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# Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer

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**Encoding and recall of memory sequences is an important process. Memory encoding is thought to occur by long-term potentiation (LTP) in the hippocampus; however, it remains unclear how LTP, which has a time window for induction of ~100 ms, could encode the linkage between sequential items that arrive with a temporal separation >100 ms. Here, we argue that LTP can underlie the learning of such memory sequences, provided the input to the hippocampus is from a cortical multi-item working memory buffer in which theta and gamma oscillations have an important role. In such a buffer, memory items that occurred seconds apart are represented with a temporal separation of 20–30 ms, thereby bringing them within the LTP window. The physiological and behavioral evidence for such a buffer will be reviewed.**

## Introduction

It is important to identify the synaptic and network mechanisms that support the learning and recall of sequences [1]. To learn a sequence, synaptic linkages must be strengthened between cells representing sequential items in the sequence. These linkages make possible the subsequent recall of the sequence. For instance, the presentation of the cue A would lead to the activation of the cells encoding A. Then, through the strengthened linkages [2], the firing of A cells would lead to the firing of B cells and, through similar chaining, evoke the rest of the sequence. The forms of LTP so far discovered have a time window for induction of ~100 ms [3–5] and cannot therefore strengthen connections between cells that fire with greater temporal separation. Because humans can learn sequences with item separation of seconds, some other mechanism must be involved. Here, we argue that the additional mechanism could be a cortical buffer capable of holding multiple items in a short-term memory buffer (used here synonymously with working memory). We argue that such a buffer can represent items in a way that preserves their order and can drive the encoding of realistic sequences within the hippocampal long-term memory system (Figure 1).

## Hippocampal involvement in sequence memory

Before considering the role of buffers in sequence encoding, we briefly review the evidence that implicates the hippocampus in the long-term storage of sequences. Various behavioral studies have shown that hippocampal lesions interfere with behaviors that require sequence learning while leaving simple forms of item recognition intact [6,7]. Electrophysiological studies have also provided evidence for hippocampal involvement. For instance, the sequences of places the animal experienced while awake are replayed in the hippocampus during slow-wave sleep, a process that might underlie memory consolidation [8–10]. Of particular interest is the 'phase precession' phenomenon that occurs when a rat runs along a well known path. The precession depends on prior learning [11] and has been interpreted as cued recall of the sequence of upcoming places [12–15] (Figure 1c). The importance of storing sequences is that they can be used by the animal to predict the places or events that are likely to happen next (Figure 2a). As such, the phase precession can be considered 'prospective' (what will happen in the future). This contrasts with the activity of hippocampus during the encoding of memory: if activity depends on a memory buffer, activity will represent the recent past – that is, be 'retrospective'. The electrophysiological evidence for such retrospective coding will be discussed at the end of the next section.

## Evidence of a short-term memory buffer

Behavioral analysis of human memory studies has revealed important properties of short-term memory. In a recall experiment, a list of $n$ items is presented and the subject is asked to repeat the list in order. For $n<7$, recall is nearly perfect, but for $n>7$ recall falls dramatically [16]. This led to the idea that the short-term memory buffer can store ~7 items (chunks) and drive the incorporation of information into long-term stores. Models of this kind account for a wide range of measured properties of human memory [17]. Information about the temporal organization of this buffer has been provided by the Sternberg task [18]. In this task, a list of $n$ items is first presented; the subject is then presented with a test item and responds as quickly as possible whether the test item was or was not on the list. The key finding is that response time increases linearly with $n$, the slope being ~30–40 ms per item. The

