

Time, Memory, and the Legacy of Howard Eichenbaum

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Abstract:

Over the past 15 years, there has been an explosion of new research on the role of the hippocampus in representation of information about time in memory. Much of this work was inspired by the ideas and research of Howard Eichenbaum, who made major contributions to our understanding of the neurobiology of episodic memory and the neural representation of time. In this paper, I will review evidence regarding the role of time in understanding hippocampal function. This review will cover a broad range of evidence from studies of humans and nonhuman animals with a narrative arc that follows Howard's major discoveries. These studies demonstrate that the hippocampus encodes information in relation to an episodic context, and that time, as well as space, serves to define these contexts. Moreover, the research has shown that the hippocampus can encode temporal, spatial, and situational information in parallel. Building on this work, I present a new framework for understanding temporal structure in human episodic memory. I conclude by outlining current controversies and new questions that must be addressed by the field in the years to come.

Inspired by Milner's studies of H.M. and other amnesic patients (Milner et al., 1968; Scoville and Milner, 1957) generations of researchers have worked to understand the role of the hippocampus in memory. In their book, "The Hippocampus as a Cognitive Map," O'Keefe and Nadel (1978) proposed that the hippocampus supports memory by mapping experiences according to when and where they took place. O'Keefe and Nadel's model helped to integrate the recent discovery of place cells in the hippocampus (O'Keefe and Dostrovsky, 1971; Ranck, 1973) with Tulving's (1972) idea that people have a specialized ability to remember spatiotemporally-indexed events ("episodic memory"). The lack of straightforward behavioral paradigms and cellular signals to probe memory for episodic memory in animal models, however, led prominent researchers (e.g., Burgess et al., 2002; McNaughton et al., 2006; Moser et al., 2008) to focus instead on testing the simpler and more experimentally tractable hypothesis that the hippocampus supports spatial representation by integrating visual, motor, and vestibular signals. In contrast to the predominant research focus on the spatial functions of the hippocampus in behavioral neuroscience, Howard Eichenbaum took inspiration from research on human amnesia, and he sought to bridge the gap between human memory and work on functions of the hippocampus in animal models.

Howard often introduced his work with Endel Tulving's (1972) definition of episodic memory as "information about temporally dated episodes or events, and temporal-spatial relations among these events." (p. 385). Tulving, however, argued that episodic memory is a uniquely human ability, and Howard sought to challenge this idea by demonstrating that rodents possess the capacity of episodic memory, and that studies of rodents can reveal insights into the neural mechanisms of human episodic memory. Howard also was inspired by Aristotle's

proposal that memory, “implies a time elapsed; consequently only those animals which perceive time remember, and the organ whereby they perceive time is also that whereby they remember.” Howard dedicated much of his scientific career to understanding the role of the hippocampus as the critical “organ” for representation of temporal context in memory.

In this paper, I will provide a broad review of our understanding of the neural representation of time in memory, with a narrative arc that follows Howard Eichenbaum’s major contributions. Howard’s research and theoretical work consistently emphasized the importance of theories and ideas that bridge findings across species and levels of analysis. Consistent with his vision, I will highlight the remarkable convergence of evidence for hippocampal representation of time across species, experimental approaches, and task paradigms. I will close by summarizing what I believe to be the central themes to emerge from this research and point to new directions and questions to be addressed in future research.

### *Critical Role of the Hippocampus in Episodic Memory*

Neal Cohen and Howard Eichenbaum (1993) published a landmark book that attempted to synthesize work on hippocampal function in rodents with the research on human amnesia. Cohen had previously demonstrated that patients with severe amnesia could still express memory without awareness (Cohen and Squire, 1980), but the field lacked a theory that described, at the representational level, the role of the hippocampus in memory and cognition in humans and rodents. O’Keefe and Nadel (1978) dealt with this issue to some extent, but their theory relied heavily on research on spatial cognition in nonhuman animals. Cohen & Eichenbaum’s theory

cast the work on human amnesia and the work on spatial processing in rodents as converging sources of evidence for the idea that the hippocampus represents relationships between items in memory, or “declarative memory” (Cohen and Eichenbaum, 1993). The theory proposed that patients with amnesia can learn associations via perceptual, motor, or cognitive systems, and that their central deficit is an inability to acquire memories for the relationships between representations processed by these various systems. The theory reframed findings on hippocampal processing of space in rodents as a subset of its more general role in declarative memory, which they proposed to support, “all manner of relations” (Cohen and Eichenbaum, 1993). Eichenbaum set out to test this idea by developing behavioral paradigms to study whether the rodent hippocampus is necessary to support new memories for events, even when spatial information could not be used to solve the task<sup>1</sup>.

Eichenbaum believed that the evidence for spatial coding in the hippocampus (O’Keefe and Nadel, 1978) reflected the fact that space is a highly salient variable for organizing experiences. Because foraging rats naturally explore their environment through olfaction, Howard reasoned that odors should be salient, independent of spatial context. Eichenbaum’s lab found that hippocampal neurons were sensitive to odor recognition (Otto and Eichenbaum, 1992b; Wood et al., 1999), but they also found that odor recognition memory was generally spared after hippocampal lesions (Bunsey and Eichenbaum, 1996; Dudchenko et al., 2000; Fortin et al., 2002).

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<sup>1</sup> It is important to also note the work of Ray Kesner, who conducted many important lesion studies to investigate the role of the rodent hippocampus in nonspatial memory (cf. Kesner RP. 2016. Exploration of the Neurobiological Basis for a Three-System, Multiattribute Model of Memory. *Curr Top Behav Neurosci*, Kesner RP, Rolls ET. 2015. A computational theory of hippocampal function, and tests of the theory: new developments. *Neurosci Biobehav Rev* 48:92-147.)

Other researchers also noted that hippocampal lesions in nonhuman primates (Baxter and Murray, 2001) and humans (Aggleton and Shaw, 1996; Vargha-Khadem et al., 1997) had inconsistent, and sometimes minimal effects on item recognition memory. These findings stood in contrast to the severe deficits in object (Baxter and Murray, 2001) and odor (Otto and Eichenbaum, 1992a) recognition seen after perirhinal cortex damage. To explain these findings, Aggleton and Brown (1999) proposed that the hippocampus might specifically support recognition based on recollection, whereas the perirhinal cortex is needed to support object recognition based on familiarity. Using receiver operating characteristic (ROC) analyses of recognition confidence ratings to estimate the contributions of recollection and familiarity to item recognition, researchers demonstrated that humans with hippocampal damage exhibited selective impairments in recollection-based recognition memory (Aggleton and Shaw, 1996; Yonelinas et al., 2002; see also Tsivilis et al., 2008; Vann et al., 2009). Results from neuroimaging studies relating brain activity to recognition confidence or subjective recollection judgements added to the story by demonstrating that hippocampal activity was reliably associated with recollection, whereas perirhinal cortex activity was associated with gradations in familiarity-based recognition (Eldridge et al., 2000; Haskins et al., 2008; Montaldi et al., 2006; Ranganath et al., 2003). Although the constructs of recollection, familiarity, and confidence are intimately linked with subjective experiences that cannot be directly measured in nonhuman animals (Tulving, 1985; Yonelinas, 2001), Fortin et al. (2004) developed an ingenious paradigm to measure these constructs in rats through ROC analyses of odor recognition memory. Rather than using confidence ratings, as in human lesion and fMRI studies, Fortin et al. (2004) manipulated response difficulty and reward contingencies in order to change animals' response bias. Thus, under circumstances that encourage a conservative response bias, a rat would have to

