Review

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

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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.

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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).