Review

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How the hippocampus preserves order: the role of prediction and context

Lila Davachi and Sarah DuBrow

Department of Psychology, New York University, 6 Washington Place, Room 871, New York, NY 10003, USA

Remembering the sequence of events is critical for deriving meaning from our experiences and guiding behavior. Prior investigations into the function of the human hippocampus have focused on its more general role in associative binding, but recent work has focused on understanding its specific role in encoding and preserving the temporal order of experiences. In this review we summarize recent work in humans examining hippocampal contributions to sequence learning. We distinguish the learning of sequential relationships through repetition from the rapid, episodic acquisition of sequential associations. Taken together, this research begins to clarify the link between hippocampal representations and the preservation of the order of events.

Sequences in memory

Much of our experience is perceived and understood through the sequences of events that occur. Episodic memory, which allows us to relive events from our past, is defined by the recovery of the unique context in which the event occurred [1]. The context can, but need not always, include spatial details and various forms of temporal detail including how the event unfolded in time. Furthermore, many of our everyday experiences are repeated sequences of highly similar events, such as one's morning commute to work. Thus, learning the sequential order of events that are commonly encountered allows us to form predictions about the impending future and plan upcoming actions accordingly. Since sequential representations play such a defining role in learning and memory, understanding how sequences of events are encoded in a way that preserves their temporal order is fundamental to understanding memory.

The importance of the human hippocampus in associative encoding more broadly is well established (for reviews see [2–5]). However, whether and how the human hippocampus encodes sequential representations is a strong focus of current investigations. Initial evidence that the hippocampus plays an important role in representing sequential representations was revealed by the groundbreaking result from rodent electrophysiology that hippocampal place cells replay (see Glossary) in the same sequential order as during a prior learning experience [6]. More recently, new evidence has emerged that hippocampal cells, referred to as 'time cells', may code specific moments in time or temporal positions [7,8]. While studies on rodents and nonhuman primates are beyond the scope of this review (but see Box 1), these findings highlight potential hippocampal mechanisms for encoding and preserving the sequence of encountered events. However, the vast majority of the studies identifying sequential neural firing during an experience and post-experience replay are of rodents who are navigating through space over hundreds of trials. Thus, many questions remain regarding how a sequence of events is encoded after only a single experience and in the absence of spatial navigation. Furthermore, which aspects of the temporal coding of experience are related to the successful recovery of temporal information in memory remains not well understood. Thus, this review highlights recent investigations of the role of the human hippocampus in the encoding and representation of temporally extended sequences. We organize our discussion by offering a potential distinction between the representation of sequences acquired over multiple learning repetitions and the episodic encoding of novel sequences.

Laying the groundwork

Theoretical models have proposed various potential mechanisms by which hippocampal processes could bridge temporally disparate events into coherent, bound associative memories. One proposal is that context-sensitive cells may develop from background neural firing in the hippocampal subregion CA3 due to its recurrent excitatory connections [9]. Associations formed between cells coding items in a sequence and these background context cells could

Glossary

Delay conditioning: conditioning in which the conditioned and unconditioned stimuli overlap in time.
Place cells: hippocampal neurons that fire when an animal is at a particular location in space.
Replay: sequential pattern of hippocampal place cell responses during offline periods that corresponds to the response pattern during a prior experience.
Temporal context: defined by the temporal context model [22] as a slowly drifting representation that binds to and updates with each newly encountered item. Retrieval of temporal context has been hypothesized to support associative recall.
Theta rhythm: oscillatory pattern in the 4–12 Hz range observed most strongly in the rodent hippocampus during action and rapid eye movement (REM) sleep.
Time cells: hippocampal neurons that fire at specific moments in time, or serial positions, within a temporally structured event while controlling for an animal's location and movement (see [8] for a review).
Trace conditioning: conditioning in which the conditioned stimulus ends before the unconditioned stimulus begins and bridging a temporal gap is therefore required to learn the association.

Corresponding author: Davachi, L. (lila.davachi@nyu.edu).
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Box 1. Contributions of research on nonhuman animals

Although the focus of this review is the human hippocampus, much of the existing literature on sequence learning comes from work on nonhuman animals. These studies offer the unique ability to directly record neuronal activity from healthy tissue as well as create focal lesions to assess the necessity of a region for a behavioral task. Thus, we provide some discussion of this here but refer readers to other recent reviews for more in-depth discussion [8,64–67].