be highly “confident” in order to identify an odor as previously studied. With this approach, the authors were able to estimate the contributions of recollection and familiarity to recognition ROC curves in rats. The results of Fortin et al. (2004) perfectly matched the results from human ROC analyses (Eichenbaum et al., 2010; Eichenbaum et al., 2007), indicating that the hippocampus specifically supports recollection-based recognition (Eacott and Norman, 2004; See also Easton and Eacott, 2009; Eichenbaum et al., 2010; Eichenbaum et al., 2012; Eichenbaum et al., 2008). Work by Sauvage and Eichenbaum built on the findings by showing that hippocampal damage had opposite effects on recollection and familiarity in an associative recognition paradigm (Sauvage et al., 2008), and that lesions to the medial entorhinal cortex, like the hippocampus, selectively affected recollection-based recognition (Sauvage et al., 2008).

The work on recognition memory added to the emerging body of evidence suggesting that regions of the medial temporal lobes make different contributions to memory. One key proposal along these lines was from Mishkin et al. (1997), who proposed that the hippocampus plays a special role in episodic memory by virtue of its unique anatomical connectivity (Burwell and Amaral, 1998; Suzuki and Amaral, 1994)<sup>2</sup>. Specifically, Mishkin et al. (1997) hypothesized that the perirhinal cortex processes information about objects, the parahippocampal cortex processes spatial information, and that these kinds of information could be sufficient to support acquisition of general knowledge, or semantic memory. In contrast, they argued that the hippocampus makes essential contributions to episodic memory by integrating object and spatial

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<sup>2</sup> The anatomical evidence was originally interpreted as suggesting that the dorsal and ventral visual processing streams converge in the MTL. In fact, much of the “spatial” information arriving in the hippocampal formation is conveyed via information about visual gist processed by ventral stream inputs to the parahippocampal/posterior cortex, and via self-motion and head direction signals conveyed via the mammillothalamic tract and retrosplenial cortex. The classic dorsal stream areas, such as the intraparietal sulcus (corresponding to area LIP in the monkey), are not extensively interconnected with MTL regions (see Ranganath and Ritchey (2012) and Kravitz et al. (2011) for review).

information processed during an event. Eacott and Gaffan (2005) advanced these ideas in a significant way, by proposing that the parahippocampal cortex supports the processing of spatial context, whereas the hippocampus is needed to remember factors that are unique to the event (i.e., which items were seen in which locations in which context). Knierim et al. (2006) adopted a similar framework, highlighting additional evidence showing that object and spatial input from parahippocampal and perirhinal cortex are differentially processed by the medial and lateral entorhinal cortex (Lavanex and Amaral, 2000; Witter et al., 2000). Davachi (Davachi, 2006) interpreted human neuroimaging studies of memory encoding along these lines, such that the unique role of the hippocampus was to integrate object and spatial information conveyed by perirhinal and parahippocampal cortex.

Howard thought that episodic memory involves more than simply distinguishing between objects and spatial locations, and his lesion work demonstrated that the hippocampus could contribute to recollection-like odor recognition. Moreover, he recognized the importance of evidence from human neuroimaging and neuropsychological studies showing that the hippocampus is also necessary for encoding and retrieval of information about temporal or situational context and information about associations between concurrently presented items. Howard recruited Andy Yonelinas and I to develop a framework for hippocampal function that could encompass a broad range of findings, including the ROC findings from rats and humans, the relevant neuroimaging evidence, and models of memory and cognition. Our model, which later became known as the “Binding of Items and Contexts” (BIC) model (Diana et al., 2007), extended the Cohen and Eichenbaum (1993) model by differentiating between memory for *who*

or *what* was in an event (“items”)<sup>3</sup> and information about the *time, place, and situation* (“context”) in which the event occurred (Eichenbaum et al., 2007). The BIC model also went beyond the “what/where” model of hippocampal function by clarifying that context could be defined entirely on the basis of nonspatial factors, including most notably, time. Specifically, we understood that contexts remain stable in time (e.g., a room typically does not move), and Howard therefore dedicated much of his work to specifying the nature of hippocampal processing of temporal context.

*Critical role of the Hippocampus in Sequence Memory.*

Many studies of nonspatial memory in rats focused on learning of static associations, but these kinds of paradigms do not capture an essential aspect of episodic memories—when one recalls a real-life episode, the corresponding events unfold over time in a manner that resembles a temporally-ordered sequence. In a similar vein, one can consider goal-directed navigation as a sequence of events (e.g., traversing through a series of street intersections in order to reach the baseball park). Consistent with this idea, previous work (Gothard et al., 1996; McNaughton et al., 1983; Redish et al., 2000) suggested that, during traversals of a linear track, the firing of hippocampal place cells depended on the animal’s direction of travel. In other words, hippocampal place cells “remapped” depending on the journey taken by the animal.

Eichenbaum considered the possibility that the direction selectivity of place cells on a linear track reflected the fact that the cells were not encoding locations per se, but rather a

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<sup>3</sup> Howard generally assumed that, in his tasks, odors were represented as “items” or “objects.” For the sake of simplicity, I follow his interpretation in this paper, but the issue is not straightforward. For instance, it is unclear whether a human or a rat would process a cinnamon-scented sandbox as an item or a spatial context—the answer would probably depend on the task and/or situational context.

sequence of spatial locations. Wood et al. (2000) set out to more directly test this idea by recording hippocampal neurons as rats performed a delayed alternation test in a “t-maze”. In this task, an animal must walk through a passageway (the “stem”) and then choose to make a left or right turn. To gain a reward, the animal must alternate turns across successive journeys. Consistent with their hypothesis, Wood et al. (Wood et al., 2000) found that, at the same locations in the stem, different hippocampal place cells fired depending on the place that the animal had been in the recent past. These findings, along with those of Frank, Brown, & Wilson (2000), who found converging results with a different maze topology (see also Ferbinteanu and Shapiro, 2003), led Wood et al. to conclude that, “hippocampal network activity reflects a fundamental coding of the animal's position and behavior within a sequence of repeated events and places.” Their conclusion was controversial, but now there is little doubt that, during memory-guided navigation<sup>4</sup>, hippocampal neurons encode sequence information, as well as temporal intervals (see *Encoding of Temporal Intervals* below). Moreover, findings in the rat appear to generalize to humans, as fMRI studies have shown that hippocampal activity patterns show journey-selectivity during virtual navigation in mazes that have overlapping components (Brown et al., 2016; Chanales et al., 2017).