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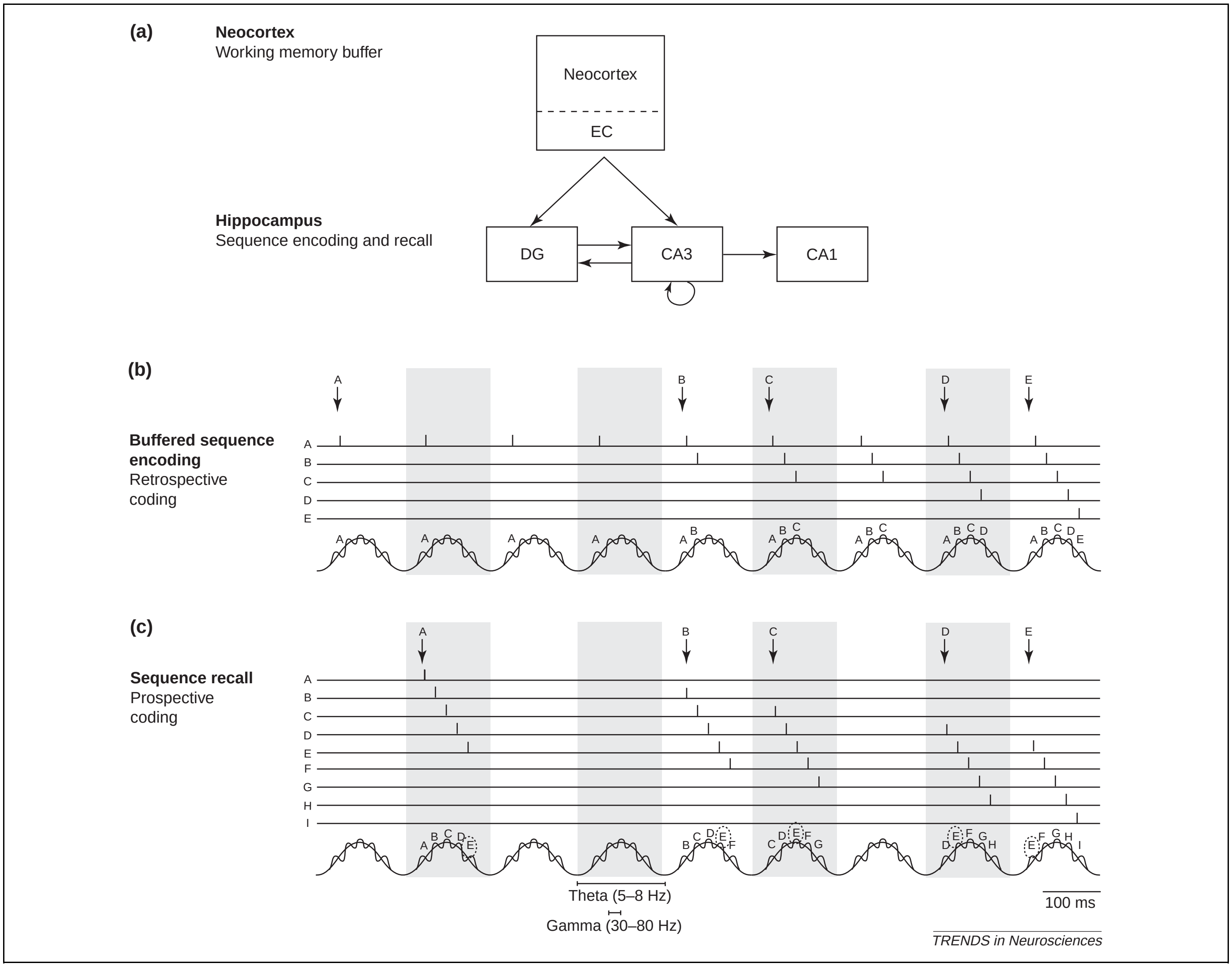

**Figure 1.** Retrospective and prospective coding of place cells. **(a)** Brain structures involved in memory encoding and recall. The neocortex contains a short-term memory buffer. This buffer actively stores multiple items and presents them to the hippocampus through the entorhinal cortex (EC). The sequence is then encoded in hippocampal networks of CA1, CA3 and the dentate gyrus (DG) by LTP-dependent processes. **(b)** Neocortical activity during and after presentation of multiple items at realistic presentation rates. After the cue, A, is presented, the cell that represents A continues to fire on each subsequent theta cycle. This subsequent activity represents the past and is therefore 'retrospective'. Item B is presented ~1 s after A. The cell that represents B now fires on every subsequent theta cycle, but at a different phase to that representing A; specifically, cell A fires in the first gamma cycle and cell B in the second gamma cycle of each theta cycle. During retrospective coding, the neocortical activity is also present in the hippocampus, allowing sequence encoding. **(c)** Hippocampal activity during cued recall, as might occur during phase precession. Synaptic weights for the sequence have already been encoded. When the animal is presented with item A (here considered a position), A is represented in the hippocampus at an early theta phase and, by a synaptic chaining process, evokes the firing of subsequent items (places) in subsequent gamma cycles. Several theta cycles later, the rat has advanced to place B, which now serves as the cue. B causes recall of the stored sequence. As a consequence of this time-compressed sequence recall, cell E will fire at earlier and earlier phases (marked by circled Es) as the rat advances, producing a phase precession. (In Fig. 1c of the paper by Melamed *et al.* [1], the mechanisms for phase precession based on time-compressed sequence read-out as suggested by several groups [12–15] was drawn incorrectly. The correct mechanism is illustrated in Figure 1c of this article.)

simplest interpretation of these results is that sequential items are held in active memory with a temporal separation of ~30 ms.