Lesion work in rodents clearly demonstrates the necessity of the hippocampus for sequence memory [68,69]. Complementary electrophysiological data have allowed researchers to characterize changes in the hippocampal neural signature with sequence repetition. For example, place cells that initially fire late in a theta cycle have been found to fire at earlier phases of theta as the rodent repeatedly traverses a track or maze. This process, dubbed 'theta phase precession', is interpreted as evidence for a prospective code in the hippocampus that may be used to predict upcoming locations [70]. Furthermore, representations of recent and upcoming locations in place cell assemblies are coded within the theta cycle as compressed, ordered sequences [65,66]. Importantly, the content of these theta sequences depends on environmental context and distance from surrounding landmarks [71,72], supporting the notion that these sequences provide a memory-based prediction of possible upcoming spatial locations. One possibility is that this predictive, sequential representation of items in the theta cycle may provide a cellular mechanism for the sequence learning through repetition described in the main text.

In addition to hippocampal representations of place cell sequences, recent work provides evidence for hippocampal neurons that respond at particular moments in time, or temporal positions, during a delay period (dubbed 'time cells'; see [8] for a review). Coding of temporal position has also been reported in the monkey hippocampus during performance of an order memory task [73]. Beyond these relatively short-scale temporal representations, a recent study found that place cells in hippocampal subregion CA1 show a gradually changing firing pattern across multiple days compared with a more stable pattern in subregion CA3 [12]. Together these data suggest that hippocampal neural activity may provide a substrate for representing temporal information across multiple timescales. The more stable signals may provide a cellular mechanism that could potentially support the context-mediated episodic sequence encoding discussed in the main text.

result in indirect associations between items that span a temporal delay. Similarly, other models have proposed that integrator or time cells in the medial temporal lobe (MTL), which change their firing rates slowly, may provide a background context representation that can serve as a substrate for linking items across time [10,11]. Interestingly, recent evidence has shown that population activity in hippocampal subregion CA1 changes gradually over time [12,13], consistent with this notion of a slowly changing background context representation. Another proposed theory highlights the potential role of slow hippocampal oscillations in linking sequential items through their subsequent maintenance [14]. Specifically, this theory posits that recently active items can be maintained in a temporally compressed buffer within the hippocampal theta oscillation such that cells representing each item can fire sequentially within the short time range of long-term potentiation (also see Box 1).

In experimental work, recent neuroimaging data have linked the magnitude of the hippocampal response with successful mnemonic binding of representations across time. For example, the fMRI signal in the hippocampus, as well as in the MTL cortex, is significantly greater during successful versus unsuccessful encoding of associations presented across temporal delays [15–17]. Furthermore, the magnitude of this hippocampal subsequent memory effect has been shown to increase with the degree of spatiotemporal discontinuity between the studied representations [18].

Interestingly, the role of the hippocampus in bridging representations across time does not appear to be limited to episodic memories. It has been shown that patients with hippocampal damage are intact on delay conditioning but impaired on the acquisition of trace conditioning when the conditioned and unconditioned stimuli do not overlap in time [19] and likewise show impairments in probabilistic learning when a short delay intervenes before feedback [20]. Thus, it is clear that the demand on hippocampal processing increases with temporal gaps and that this is related to the successful binding of the presented representations. However, these studies do not directly address to what extent hippocampal function is related to maintaining the fidelity of sequential associations such that their temporal order can later be retrieved. Thus, the remainder of this review focuses on recent empirical work aimed at addressing how the human hippocampus might support the encoding and subsequent recovery of sequential relationships.

Two routes to sequence learning?

It is important to consider that there may be multiple cognitive and neural mechanisms that support hippocampal sequence learning. In particular, we suggest that there may be a distinction between single-trial or episodic sequence encoding and the representation of a well-learned, repeated, predictable sequence because each re-exposure to a sequence may modify the learned representation. Thus, recent work examining changes in hippocampal activation as a function of many sequence repetitions is summarized separately from work examining episodic encoding of novel sequences.