Given that the findings described above were observed during spatial navigation, it is reasonable to wonder whether the hippocampus might encode sequence information even when spatial information is totally irrelevant to the task. To answer this question, Ray Kesner and Howard Eichenbaum ran concurrent studies to investigate whether the hippocampus is needed to

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<sup>4</sup> It is interesting that research on place cells predominantly focuses on random foraging, even though the results are often interpreted with respect to “navigation.” The work of Wood and Eichenbaum, Matthew Shapiro, and others suggests that, during actual goal-directed navigation, the hippocampus represents points along a journey. Accordingly, it might be more appropriate to interpret classic place cell responses during random foraging as reflecting “orientation,” rather than “navigation”.

learn nonspatial sequences. In these paradigms, rats were exposed to a sequence of odors and then required to identify which of two odors was presented first. Fortin et al. (2002) and Kesner et al. (2002) both found that rats with hippocampal lesions were severely impaired at the temporal order memory tasks, despite normal performance on a task that required discrimination between novel and familiar odors. In other words, the hippocampus seems to be necessary for remembering a sequence of items, but not for recognizing that an item has been presented. Subsequent work from Kesner's lab demonstrated that subfield CA1 may be particularly critical for performance on this task (Kesner et al., 2010).

As noted above, Wood et al. (2000) concluded that their findings in the t-maze task reflected a role for the hippocampus in disambiguating sequences of events that occurred in the same place. If this interpretation is correct, one would expect the hippocampus to contribute to disambiguation of sequences even when spatial information is task-irrelevant. Consistent with the conclusions of Wood et al. (2000), Agster et al. (Agster et al., 2002) demonstrated that hippocampal lesions impaired performance on a task that required discrimination of odors in overlapping sequences. Ginther, Walsh, and Ramus (Ginther et al., 2011) recorded activity from neurons in dorsal hippocampus during performance of a similar task and found that hippocampal neurons differentiated between odors in overlapping sequences.

In the odor sequence tasks described above, spatial information was task-irrelevant, but it still could be argued to play a role, as animals were required to actively move in order to explore the odor stimuli. To rule out this possibility, Tim Allen and Norbert Fortin developed a sequence memory paradigm in which rats were required to remain stationary in order to sniff odors via a nose port (Allen et al., 2014). Allen et al. (2016) found that ensembles of hippocampal neurons

differentiated between familiar odors according to whether or not they were in the correct sequence order. Moreover, Allen et al. found that a large proportion of hippocampal neurons did not simply encode information about odors, but rather they encoded information about odors specific to a sequence context.

Consistent with the single-unit recording work, fMRI studies have shown that hippocampal activity is enhanced during learning and retrieval of nonspatial temporal sequence information (Azab et al., 2014; Barnett et al., 2014; Hsieh et al., 2014; Kumaran and Maguire, 2006; Ross et al., 2009; Schendan et al., 2003; Tubridy and Davachi, 2010). Akin to the ensemble analyses reported by Allen et al. (2016), researchers have examined population-level patterns of hippocampal activity (using vectors of voxel-level activity, rather than vectors of single-neuron activity), and these studies have consistently revealed that hippocampal voxel patterns reflect the content of learned sequences (Hsieh et al., 2014; Kalm et al., 2013).

Hsieh et al. (Hsieh et al., 2014) scanned participants while they made semantic decisions on a continuous stream of objects that were either in fixed sequences or in a randomized sequence. Although there were no demands for explicit retrieval during scanning, participants made faster semantic decisions about objects in fixed sequences than for objects in random sequences. Moreover, responses were considerably lagged for the first object in each sequence, suggesting that participants segmented the continuous stream of objects into discrete five-object sets. Voxel pattern similarity analyses revealed that hippocampal activity during retrieval of learned object sequences reflected both the identity and temporal position of each object. Voxel patterns were correlated across repetitions of the same object in learned sequences, and participants who showed larger hippocampal sequence representation effects were better able to

use sequence knowledge to optimize decisions. Critically, these effects were specific to the hippocampus—the perirhinal and parahippocampal cortex, for instance, exhibited activity patterns consistent with coding of object and position information, respectively. Finally, voxel patterns differentiated between repetitions of the same object in distinct, but overlapping sequences. These findings converge with the lesion and single-unit recording data in rats to suggest that the hippocampus plays a critical role in encoding sequences of events (Cohn-Sheehy and Ranganath, 2017; Ranganath and Hsieh, 2016).

#### *Hippocampal encoding of continuous temporal intervals*

A number of computational models have been proposed to explain how the hippocampus could come to represent sequences (Wallenstein et al., 1998). These models assume that recurrent connectivity within CA3 is sparse and asymmetric, and under these conditions, the network generates “context cells” that intrinsically fire at different time points (Levy, 1996; Wallenstein et al., 1998). The models suggested that, at least in theory, an ensemble of hippocampal neurons could effectively encode intervals of time within an event. Put another way, because different subsets of context cells are active at different points in time, the population code gradually changes, or “drifts” over time. The population-level drift of context cells in these models parallels mathematical models designed to account for temporal structure in human memory (Burgess and Hitch, 2005). In these models, “temporal context” is operationalized as a set of elements that randomly fluctuate over time (Davelaar et al., 2005; Estes, 1955; Howard and Kahana, 1999; Polyn et al., 2009a), and, at least in theory, such a

representation could be encoded by ensembles of “context cells” in the hippocampal models described above<sup>5</sup>. Indeed, Marc Howard, Mike Hasselmo, Howard Eichenbaum, and others have explicitly argued that temporal context models can account for the role of the hippocampus in temporal coding (Howard and Eichenbaum, 2013; Howard and Eichenbaum, 2015; Howard et al., 2005; Howard et al., 2014).

Interestingly, models of sequence representation in the hippocampus proposed the existence of “context cells” based purely on computational assumptions, but such cells were actually discovered in subsequent work. Hinting at this finding, Redish and colleagues (Redish et al., 2000) observed that, on a linear track, hippocampal cells more closely tracked elapsed time than spatial cues (although the results were interpreted in the context of computational models of spatial processing). Stronger evidence came from Pastalkova et al. (2008), who recorded from the hippocampus as rats ran on a wheel placed in the stem of a t-maze. Despite the fact that the animal remained in the same location relative to the box, hippocampal neurons exhibited temporally specific firing, such that different neurons fired at different time points during the interval on the wheel (Pastalkova et al., 2008). Consistent with the findings of Wood et al. (2000), some of these cells exhibited differential firing on the treadmill according to the animal’s previous location in the T-maze.

Building on the findings of Pastalkova et al. (2008), Eichenbaum’s lab demonstrated that a large population of hippocampal neurons, termed “time cells,” also exhibited temporal coding during a test of memory for associations between objects and odors (MacDonald et al., 2011).

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<sup>5</sup> Temporal context models are similar to the sequence coding models in that there is explicit coding of activity dynamics that drift over time. However, temporal context models do not account for the sequential firing of hippocampal time cells described later in this section.

