predictions: 1. The delay important for heteroassociative learning is not predicted by the current account of phase precession. 2. The relative timing of layers 2 and 3 of the entorhinal cortex is important for phase precession. 3. The firing rate of CA3 cells is important for phase precession.</td>
</tr>
<tr>
<td>Basis of the biomodality of the phase precession</td>
<td>Predictions: 1. The delay important for heteroassociative learning is not predicted by the current account of phase precession. 2. The relative timing of layers 2 and 3 of the entorhinal cortex is important for phase precession. 3. The firing rate of CA3 cells is important for phase precession.</td>
</tr>
<tr>
<td>Role of high frequency firing in dentate and the resulting facilitation of mossy fiber synapses</td>
<td>Predictions: 1. The delay important for heteroassociative learning is not predicted by the current account of phase precession. 2. The relative timing of layers 2 and 3 of the entorhinal cortex is important for phase precession. 3. The firing rate of CA3 cells is important for phase precession.</td>
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