Sequence learning through repetition refers to the learning of sequential relationships over multiple repeated trials that can, but does not have to, occur without explicit awareness. The notion is that repeated exposures to temporal regularities might drive the development and strengthening of a predictive code in the hippocampus [21] that contains information about the order in which the sequence of items typically occurs (Figure 1A). Through repetition, it may be more adaptive for sequential associations to be supported by features that are invariant across repetitions (in this case, the relationships between items). By contrast, episodic sequence encoding describes the encoding of a novel sequence of events. In this case, by definition, there is no repetition of the same item pairings and, thus, sequential encoding may be biased to rely more on the unique contextual features of the event. Similarity in contextual features across items in a sequence may promote binding of those representations in a manner that preserves the temporal structure of the event and facilitates later sequence retrieval. The contextual features that may be shared could include a slowly drifting temporal context representation (e.g., [22]) but may also include other stable internal or external features such as a spatial context (e.g., [23]), a schema (e.g., [24]), or an event model (e.g., [25]) (Figure 2A).

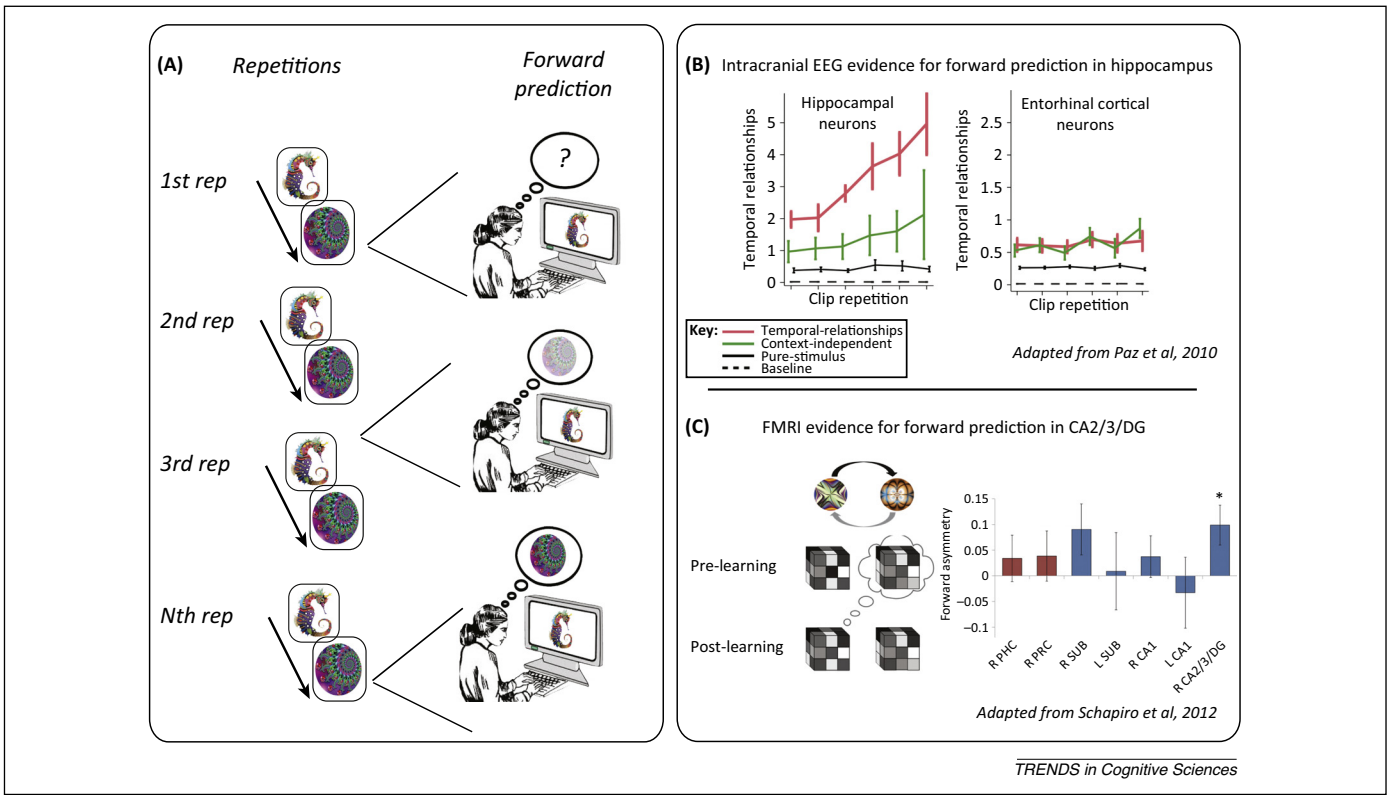

Figure 1. Sequence learning through repetition. **(A)** Schematic of learning the temporal relationship between sequential items with repetition. Across repeated exposures to the first item (*N*) followed by the second item (*N* + 1), a forward prediction gradually emerges such that exposure to item *N* triggers the recovery of item *N* + 1. **(B)** Neural evidence for forward prediction in the hippocampus. With repeated exposure to the same movie clips, firing rates of neurons at time *N* became more similar to firing rates at time *N* + 1 in single units of the hippocampus but not in the entorhinal cortex. Red line, temporal relationships during clip presentation; green line, temporal relationships during blank-screen preceding clip; black line, relationship between time points shuffled across repetitions (i.e., stimulus driven); broken line, relationship between time points shuffled within clip (i.e., baseline). Reproduced, with permission, from [39]. **(C)** Functional MRI evidence for forward prediction in the hippocampus. After repeated exposure to two stimuli (fractals), *N* and *N* + 1, fMRI patterns in the right CA2/3/dentate gyrus subregions elicited by item *N* became more similar to the pre-learning pattern of *N* + 1 compared with the extent to which the pattern elicited by *N* + 1 became similar to the pre-learning pattern of *N*. This measure is referred to as forward asymmetry. Reproduced, with permission, from [42].