MacDonald et al. reported that CA1 units called “time cells” fired at specific intervals during the delay between the object and odor presentation. Because the animal remained stationary during the delay, the firing of time cells could not be attributed to active movement on a running wheel. MacDonald et al. (MacDonald et al., 2013) replicated these findings in an odor-odor association task that required animals to remain immobilized, further ruling out the possibility that the firing of time cells was driven by navigation or movement.

Eichenbaum’s lab discovered striking parallels between hippocampal representations of space and time. Just as hippocampal place cells exhibit different firing fields in different spatial contexts (i.e., “remapping,” Muller and Kubie, 1987), different ensembles of time cells fired during trials that involved different odor combinations (i.e., “retiming,” MacDonald et al., 2013). Moreover, most time cells also showed spatially selective firing—in other words, MacDonald et al. found that most hippocampal neurons are both time cells and place cells. Following up on these findings, Kraus et al. (2013) investigated the relationship between spatial and temporal coding in the hippocampus by examining neural firing as a rat ran on a treadmill. By independently varying treadmill speed and running duration, Kraus et al. (Kraus et al., 2013) could separately investigate neural coding of the distance run on the treadmill and the duration of running time. The results revealed that both of these variables independently contributed to the firing of most CA1 units, suggesting that the hippocampus encodes both spatial and temporal information. This finding suggests that hippocampal ensembles carry a multiplexed representation that could be used to localize an event in time, space, or both (Eichenbaum, 2017a). The findings of time cells in rodents appear to generalize to primates. In monkeys, Suzuki and colleagues (Naya and Suzuki, 2011; Sakon et al., 2014) have shown that

hippocampal neurons track elapsed time in memory tasks, even when the information is task-irrelevant. Similar to Eichenbaum's work in rats, the findings suggest that the hippocampus may track temporal context as a basis for structuring memory representations as an event unfolds over time.

Inspired by studies of spatial coding by grid cells in the medial entorhinal cortex (MEC), Eichenbaum directed his attention towards determining whether MEC might also encode temporal information. Kraus et al. (2015) first identified a population of MEC grid cells that showed hexagonally distributed firing fields during free foraging in an open field, and they next investigated the firing characteristics of these neurons as rats ran on a treadmill. Interestingly, during the treadmill task, grid cells showed precise encoding of intervals, with most cells signaling both time spent on the treadmill and distance traveled. Robinson et al. (2017) next addressed whether MEC neurons play a causal role in determining temporal coding in CA1 by using an innovative combination of optogenetic inactivation and single-unit recording. Results showed that inactivation of MEC neurons significantly impaired memory performance and dramatically attenuated temporal coding in CA1. Surprisingly, location coding (i.e., place fields) in CA1 remained stable in the face of inactivation, suggesting that spatial and temporal representations in the hippocampus may be dissociable, and that MEC plays a disproportionately important role in temporal coding.

Although time cells encode fairly short temporal intervals, some evidence suggests that the hippocampus encodes intervals on longer timescales as well. For instance, Manns et al. (2007) examined population-level hippocampal activity patterns as rats performed a task modeled after the sequence memory experiment by Fortin et al. (Fortin et al., 2002). Results

showed that population-level activity patterns in CA1 drifted such that patterns were increasingly dissimilar between trials with increasing lags (Manns et al., 2007). The lag-sensitive differences in hippocampal activity patterns were only seen on correct trials, suggesting that changes in ensemble coding over time could have supported recency memory in the task. Mankin and colleagues (Mankin et al., 2015; Mankin et al., 2012) extended these findings by demonstrating that the ensemble code for spatial location in CA1 drifts considerably across successive days (see also Rubin et al., 2015, for similar findings; Ziv et al., 2013), and in area CA2, population codes changed considerably over the course of hours. These findings suggest that temporal context might be an important mechanism by which the hippocampus may support episodic memory (Eichenbaum, 2017a; Ekstrom and Ranganath, 2017; Ranganath and Hsieh, 2016). For example, temporal drift in hippocampal coding could allow the hippocampus to assign different representations to successive events that occurred in the same spatial context (e.g, last night's dinner party vs. last month's dinner party).

Considerable evidence suggests that neural coding in the human hippocampus also supports temporal context representation across coarse timescales. For instance, Luke Jenkins and I (Jenkins and Ranganath, 2010) showed that the magnitude of hippocampal activity evoked during processing of objects predicted the accuracy of subsequent estimates of the time at which the object was studied over the course of the hour-long experiment. Study items that subsequently elicited accurate temporal estimates were associated with greater hippocampal activation than items with inaccurate temporal estimates (Jenkins and Ranganath, 2010). Inspired by the work of Manns et al. (2007), we (Jenkins and Ranganath, 2016) went further by testing whether time-dependent changes in population-level hippocampal activity patterns, estimated

with fMRI, relate to memory for temporal order. Jenkins & Ranganath assumed that, if hippocampal activity patterns drift over time, then the degree of drift between different events should make it easier to discriminate the order in which the events occurred. Consistent with this idea, hippocampal pattern change during encoding of objects predicted participants' ability to discriminate which item was presented first in the list, such that pattern change differences were larger during encoding of items that were associated with correct recency decisions than during encoding of items that were associated with incorrect decisions. Complementing the findings of Jenkins & Ranganath (2016), subsequent work has shown that, during memory retrieval, activity patterns are more similar for recalled events that had occurred in close temporal proximity than for events that were relatively far apart in time (Deuker et al., 2016; Dimsdale-Zucker et al., 2018; Lositsky et al., 2016; Nielson et al., 2015).

#### *Conclusions and Questions for future research*

Howard Eichenbaum studied temporal coding in the hippocampus as a step towards the larger goal of understanding its contributions to episodic memory. Even if the hippocampus encodes all aspects of experience, Eichenbaum's work suggests that the hippocampus may be disproportionately important for laying down a temporal context that binds elements of an episode (Ekstrom and Ranganath, 2017). His studies, along with those of trainees and colleagues, demonstrate that temporal information is encoded by hippocampal neurons, at fine and coarse timescales, even when it is not directly relevant to the task (Eichenbaum, 2014). Conversely, disruption of temporal coding in the hippocampus (Robinson et al., 2017), or lesions to the hippocampus (Fortin et al., 2002), severely impair performance of memory tasks, particularly when those tasks have a temporal component. The results suggest that the hippocampus does not

merely record information about what happens—the hippocampus lays the foundation for an event-based representation of what happened and when it occurred (Eichenbaum, 2013; Eichenbaum, 2017c). This is an important discovery, and as I describe below, the findings also raise many fundamental questions about time, memory, and the hippocampus:

What is the relationship between spatial and temporal coding? (Lisman et al., 2017).