Physiological experiments provide direct evidence for a buffer. Single-cell recordings show that many neurons that encode an object will continue to fire during the delay period of short-term memory tasks (i.e. during a period after the item is removed). This form of activity is thus retrospective. It is not yet clear how single-unit activity is affected when multiple items need to be stored. However, functional magnetic resonance imaging (fMRI), magnetoencephalogram (MEG), and electroencephalogram (EEG) methods show signals that vary strongly with the number of items stored, consistent with the idea that multiple memories are actively stored in neocortex [19–21].

Although it is clear that short-term memory is stored in neocortex and does not require the hippocampus, the neocortical buffer could be required for the learning of sequences by the hippocampus [22]. Specifically, a buffer produces the repetitive firing necessary to induce strong LTP. The entorhinal cortex, which provides the direct input to the hippocampus, has been demonstrated to have persistent (retrospective) activity characteristic of a buffer [23,24] (Figure 2b). Evidence that the cortical buffer provides input to the hippocampus comes from the study of brain oscillations. Human intracranial recordings have shown that the theta rhythm occurs in the human neocortex [25] and hippocampus [26–29]. It has further been shown that the neocortical theta rhythm is often directly gated during the period of working memory [25].

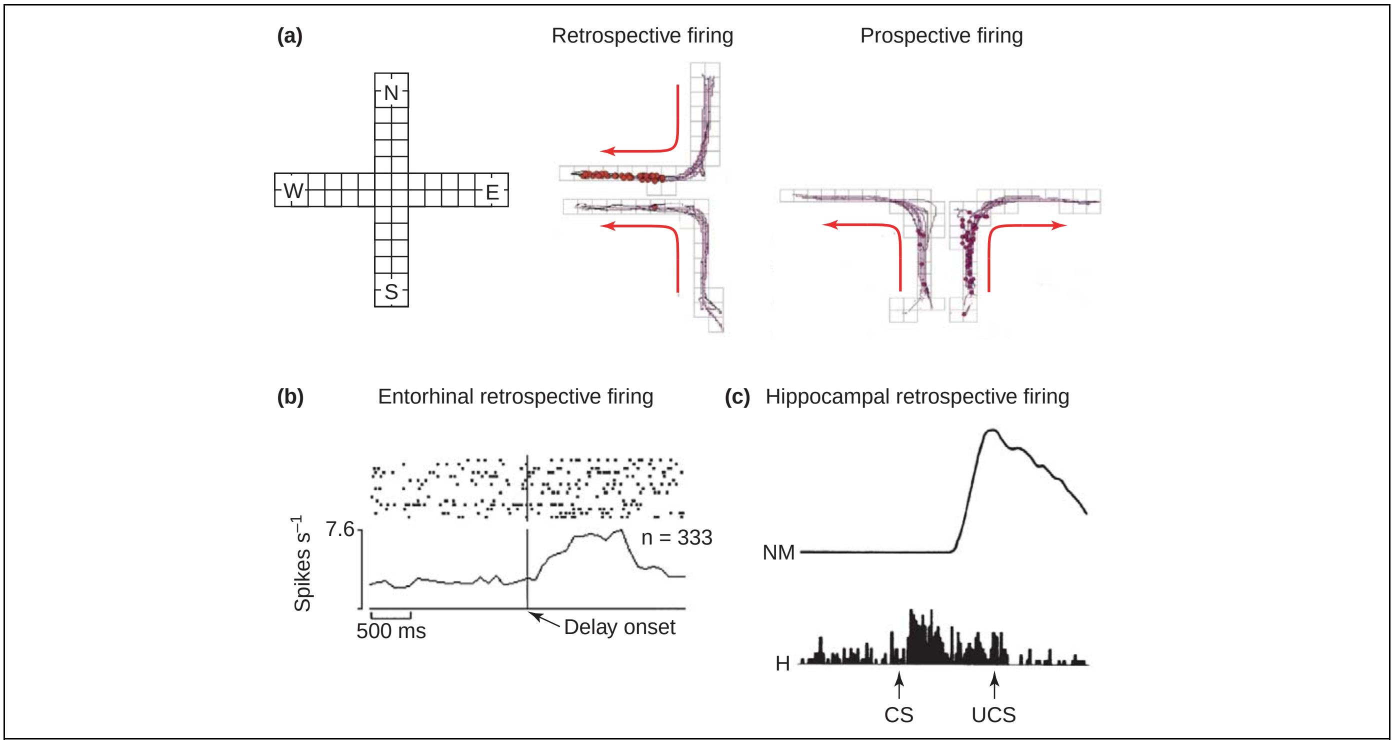

**Figure 2.** Retrospective firing ('buffered' activity) is present in the hippocampus and the entorhinal cortex. **(a)** Recordings from hippocampal place cells identified retrospective and prospective firing in rats running in a plus maze [38,55]. Retrospective firing occurred when the rat entered the west (W) arm coming from the north (N) arm but not from the south (S) arm. Thus, the firing reflected the past trajectory. Prospective firing occurred in the S arm before the rat went to the east (E) arm but not to the W arm. Thus, the firing predicted the upcoming trajectory. **(b)** An entorhinal cell in the rat showing sustained activity during the delay period of an odor-guided delayed nonmatching-to-sample task. The firing was odor specific [23]. **(c)** A hippocampal cell in the rabbit showing sustained activity following a conditioning stimulus (CS) in a classical conditioning task. The unconditional stimulus (UCS) was an air-puff 250 ms after the CS, provoking a nictitating membrane (NM) response [36]. There is important additional evidence for prospective firing in Ref. [56] and for retrospective firing in Ref. [57]. Panel (a) reproduced, with permission, from Ref. [38]; (b) reproduced, with permission, from Ref. [23] © (1997) the Society for Neuroscience; (c) reproduced, with permission, from Ref. [36] © (1983) the American Physiological Society.