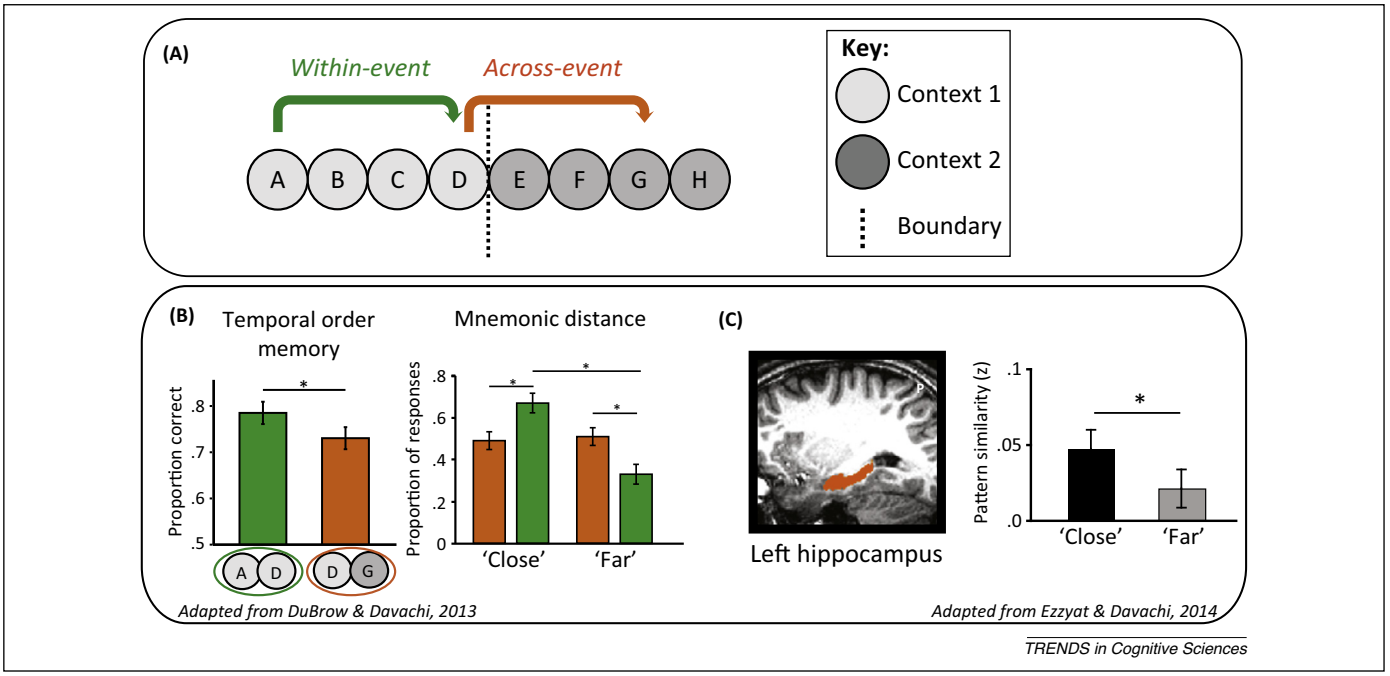

Figure 2. Episodic sequence encoding. **(A)** Schematic of a sequence of items in which the first four items share a context whereas the second four items share a different context. Sequence memory for items within a shared context may be enhanced compared with items in different contexts that span a boundary. **(B)** Behavioral data showing that, compared with across boundaries, order memory is relatively greater within events (left; [60]) and items within events are rated as having occurred more closely together (right; reproduced, with permission, from [61]). **(C)** fMRI evidence that the hippocampus contributes to temporal memory. Patterns of activation in the left hippocampus during encoding of items in a sequence show greater similarity when those items are later rated as having occurred more closely together [61].

Sequence learning through repetition

There is now growing evidence that the human hippocampus is sensitive to repeating sequences. Prior fMRI work across various sequence learning paradigms has shown that hippocampal activation is generally enhanced during sequence learning [26–28] and a recent case study showed that a patient with complete loss of the bilateral hippocampus and some surrounding cortex failed to show learning of even simple sequential associations despite showing intact item memory [29].

Recent fMRI work has begun to test specific mechanistic hypotheses by examining hippocampal activation on individual trials embedded in repeating sequences. For example, it has been shown that activation in the hippocampus is enhanced both when encountered items predict the next item in a sequence [30] and at the branch point of two overlapping sequences where there may be ambiguity over the content of the next item in the sequence [27,28,31,32]. In these cases where there are multiple possible transitions, the increased hippocampal activation may reflect hippocampal pattern completion. That is, when presented with a partial input of the first one or more items in a previously experienced sequence, hippocampal subregion CA3 may serve the role of completing the prior pattern or the remaining elements of the sequence, thereby generating a prediction about what will be seen next [33–35]. Thus, this pattern completion may underlie the increase in the hippocampal response at the time in which the prediction is triggered, perhaps especially at branch points where uncertainty about the next item in the sequence could result in the generation of multiple competing predictions in the hippocampal network that need to be resolved. Furthermore, ambiguity might additionally recruit top-down retrieval mechanisms that have previously been shown to enhance the hippocampal response [36].