Although Eichenbaum coined the term “time cell,” he was well aware that there are no such things as time or place cells—instead, he argued that hippocampal neurons encode “multiplexed maps of space and time” (Eichenbaum, 2017b). Studies of time cells indicate there is no obvious correspondence between the time and place fields of hippocampal neurons, suggesting that the hippocampus encodes space and time in parallel (Eichenbaum, 2014). This finding accords with work showing that temporal coding in the hippocampus can be disrupted even while spatial coding is preserved (Robinson et al., 2017; Wang et al., 2015)<sup>6</sup>. Consistent with this idea, fMRI studies suggest that, for memories acquired during virtual navigation (Deuker et al., 2016) and for real-life memories acquired across long time scales (Nielson et al., 2015), hippocampal activity patterns mark the relative order of events in time, and the relative locations of events in space, along with the conjunction of the two. Ekstrom and colleagues have gone further by demonstrating that the hippocampus can encode relatively distinct representations of the spatial and temporal context of the same event (Copara et al., 2014; Kyle et al., 2015). Conversely, Halle Dimsdale-Zucker and I (Dimsdale-Zucker et al., 2018) showed that activity patterns in hippocampal subfield CA1 can reflect the integrated spatiotemporal context of past events. These

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<sup>6</sup> One caveat: Although place fields in CA1 can be, more or less, preserved even when temporal coding is eliminated, it is not clear that spatial memory is intact under these conditions. Even if extrinsic sensory inputs are sufficient to drive place cell firing, it is still possible that temporal coding is necessary to enable spatial memory retrieval. We cannot assume that there is any fundamental relationship between hippocampal place fields and spatial memory performance.

findings raise the possibility that the hippocampal code for events may be highly flexible (Cohen and Eichenbaum, 1993; Ekstrom and Ranganath, 2017; Zeithamova and Preston, 2010; Zhang and Ekstrom, 2013)—that is, if an entire event is encoded by a large hippocampal cell assembly, different subsets of the cell assembly might be activated in the service of behavior that requires information about space (e.g. remembering the location of your seat at the baseball stadium), time (e.g., remembering the inning in which the home run took place), or both e.g., recollecting that you happened to return to your seat in the bleachers at the right time to grab the ball that scored the winning home run). This prediction could be experimentally tested by examining hippocampal activity patterns in humans during initial exposure to a sequence of objects in a virtual environment and then examining representational similarity to the same event as a function of whether one needs to recall spatial, temporal, object information, or a combination of these factors. If my prediction is correct, it would mean that there is no single stable hippocampal memory trace (or “engram”, Josselyn et al., 2015) for an event. Instead, different “engrams” may be constructed on the fly as needed in different behavioral contexts.

Does the hippocampus segregate temporally distinct experiences or does it integrate them? Although there is no doubt that the hippocampus is especially important for representing information about people and things encountered in a specific spatiotemporal context, another body of research has suggested that the hippocampus plays a broader role in integrating associations across events that occurred at different times. One classic example comes from Eichenbaum’s classic studies of “transitive inference” (Bunsey and Eichenbaum, 1996; Dusek and Eichenbaum, 1997). In this paradigm, rats learn to discriminate between pairs of odors that overlap with one another (i.e., odor “A” > odor “B” ; odor “B” > odor “C”, odor “C” > odor “D”,

etc.). After learning the individual associations, an animal could theoretically build a more integrated representation of the odor hierarchy, thereby enabling “inferences” about relationships between pairs of odors that were not previously learned (e.g., odor “B” > odor “D”). Bunsey and Eichenbaum (Bunsey and Eichenbaum, 1996) found that healthy rats and rats with hippocampal lesions could learn the individual discriminations, but only the healthy rats could correctly infer the novel response when faced with a novel discrimination that required integration across the learned associations (odor “B” > odor “D”). Inspired by Eichenbaum’s work, Preston and colleagues developed a variant of the task that requires learning of pair associations, rather than discriminations. Preston’s work has shown that the hippocampus is extensively engaged during learning and retrieval of overlapping associations (Preston et al., 2004; Schlichting et al., 2015; Schlichting and Preston, 2015; Schlichting et al., 2014; Zeithamova et al., 2012a; Zeithamova and Preston, 2010; Zeithamova et al., 2012b). In a similar vein, Shohamy and colleagues have shown that the hippocampus supports generalization of reward associations across multiple, overlapping events (Shohamy and Wagner, 2008; Wimmer and Shohamy, 2012). Collectively, these findings indicate that the hippocampus can integrate information across temporally-distinct episodes, a phenomenon that has been dubbed “memory integration” (Schlichting and Preston, 2016) or “integrative encoding” (Shohamy and Wagner, 2009).

How does hippocampal representation of temporal context relate to memory integration?

Using simulations of the Temporal Context Model, Howard et al. (Howard et al., 2005) demonstrated that memory integration can be understood as a consequence of the role of the hippocampus in encoding item information relative to the temporal context in which the item was encountered. In short, the model proposes that, when one learns a simple association

between items A and B, the hippocampus encodes the link between A, B, and a representation of the temporal context in which the event took place. When B is later encountered with item C, presentation of B triggers reactivation of the previously encountered temporal context representation, thereby enabling retrieval of A. As a result, the hippocampus now forms what Howard et al. termed an “intermediate representation” that links A and C (see Figure 1A). In other words, retrieval of the A-B association leads A to become associated with B and C, in a new temporal context. Their model suggests that, at least in principle, the hippocampus can link representations for separate experiences if one assumes that the representation of temporal context for a previous experience can be retrieved and associated with a new, overlapping experience. Interestingly, in their model of Bunsey and Eichenbaum’s (1996) study, Howard et al. estimated the similarity of temporal context representations associated with linked items in the transitive inference task—their estimated similarity matrix shows striking parallels to results from Hsieh et al.’s (2014) analysis of hippocampal activity patterns during processing of items linked within a temporal sequence context (Figure 1B). Thus, it is reasonable to think that the same mechanisms that enable the hippocampus to bind items to specific temporal contexts can also enable integration of memories for overlapping experiences that occurred at separate times.

Having said this, the idea that the hippocampus integrates memories for events that occurred at different times seems inconsistent with the idea that the hippocampus plays a critical role in episodic memory (Eichenbaum et al., 2007) and sequence disambiguation (Wallenstein et al., 1998), each of which depend on the ability to differentiate between events that occurred at different places and times. Indeed, recent work has shown that hippocampal representations of overlapping events can become hyper-differentiated from one another (Chanales et al., 2017;

Dimsdale-Zucker et al., 2018). Another recent study found that the anterior hippocampus appeared to integrate overlapping associations learned at separate times, whereas the posterior hippocampus differentiated between overlapping associations (Schlichting et al., 2015). The simplest explanation for these various results is that, at least in the intact brain, the hippocampus is not a simple autoassociator—that is, the hippocampus most likely does not simply encode and retrieve information irrespective of one’s goals or behavioral state. Instead, the degree to which the hippocampus integrates or segregates temporally distinct events might depend on one’s current goals or situation (Richter et al., 2016). More generally, hippocampal representations of past events can vary according to task or situational context (Ekstrom and Ranganath, 2017)—as I describe later, this information might be conveyed by prefrontal cortex.