Importantly, a memory task can enhance the synchronization of theta and gamma oscillations between the neocortex and hippocampus, providing evidence of their functional coupling [30,31]. Related experiments have been conducted using rats [32,33]. The idea that the cortex can drive the hippocampus is further supported by the observation that the retrospective activity seen in the neocortex also occurs in the hippocampus. For instance, in delayed nonmatching-to-sample working memory tasks, activity in the rat hippocampus outlasts the stimulus [34]. Similarly, work in rabbits shows that the firing induced by a novel stimulus outlasts the stimulus [35]. In a classical conditioning paradigm, sustained firing of rabbit hippocampal neurons in the delay period has been observed [36] (Figure 2c). Place cells in the rat hippocampus provide a simple way of testing for retrospective encoding: as the rat moves, activity in a buffer will reflect places the rat has just left (Figure 2a). Indeed, several groups have identified entorhinal and hippocampal cells that have such a firing pattern [37,38]. A similar interpretation can be given to the 'momentum effect', in which a cell continues to fire after it leaves the classic place field (but only after unusual deviations from the standard trajectory) [39].

Although the mechanisms of working memory have been extensively studied by both experimentalists and theorists, this work has concentrated on how single items can be actively stored by cortical networks. The question of how multiple items are stored has received little attention. Given both the behavioral and the physiological evidence for a multi-item short-term memory buffer, it is important to develop neural network models of how multiple items can be actively stored within a network.

## A physiologically based model of a neocortical multi-item buffer: the role of theta and gamma oscillations

Figure 3a shows the model we have put forward for multi-item working memory [40,41]. The idea is that the same network can store multiple items using a temporal multiplexing mechanism that is clocked by the theta and gamma oscillations known to exist in these structures [33]. According to this model, the group of cells that represents a single (chunked) item fires on each theta cycle, but only in a given gamma subcycle. Sequential items are active in sequential gamma subcycles, thereby encoding sequence order. This model explains the limited capacity of short-term memory by the fact that there are ~7 gamma cycles within a theta cycle (see Ref. [42] for a related model). Furthermore, the gamma frequency (30–80Hz) produces a cycle period consistent with item-separation time deduced from the Sternberg experiment. Indeed, many of the detailed properties of recall in the Sternberg task can be accounted for quantitatively by physiologically based models of this kind [43]. Exploration of this class of models has shown that simple mechanisms can account for the loading of each item in the appropriate gamma subcycle [41]. There has also been progress in understanding the mechanisms that produce persistent firing in the appropriate gamma subcycle. It was