In cases where sequence acquisition involves the generation of predictions about the content of the next possible item, subsequent presentation of that item may result in an attenuated response in the same way that an attenuated response is observed on the second presentation of perceptually repeating items [37]. In this way, predicting and then seeing an item may look similar to seeing an item twice and hence result in repetition attenuation. An enhanced repetition attenuation effect has been observed in the parahippocampal gyrus for repeated scenes predicted by the preceding sequence [38].

Another approach to identifying whether sequence acquisition is associated with forward prediction has been to look for evidence of representational change across repetitions that would suggest a forward reinstatement process. For example, the pattern of neural firing or fMRI activation during earlier parts of a sequence may become more similar to those present in later parts of a sequence. Consistent with this notion, recent data have shown that the firing rate of hippocampal neurons becomes increasingly similar with repetition. Researchers [39] recorded from the hippocampi of epileptic patients while the patients viewed repeating movie clips. They found that the firing rates of hippocampal neurons between successive time points gradually became more similar to each other as the movie clips were repeated (Figure 1B). Specifically, the population firing at time N began to resemble that seen at $N + 1$, and this effect was observed only in the hippocampus and not in surrounding entorhinal cortex. Furthermore, the extent to which an individual showed an increase in hippocampal temporal similarity with repetition was related to his or her later memory for the content of the movie clips.

Similarly, using fMRI, two recent experiments provide evidence that hippocampal patterns of activation also increase in similarity with sequence learning. In one study [40], participants were scanned while encoding repeating sequences of letters for immediate serial recall. Across repetitions of identical sequences, the pattern of hippocampal activation gradually increased in similarity. Interestingly, of the few brain regions that showed this increase, only the hippocampus additionally showed that the similarity between distinct sequences decreased with repetition. Importantly, the repeating and distinct sequences all contained the same items; thus, the enhanced and decreased hippocampal pattern similarity with learning highlights that the hippocampal representation is sensitive to the order of items in the sequences.