Do different hippocampal subfields play different roles in processing of temporal information? Although research consistently implicates the hippocampus in temporal memory, there is no clear agreement on the roles of different subfields. Many theoretical models have emphasized the role of CA3 in temporal coding of events (Wallenstein et al., 1998), though Rolls and Kesner (Kesner and Hunsaker, 2010; Kesner and Rolls, 2015; Rolls and Kesner, 2006) have emphasized the importance of CA1. In general, single-unit recording studies have identified correlates of temporal coding in subfields CA1, CA3, and CA2, though there are some inconsistencies in the literature. For instance, Salz et al. (2016) reported evidence for time cells in both CA3 and CA1, and the response properties of the cells were comparable across both subfields. When examining drift in the hippocampal population code for space over long timescales, Mankin and colleagues (Mankin et al., 2015; Mankin et al., 2012) found that CA1 and CA2 showed a significant drift, but spatial coding in CA3 was shown to be highly stable

over time. Using calcium imaging in mice, Ziv and colleagues also have reported that spatial coding in CA1 changes considerably over the course of several days (Rubin et al., 2015; Ziv et al., 2013).

Like the single-unit recording data, lesion studies also portray a complex picture. The Eichenbaum lab showed that lesions to dorsal CA1 or dorsal CA3 lesions impaired memory in an odor-guided temporal order memory task, though the effect of CA1 lesions was only apparent if there was a long 10s gap between odor presentations (Farovik et al., 2010). Work from Ray Kesner's lab suggests that dorsal and ventral CA1 might differentially support memory for the temporal order of odors vs. spatial locations—on a test of memory for odor sequences, ventral CA1 lesions impaired memory, but dorsal CA1 lesions only caused a mild impairment (Kesner et al., 2010). On a variant of the radial arm maze task that required memory for temporal and spatial information, however, dorsal CA1 lesions impaired performance (Gilbert et al., 2001).

Little is known about the mechanisms for temporal memory in human hippocampal subfields, but a recent fMRI study by Halle Dimsdale-Zucker and I (Dimsdale-Zucker et al., 2018) suggests that CA3 and CA1 might be sensitive to temporal context in different ways (Figure 2). In this study, participants encoded lists of objects presented in virtual-reality movies that depicted navigation through two different houses (Figure 2A). During scanning, they were tested on objects from the study phase, and activity patterns during recollection of studied objects were used to determine the extent to which hippocampal subfields represent information about the spatial (i.e., which house) and temporal (i.e., which movie) context in which each object was encountered. As shown in Figure 2B, CA1 appeared to assign similar representations to items encountered in the same episode (i.e., items encountered close together in time),

whereas a combined CA2/CA3/Dentate Gyrus [DG] region appeared to hyper-differentiate representations of items encountered in the same episode. Although this pattern of results seems counter-intuitive, it makes sense when one considers that successful performance on a recognition memory test requires one to learn distinctive information about each individual object—possibly supported by hyper-differentiation of items from the same context in CA2/CA3/DG—along with information about the temporal context in which the object was encountered—possibly supported by temporal context-based generalization in CA1.

Considered collectively, the results from lesion, single-unit recording, and fMRI studies do not support any simple theory of the roles of hippocampal subfields in terms of “time.” I suspect that the best conclusion to be drawn from the research to date is that it may be overly simplistic to assume that time cells, temporal drift in spatial coding, lesion effects on complex sequence memory tasks, and fMRI studies of episodic memory all reflect the same hippocampal computations. Instead, the relative roles of different subfields might be driven by subtle task-specific factors that drive different kinds of computations (Kesner and Rolls, 2015).

#### Is hippocampal representation of time shaped by cortical representations of events?

Although much of the work on temporal representation by the hippocampus rests on the assumption that time is processed in a continuous manner (Howard et al., 2005), a growing body of evidence suggests that humans do not process time in a continuous manner, but rather that they segment the stream of experience into relatively discrete episodes or “events” (Kurby and Zacks, 2008). Considerable evidence suggests that the boundaries between events are psychologically meaningful—episodic memory is relatively impaired when one must retrieve information from a previous event, relative to retrieval of information from the current event,

even when controlling for the passage of time (Ezzyat and Davachi, 2011; Swallow et al., 2011; Swallow et al., 2009). Hippocampal activity is usually (Baldassano et al., 2017; Ben-Yakov et al., 2013; Chen et al., 2017; Ezzyat and Davachi, 2014; Hsieh et al., 2014), but not always (Ezzyat and Davachi, 2011), influenced by event boundaries. At present, we don't know much about what this means—although event boundaries affect hippocampal activity, this doesn't mean that the hippocampus performs the critical computations for event segmentation, nor does it mean that the hippocampus represents event content.

One source of confusion in this literature is that research on the role of the hippocampus in event segmentation has proceeded without reference to any theory of how events are represented. Although one can construct experiments in which transitions between item categories (Axmacher et al., 2010; DuBrow and Davachi, 2014), encoding tasks (Polyn et al., 2009b), or sequences of items (Hsieh et al., 2014) are manipulated in order to elicit prediction errors--and therefore event boundaries (Zacks and Swallow, 2007)—little thought is given to the meaning of “events” in these paradigms. Real-world events have structure and meaning, and to date, cognitive neuroscience has had little to say on the subject.

For most adults, experiences do not occur in a passive vacuum—instead, incoming experiences are interpreted with respect to structured knowledge about general classes of events, termed “event schemas”<sup>7</sup> (Hard et al., 2006). An event schema can serve as a scaffold to enable

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<sup>7</sup> Unfortunately, the term “schema” has been used to refer to very different theoretical constructs, including simple associations, collections of features, concepts and categories, and structured knowledge. I use “event schemas” in reference to a particular kind of structured knowledge about events that specifies roles for particular individuals and the relationships between them in a particular place and situation. I believe that the neural representation of event schemas is likely to differ from the representation of knowledge about people (which might depend on interactions between the Anterior Temporal Lobe and hippocampus) or representations of context-dependent rules (which might depend on interactions between Prefrontal Cortex and hippocampus).

retrieval and reconstruction of past events, rapid encoding of new events, and predictions about future events (Cohn-Sheehy and Ranganath, 2017). For example, after attending a baseball game, you can develop a schema that specifies roles (e.g., pitcher, batter, umpire, etc.) and the sequence of events that is likely to unfold (e.g., pitch, hit, run to base, etc.). Your baseball knowledge can subsequently act as a scaffold, making it easier to encode information that is distinctive about future baseball games, as compared to the games that you attended in the past. It is well known that people are much better at learning and retaining information that corresponds to pre-existing schemas (e.g., Bransford and Johnson, 1972), and it is therefore reasonable to assume that schemas can fundamentally shape hippocampal event representation (Tse et al., 2007; van Kesteren et al., 2012)<sup>8</sup>.