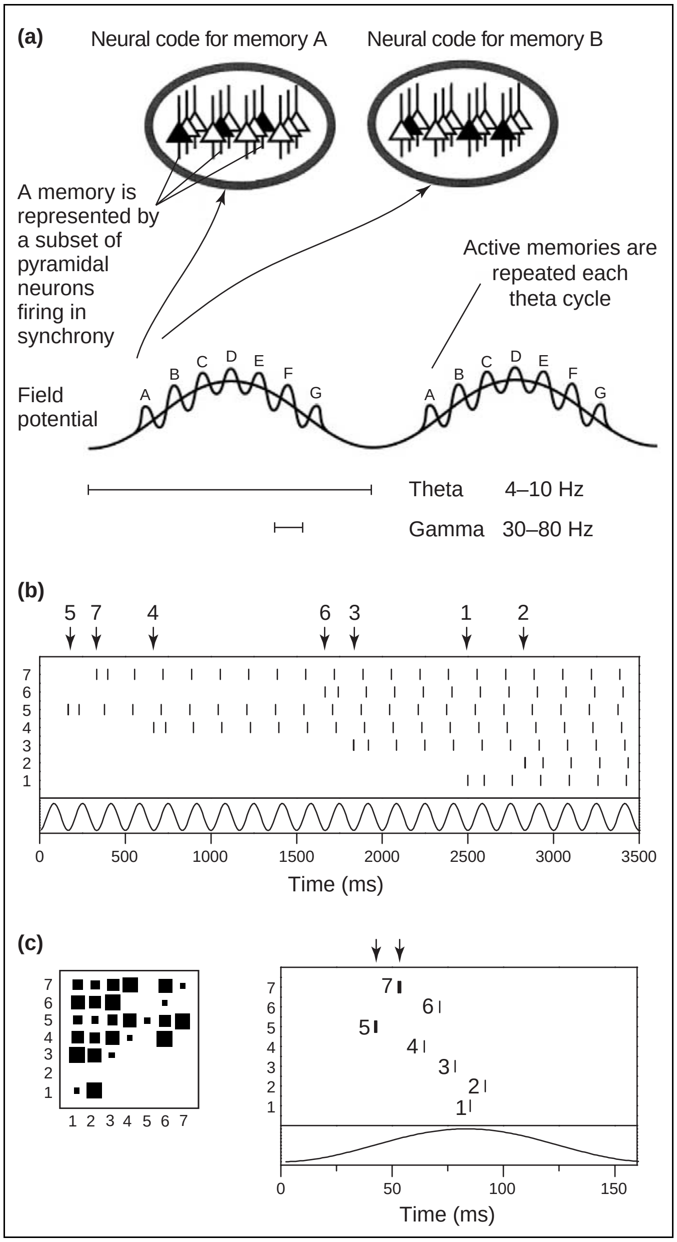

**Figure 3.** Encoding of a realistic temporal sequence into hippocampal long-term memory through action of a multi-item cortical buffer. **(a)** The buffer model. Individual items are represented by different subsets of neurons firing within a gamma cycle. Different items are firing at different gamma cycles and, within a theta cycle, the list of up to seven items is activated sequentially. A physiologically realistic network that can perform this operation has been implemented and simulated [40,41,46]. Firing is maintained as a result of a depolarizing after-potential and recurrent collateral projections. Importantly, if items are first presented in a trough of theta activity, the cells representing them will automatically fire next at the first empty gamma cycle, thereby preserving sequence order (see Ref. [41] for details). **(b)** Simulation of the network for short-term memory maintenance. After item 5 is presented, its cells reactivate on each subsequent theta cycle. In the next theta cycle, item 7 is presented. The buffer can be filled with up to 7 items. **(c)** A simulation of the hippocampal network illustrating sequence recall. As a result of learning, a synaptic weight matrix is formed (size of the squares is proportional to the weight; for instance, the row of item 5 shows that item 5 connects most strongly to item 7, then 4, and so on). When the hippocampal network is presented with the initial items of the list (items 5 and 7) as a cue, the full list is subsequently activated within that theta cycle. It should be noted that this scheme does not encode the time between memory items, but only their order. This deficiency could be addressed by incorporating an interval tag together with the item representation. Panel (a) reproduced, with permission, from Ref. [43] © (1998) Society for Neuroscience; (b,c) reproduced, with permission, from Ref. [47].