The other study examined fMRI responses to individual objects in learned sequences [41], allowing examination of position effects. It was observed that pattern similarity in the hippocampus was greater for objects in their learned sequential positions than for the same objects in random positions and different objects in identical positions. This pattern was observed only in the hippocampus, whereas the perirhinal cortex showed enhanced similarity for identical objects regardless of position and the parahippocampal cortex showed enhanced similarity to the same positions within random sequences. Interestingly, it was also observed that hippocampal pattern similarity was sensitive to sequences with overlapping features and this could be used to disambiguate these similar sequences. Thus, using different methodologies, these studies converge in showing that hippocampal patterns elicited by sequences differentiate and stabilize with repetition.

While the prior data are consistent with the idea that individual items learned in a sequence come to predict the upcoming items, items in learned sequences were never tested out of sequence. Thus, it is unclear whether intact sequential context is necessary to show sequence prediction or whether sequence learning alters the representation of individual items. Furthermore, the prior data could result from symmetric sequential representations (e.g., in an ABC sequence, B is equally predictive of A and C) rather than forward-biased pattern completion (e.g., a tendency for B to predict C over A). A recent high-resolution fMRI study directly tested the notion that sequence acquisition is associated with representational change of individual items in a forward manner [42]. After multiple presentations of pairs of items whose temporal relationships were kept constant, and hence presentation of N was always followed by $N + 1$, they found an increase in the similarity of activation patterns elicited by the N and $N + 1$ stimuli was observed in the hippocampus and MTL. Furthermore, critical to the interpretation of a forward prediction, the authors were able to measure directionality in the change in similarity with experience by including sessions before

and after learning where the individual stimuli were presented in random order. They found that the change in pattern similarity before and after learning showed asymmetry in the CA2/3/dentate gyrus subregions of the hippocampus such that the pattern elicited by the first item of the pair (N) became more similar to the pre-learning pattern of the second item ($N + 1$) than the pattern of the second item ($N + 1$) became similar to the first item (N) (Figure 1C). This asymmetry suggests that after repeated exposures to a reliable sequential relationship, exposure to the first fractal leads to a forward prediction, but not vice versa.

Taken together, these data show that exposure to repeating sequences is associated with changes in the hippocampus that yield important insights into the potential underlying mechanisms supporting sequence memory. In particular, there is preliminary evidence that, after repeated exposures, the onset of a sequence is associated with the forward reinstatement of a hippocampal representation of the remainder of the sequence. Thus, forward prediction via hippocampal pattern completion may be an important feature of sequence learning.

Episodic sequence encoding

One particular challenge for the development of theoretical approaches to understanding the mechanisms of sequence memory formation is that, outside the laboratory setting, sequence memory is often formed even after a single exposure and hence repetition as a necessary component of learning is not viable. In paradigms testing the free recall of once-presented sequences, one of the most ubiquitous findings is the tendency for recall to exhibit temporal clustering [43], meaning that recall transitions tend to be to neighboring items from encoding. This contiguity effect has been found to be asymmetric such that recall transitions also tend to be to items that appeared after the recalled item in the sequence. Thus, despite there being no constraint on the order of recall, memory behavior shows that recall is structured by the sequence of presentation as if this is rapidly and automatically encoded.

The temporal context model [22] was developed in part to account for this asymmetry in memory recall. According to the model, items are bound to a slowly drifting temporal context representation, which in turn updates the context representation [44]. During recall, it is hypothesized that when item N is recalled, this reinstates item N's corresponding temporal context and this then facilitates the recall of neighboring items ($N - 1$ and $N + 1$) that shared a similar context state. Critically, due to the asymmetric nature of the temporal context representation – namely, that the representation of N is encoded in $N + 1$ but not vice versa – this theory can account for the asymmetry in the contiguity effect. Thus, it is possible that contextual asymmetry provides sequence information that enables the reconstruction of sequential order from memory.