At present, we know very little about how event structure is represented in the brain, but it is highly unlikely that all of the necessary information is centrally localized in the hippocampus. Instead, the available evidence suggests that processing of, and memory for, real events may rely on a corticohippocampal network that extends far beyond the medial temporal lobes. Research in humans (Kahn et al., 2008; Libby et al., 2012; Maass et al., 2015) and nonhuman primates (Kaplan et al., 2016; Kondo et al., 2005) suggests that the hippocampus closely interacts with a “posterior medial” (PM) network that includes the medial entorhinal cortex, parahippocampal, retrosplenial, and ventrolateral parietal cortex, as well as the precuneus

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<sup>8</sup> This point highlights a potential shortcoming of studies of place cells—these studies typically focus on animals with little to no knowledge of the world, but adult humans learn about environments and form memories that build on a vast database of prior knowledge. A real-world-naïve animal during random foraging in a novel environment might be an appropriate model for a human infant thrown into an empty room, but it might poorly approximate an adult human as it explores a new, but somewhat familiar place. For instance, when exploring a novel environment in the real world, an adult human could use knowledge of structurally similar environments (e.g., the layouts of different Safeway™ or Waitrose™ supermarkets) as a scaffold upon which to form new memories (Ekstrom and Ranganath, 2017). Work from Richard Morris’ lab suggests that, even in rats, the dynamics of hippocampal representation of spatial contexts can differ according to whether the environment conforms to prior environmental knowledge (Tse et al., 2007).

and posterior cingulate (Ranganath and Ritchey, 2012; Ritchey et al., 2015). Activity in the PM network is elicited in studies of meaningfully structured events (see Cohn-Sheehy and Ranganath, 2017, for review). For instance, the PM network appears to process information about narratives or movies across long timescales (Baldassano et al., 2017; Chen et al., 2016; Chen et al., 2017; Milivojevic et al., 2016; Milivojevic et al., 2015), and sequences of PM network activity patterns that are observed during meaningful events are recapitulated when these events are recalled (Baldassano et al., 2017; Chen et al., 2016; Chen et al., 2017). These imaging findings suggest that regions in the PM network may contribute to the representations of event schemas. If this is the case, temporal coding in the hippocampus may be shaped by activity patterns in the PM network. Consistent with this idea, sudden shifts in representations of the current event are associated with sudden increases in hippocampal activity (Baldassano et al., 2017; Ben-Yakov and Dudai, 2011). These activity increases might reflect a phenomenon similar to the kind of “global remapping”—i.e., the change in the population-level hippocampal place cell code—that occurs when an animal moves from one spatial (Muller and Kubie, 1987) or situational (MacDonald et al., 2013) context to another.

Building on ideas developed in collaboration with Sam Gershman, Ken Norman, and Jeff Zacks, I have a speculative framework for how the PM network and hippocampus might interact to support memory for temporally evolving events (see also Cohn-Sheehy and Ranganath, 2017). As noted above, an adult human can draw upon a library of event schemas acquired and refined through years of experiences. We can envision these schemas as being instantiated through connection weights amongst cell assemblies in the PM network. Many theories propose that similar objects or scenes may be represented by overlapping neural ensembles in the ventral

stream. By the same token, overlapping cell assemblies can represent different instances of the same event type (e.g., attending a Boston Red Sox baseball game at Fenway Park vs. attending a San Francisco Giants baseball game at Candlestick Park). The set of units that are active at any given time can be thought of as encoding a “situation model”—a mental representation that specifies the possible temporal, spatial, and situational relationships between people and things at the present moment (Ranganath and Ritchey, 2012). As activity progresses through the PM network over the course of the event, the moment-by-moment state of the network may be mapped to a sparse cell assembly in the hippocampus (Figure 3A). In this framework, the hippocampus is not mapping the physical world, but rather movement through a state space whose dimensions are entirely defined by the currently active situation model in the PM network (see Eichenbaum et al., 1999, for a similar view). The key prediction here is that the hippocampus may be able to map any continuous dimension of experience (Aronov et al., 2017; Eichenbaum et al., 1999; Tavares et al., 2015), but only to the extent that these dimensions correspond to the currently active schema representation in the PM network (Baldassano et al., 2017).

By reframing hippocampal processing in terms of mapping dynamic neocortical representations, we can understand the relationship between cognitive mapping and memory (Ekstrom and Ranganath, 2017). During memory formation, information about the temporal trajectory of activity through the PM network may be associated with temporally drifting ensemble activity in the medial entorhinal cortex and hippocampus (see, for example, differences between patterns of hippocampal activity between time  $n$  and time  $n+1$  in Figure 3a). When subsequently confronted with a relevant cue (e.g., seeing someone who is wearing a Boston Red

Sox baseball cap), input to the hippocampus can trigger pattern completion, which, in turn, reinstates the approximate sequence of activity states in the PM network that occurred during the original event. The critical role of the hippocampus in this scenario is to disambiguate temporally distinct events that share similar content (Wallenstein et al., 1998). Because of temporal drift in hippocampal representations, events occurring at different times (e.g., past and future Red Sox games) would be associated with different hippocampal ensembles, thereby enabling one to reinstate the pattern of activity associated with one particular event without substantial interference from related events (Figure 3B).

What about the Prefrontal Cortex (PFC)? Regions in the prefrontal cortex (PFC) are likely to play a critical role in memory for time, and it is likely that prefrontal regions interact heavily with the hippocampus and PM network in this regard (Eichenbaum, 2017b; Preston and Eichenbaum, 2013). In rodents, hippocampal subfield CA1 has a strong unidirectional projection with the medial PFC (“mPFC” Thierry et al., 2000), which may be relatively homologous to “agranular” prefrontal areas in humans, including the subgenual anterior cingulate cortex and/or ventromedial PFC in humans (Wise, 2008). The mPFC, in turn, projects to the nucleus reuniens, which projects back to the hippocampus, thus placing it in a position to modulate hippocampal activity (Ito et al., 2015). In humans, much of the PFC is categorized as “granular” cortex (Fuster, 1989), and these areas might not have a homologue in rodents (Wise, 2008). Interactions between granular prefrontal areas and hippocampus might be mediated by entorhinal, perirhinal, parahippocampal, and retrosplenial cortex (Aggleton, 2011; Ranganath and Ritchey, 2012).

Consistent with the anatomy, available evidence indicates that regions in PFC, like hippocampus, contribute to encoding of, and memory for, temporal context. Recent work has

demonstrated the existence of time cells in the rodent mPFC and in lateral PFC regions in monkeys (Tiganj et al., 2018; Tiganj et al., 2017). Although little is known about potential differences in temporal processing between mPFC and orbital or lateral PFC—in particular, few studies have systematically investigated effects of mPFC lesions in humans—lesion studies across species generally suggest that both lateral PFC and mPFC support memory for temporal order. For instance, Devito and Eichenbaum (Devito and Eichenbaum, 2009) found that mPFC lesions in mice impaired memory for the order of items in a sequence. In humans (Milner et al., 1991; Shimamura et al., 1990) and monkeys (Petrides, 1991), lateral prefrontal lesions severely impair temporal order memory. Human neuroimaging studies, in turn, have shown that lateral prefrontal activity is enhanced during successful encoding (Jenkins and Ranganath, 2010; Jenkins and Ranganath, 2016) and retrieval (Cabeza et al., 1997; Zorrilla et al., 1996) of temporal order information.