originally proposed that this depended on a ramp-like depolarizing after-potential; this would be evoked when a neuron fires in a given theta cycle and, in turn, trigger firing of the cell on the next theta cycle. Recent experiments have provided direct evidence for such depolarizing after-potentials in the entorhinal cortex, the details of which have been incorporated in computational models [44,45]. Simulation studies have demonstrated that the mechanism of reactivation by the depolarizing after-potential is robust if the individual representations are encoded synaptically in recurrent collaterals of the network [46]. The attractor properties of the recurrent collaterals help to maintain the precise firing times of the memory representations.

## In learning mode, a multi-item buffer can drive hippocampal sequence learning by standard LTP

In the multi-item theta–gamma buffer, items presented over many seconds will be active in sequential gamma cycles – that is, with a temporal separation of ~30 ms (Figure 3a), well within the 100 ms time-window of hippocampal LTP [4,5]. When it is desirable to encode a sequence into hippocampal long-term memory, the output of the multi-item buffer will be funneled into the hippocampus (Figure 1a). Simulations demonstrate that as multiple items fire in the buffer, they can become reliably encoded in hippocampal networks by standard LTP processes [47–49]. Specifically, because sequential items fire with a temporal separation of $<30$ ms, LTP can strengthen the synapses between cells representing items in the sequence (Figure 3c; left). These linkages can then be used during recall simply by presenting the cue of the initial part of the sequence to the hippocampus; the rest of the sequence can be recalled by a chaining process (Figure 3c; right) [47]. This work thus demonstrates how the existence of a cortical buffer allows realistic sequences to be encoded into long-term memory. The question of which hippocampal synapses store sequence information is under active investigation [50].

## Closing Remarks

Recent work has suggested a process of sequence encoding that is different from that proposed here [11]. As outlined in Figure 1c, we view the phase precession as a result of sequence encoding. By contrast, other groups have argued that the importance of the phase precession might instead be to allow sequence encoding [11,51]. According to the model of Mehta *et al.* [11], the connections of the feedforward CA3 synapses onto CA1 are modified by LTP to produce a ramp of firing as the rat passes through the place field. Cells representing different nearby places will be on different parts of their ramp and, because of interaction with theta-frequency inhibition, will start to fire at different phases of the theta cycle. These differences in firing onset will be some fraction of a theta cycle ($<100$ ms) and thus appropriate for encoding linkages between sequential places using a standard LTP window. However, although this scheme is not mutually exclusive with our model, it should be noted that the mechanism proposed by Mehta *et al.* does not easily generalize to sequential items other than place: it is reasonable to assume that nearby place cells will be broadly tuned to fire in overlapping ways (i.e. will be highly correlated), but it is unlikely that such correlation exists when sequences of non-spatial items must be stored. Specifically, in general list-learning, sequential items do not have a proximity relationship comparable to that of positions along a path.

In closing, we return to the question of how realistic sequences can be encoded by LTP. We have reviewed evidence that a multi-item buffer organized by theta and gamma oscillations provides a potential mechanism for solving this problem. Several tests of this model have been undertaken, but additional ones are needed. An important prediction of the theta–gamma model is that theta oscillations should occur in cortex during short-term memory tasks. This prediction has recently been confirmed [20,25,52,53]. For instance, intracranial recordings in humans show that theta oscillations at many cortical sites are gated in a way closely linked to the working memory requirements of the task: theta power increases suddenly at the beginning of the Sternberg working memory task, stays elevated throughout the task, and is reduced rapidly at task offset [25]. Very recent results provide the first evidence [54] that single-unit activity in cortex oscillates at theta frequency during a working memory task and that firing occurs preferentially at a certain theta phase. A crucial test that remains is whether multiple memories held in short-term memory become active at different phases of theta oscillation. The observation of such a temporal difference would clearly demonstrate a multi-item cortical buffer and provide a demonstrable basis for the encoding of sequence information by LTP.

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