Recent behavioral evidence suggests that even after a single experience, context repetition can cue sequence reactivation. One such study demonstrated that after exposure to a triplet sequence (ABC), simply repeating the first two items (AB) of the sequence led to better memory for the third (C) item [45]. Using a similar paradigm, another group recently reported that on repeating the first two items (AB) in the sequence and then presenting an unpredicted novel item (D), the extent to which there was neural evidence for the prediction of the third item (C) was related to forgetting of that initial third item [46]. Despite demonstrating different behavioral outcomes, both results support the idea that items from a sequence can be reinstated after a single exposure when cued with their prior context.

The role of the hippocampus in episodic sequence encoding and retrieval has been explored in recent neuroimaging studies. Hippocampal and MTL cortical activation has been found to be enhanced during successful versus unsuccessful encoding of temporal order [47,48] as well as during successful order retrieval [49–52]. Furthermore, the hippocampus has been shown to exhibit a sequential mismatch response where, after a single exposure, there is enhanced hippocampal activation when either the latter elements of the sequence are reordered (i.e., violation of a prediction [53]) or the entire sequence is reordered [54].

One approach to examining the role of shared context in the acquisition of sequential information is to directly manipulate or effect abrupt changes in context during the encoding of items while holding constant the time passed. These changes have been referred to as event boundaries [25] and have been shown to have a lasting effect on associative memory. Specifically, long-term explicit and implicit measures of sequential memory are enhanced for items encountered within events compared with across event boundaries [55,56]. This event segmentation process may be analogous to hierarchical grouping in short-term serial recall (e.g., [57–59]). Recent behavioral work has shown that temporal order memory is more accurate for items presented in the same context compared with across event boundaries [60] and that items appearing in the same context are later rated as having appeared more closely together [61] even though actual distance is the same. Taken together, these behavioral data provide evidence that encoding context influences multiple forms of temporal memory and raise the possibility that shared context provides mnemonic support for the encoding of sequences after a single experience.

In one study designed to investigate the neural mechanisms influencing the modulation of long-term memory by event structure, participants were scanned while reading narratives that contained temporally-defined event boundaries [55]. Fluctuations in the fMRI response in the MTL cortex [as well as in the caudate and medial prefrontal cortex (PFC); see Box 2] were sensitive to events in a manner that predicted the structuring of those same representations in memory. Specifically, these regions exhibited increasing activation across sentences within the same event that dropped off at event boundaries. The extent to which these regions showed event-level modulation of fMRI activity predicted aspects of later temporal memory. These results suggest that an increase in the neural response across sequential items within an event context may support their sequential binding. One possibility is that this univariate activity may reflect increased working memory maintenance or integration across the event such

Box 2. Examining sequence memory outside the MTL

While this review focuses on the hippocampus, it is important to note that regions outside the MTL also contribute to temporal memory. In particular, the PFC and striatum have both been implicated in the acquisition of sequential relationships and temporal memory. Thus, characterizing the unique contributions of these regions is an important step in building a systems-based view of sequence learning.

Research has shown that frontal lobe damage is associated with disproportionate impairments in temporal order memory and sequence learning even when compared with patients with MTL damage [74–82]. Furthermore, the associative encoding of items that span a temporal gap evokes enhanced fMRI activation in the PFC [15,62,83,84] and is associated with enhanced frontal theta power [85]. Furthermore, both PFC and MTL regions exhibit successful encoding effects. For example, one study [47] reported a region in the left ventrolateral PFC whose activation during encoding predicted subsequent order memory success and another [55] found that activation in the ventromedial PFC was related to the sequential binding of items within events. Furthermore, another group found that the degree of fMRI pattern change in the rostrolateral PFC was related to subsequent coarse temporal estimates [48]. Together these results suggest that the PFC plays an important role in remembering when items were encountered, and this is consistent with its hypothesized role in maintaining a representation of temporal context [44]. However, the fMRI work also highlights a great deal of heterogeneity in the precise localization of regions in the PFC that contribute to temporal memory, and whether and how these regions contribute to general executive functions, such as strategic processing, need to be addressed [86].

The striatum is another region often implicated in neuroimaging studies of temporal memory. As with the PFC, striatal activation has been associated with successful temporal memory encoding [48], memory for the relative order of multiple items [47], and within-event forward recall [55]. While this review focuses on sequences of stimulus–stimulus associations, the striatum has been consistently associated with encoding sequences of stimulus–response associations [26,77]. Thus, its role in sequence acquisition may be related to the learning of rigid stimulus–response associations, which may complement more flexible sequence learning by the hippocampus [87]. The striatum has also been implicated in representing time on the order of seconds to minutes [88], whereas the hippocampus has been shown to be detrimental at such short timescales [89]. Finally, the striatum and hippocampus may interact to calculate the reward value of a spatial sequence and support value-based action selection [90].

that the items within the current event remain accessible and become associated in memory (e.g., [62]).

Finally, more recent work has used multivariate approaches to examine the role of across-trial stability in preserving the sequence of presented items. Two recent reports showed that pattern similarity in hippocampal activation patterns across extended sequences is related to subsequent judgments of temporal distance [61] (Figure 2C) and temporal order [63]. This suggests that hippocampal stability across a presented sequence promotes the associative binding of items in a sequence. Furthermore, temporal order judgments after a single encoding experience were associated with behavioral and neural evidence for the reactivation of intervening items in the sequence [60,63]. Specifically, when presented with items A and E from the studied sequence (ABCDE) and asked to recover the temporal order (i.e., 'Which was more recent?'), there was neural evidence of category-level reactivation of the intervening items as well as greater behavioral priming to those items. Thus, taken together, these data suggest that the hippocampus plays a role in acquiring and expressing episodic sequence memory through encoding stability and reactivation during retrieval.

Concluding remarks

Here we have reviewed emerging evidence characterizing human hippocampal involvement in sequence learning. We draw a possible distinction between sequence learning that may involve extracting temporal regularities through multiple repetitions and rapid, novel episodic sequence encoding. Further, we propose that the underlying processes and representations by which sequence information is acquired in these two cases may be biased by their learning context. On the one hand, episodic sequence encoding may be more likely to be supported by the binding of novel sequential items to their shared context, which helps to delineate their temporal order. Binding according to shared context is theoretically able to operate on longer time-scales and thus is well suited to mediate the encoding of sequences that occur over large temporal gaps. On the other hand, sequence representations acquired through multiple repetitions may be additionally supported by a growing tendency for individual items to trigger forward pattern completion of the sequence, a process that may be mediated by the hippocampus. Importantly, this type of learning may operate on relatively shorter timescales (i.e., short delays between items in a sequence).

While we find it useful to characterize the mechanisms that support episodic versus repeated sequence learning as distinct, it is important to highlight that these processes are by no means mutually exclusive. Robust single-trial sequence encoding may result in subsequent forward prediction (e.g., [45]) and shared context may benefit sequence acquisition through repetition to the extent that encoded contextual features are also repeated. Instead, we suggest that the episodic or repeated nature of an experienced sequence may bias the source of temporal information for that sequence. Temporal information based on a single

Box 3. Outstanding questions

- If different ways of acquiring sequence information lead to distinct memory representations, do they offer unique contributions to adaptive behavior? For example, does sequence acquisition dependent on shared context provide a more flexible representation whereby indirect item–item relationships can be accessed?
- How does stability and dissimilarity in hippocampal patterns differentially contribute to memory? It has been shown both that stable hippocampal patterns across time promote binding [60,61] and that coarse temporal memory is better for items showing greater dissimilarity with neighboring items [48]. Thus, one possibility is that similarity and dissimilarity differentially promote associative encoding and item encoding.
- Are there human homologs of the hippocampal time cells and theta sequences observed in nonhuman animals? If discovered, this may help us understand the unique contributions of each to memory behavior as well as the relationship between them.
- What are the unique contributions of MTL cortical regions to sequence encoding and retrieval? MTL sequence learning effects have mirrored those observed in the hippocampus in some cases [42,47] but not in others [41,61,73].

experience may be biased toward relying on contextual features (e.g., [60,61]), whereas repetition may bias the source of such information away from a specific spatiotemporal context and toward cued prediction of subsequent items in a sequence. Importantly, the current experiments have not been designed to test these two possibilities simultaneously and thus future work will be needed to address this possible distinction. While many open questions remain (Box 3), converging evidence across both human and animal studies (Box 1) suggests that the hippocampus learns and represents the sequential structure of events both by encoding information about items in their contexts and by exhibiting a predictive code of upcoming events.

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