Although there are significant parallels between the functional properties of the hippocampus and PFC, it is clear that lesions to these regions have very different effects. Humans with PFC lesions can often exhibit spared learning in situations where learning strategies are constrained and when external cues are provided during retrieval, but these measures have less of an impact for patients with hippocampal damage (Ranganath and Blumenfeld, 2008). A common interpretation of these results is that the hippocampus supports memory, whereas the PFC supports the use of information in memory to inform decisions and actions. Put another way, hippocampal neurons may represent information according to spatiotemporal context, whereas prefrontal neurons may represent information according to

relevance to actions, decisions, and goals (Ferbinteanu et al., 2006; Eichenbaum, 2017b; McKenzie et al., 2016; Preston and Eichenbaum, 2013).

Given that neurons in both PFC and hippocampus have mixed selectivity and are sensitive to behavioral context, it is likely that, in many cases, cell assemblies in these areas may be functionally intertwined. For instance, sequential firing of hippocampal cell assemblies during retrieval of a past event could trigger activation of prefrontal cell assemblies representing actions and goals that are relevant to the episodic context (Benchenane et al., 2010; Hannula and Ranganath, 2009). Conversely, during recollection of a past event, prefrontal representations of one's current goals could determine whether the hippocampus activates representations of the spatial, temporal, or combined spatiotemporal context of a past event (Copara et al., 2014; Dimsdale-Zucker et al., 2018; Kyle et al., 2015).

*A personal note*

Howard Eichenbaum was notable for the fact that he was as interested in neuropsychological and neuroimaging research on humans as he was in lesion and neurophysiology research in rats and monkeys. Howard's broad vision was evident at the Center for Memory and Brain at Boston University, where he led a cohesive, interdisciplinary group, including Mike Hasselmo (Computational Neuroscience), Chantal Stern (Cognitive Neuroscience), and Marc Howard (Cognitive Psychology and Computational Neuroscience). Beyond the Center, Howard actively sought out interactions with researchers in human cognitive neuroscience, and he organized symposia and special issues in order to promote the relevant work of many junior cognitive neuroscientists. In doing so, Howard established a scientific

community of researchers working with different paradigms, methods, and species, but bound by a shared desire to unravel the mysteries of memory. Through his leadership and mentorship, Howard had an impact on an entire generation of researchers. Howard certainly played a critical role in motivating my lab's research on the neural representation of time by the hippocampus (Hsieh et al., 2014; Jenkins and Ranganath, 2010; Jenkins and Ranganath, 2016; Roberts et al., 2017), and more generally, he encouraged me to think more deeply and more creatively about the neurobiology of memory.

Howard invited me to contribute this paper about a year ago. Unfortunately, I was not able to get a draft to him before his untimely and tragic death. His passing stimulated a number of eloquent scientific obituaries (Cohen, 2017; Hasselmo and Stern, 2017; Howard et al., 2017; Morris and McKenzie, 2017) and an outpouring of remembrances on social media. I suspect that Howard would have been content to be remembered for his work, and for the work that he inspired. The research reviewed here indicates that his legacy will live on and continue to inspire researchers in the years to come.

## Figure Captions

**Figure 1. Temporal Context, Integrative Encoding, and Sequence Representation:** (A) Howard et al. (2005) used the Temporal Context Model to estimate how learning overlapping associations can lead items to become associated with one another in the paradigm used by Bunsey and Eichenbaum (1996). A matrix illustrates similarity in model representations of six items (labeled A-F), and darker colors indicate higher similarity. Before learning (far left) representations are uncorrelated with one another, but after 1 learning trial, and especially after 5 learning trials, representations of items that were not directly encountered together became increasingly associated with another (i.e., dark squares in the off-diagonal cells) if they were linked via overlapping associations (such as C-D and then D-E). (B) Hsieh et al. (2014) scanned participants as they processed sequences of objects that were learned prior to scanning. A correlation matrix depicts the similarity of hippocampal representations between each item in the sequence, with hotter colors indicating higher similarity. In this study, items in temporally contiguous positions had greater representational similarity. This effect was not evident for random sequences of objects, suggesting that the similarity effect was driven by learning. It is possible that in the study of Hsieh et al., the hippocampus associated items in sequences due to their temporal contiguity, and in the study of Bunsey and Eichenbaum (2006), retrieved representations of temporal context from a previous experience became associated with new, overlapping experiences.

**Figure 2. Representation of Temporal Context in Subfields of the Human Hippocampus.** (A) Paradigm from Dimsdale-Zucker et al. (2018). In this paradigm, virtual reality software was used to create movies, enabling participants to passively navigate through two different spatial contexts (Encoding). At test (Object Recognition), participants were scanned while seeing items that had been encountered in previously studied movies. Representational Similarity Analysis was used to examine the similarity of hippocampal activity patterns across objects that were seen in the same spatial and temporal context (i.e., same video/same house), objects that were seen in the same spatial context but different temporal contexts (i.e., different video/same house), and objects that were seen in different spatial and temporal contexts (i.e., different video/different house). (B) In CA1 (left), activity patterns were more similar across items seen in the same spatial and temporal context than across items seen in different temporal or spatial contexts. In CA2/3/DG, however, items from the same spatial and temporal context elicited more sharply differentiated activity patterns (i.e., lower similarity) than items in different contexts. Note that, to successfully recollect studied items in this paradigm, participants needed to form distinctive representations of each studied item, and at the same time, link the items to a shared context. The neural pattern similarity results from CA1 and CA2/3/DG correspond well to these two demands.

**Figure 3. Schematic Depiction of Neocortical and Hippocampal Representations of Complex Events.** (A) Colored circles depict hypothetical activity patterns in the Posterior Medial Network (PMN) and the Hippocampus (Hipp) during encoding of three events—a Boston Red Sox baseball game (Fenway Park), a Chicago Cubs game (Wrigley Field), and a memory conference in Boston (Charles River Association for Memory). Red arrows depict the hypothetical flow of information between the PMN and Hipp at each time point, and gray arrows depict the passage of time. At time point  $n$ , patterns of activity in the PMN overlap considerably across the two baseball games, whereas the pattern is different during the memory conference. Relative to the PMN, activity patterns in the hippocampus are more sparse and they differentiate between all three events. Within a given event, however, activity patterns in both the hippocampus and PMN overlap between time  $n$  (left) and time  $n+1$  (right). (B) When information from a retrieval cue is processed by the hippocampus (seeing a person in a Boston Red Sox cap), the hippocampal activity pattern from the Boston Red Sox game can be reconstructed. This in turn triggers reconstruction of the original activity pattern in the PM network corresponding to the Boston Red Sox game, and from this point, the PM network can reinstate the sequence of events within that episode. Note that at time  $n+1$ , the PM network does not fully recapitulate the pattern of activity observed during the initial event—instead, the activity patterns reflect the overlap across the Boston Red Sox and Chicago Cubs games, as the trajectory of activity in the network tends to drift towards statistical regularities across events (i.e., recall is schema-driven).

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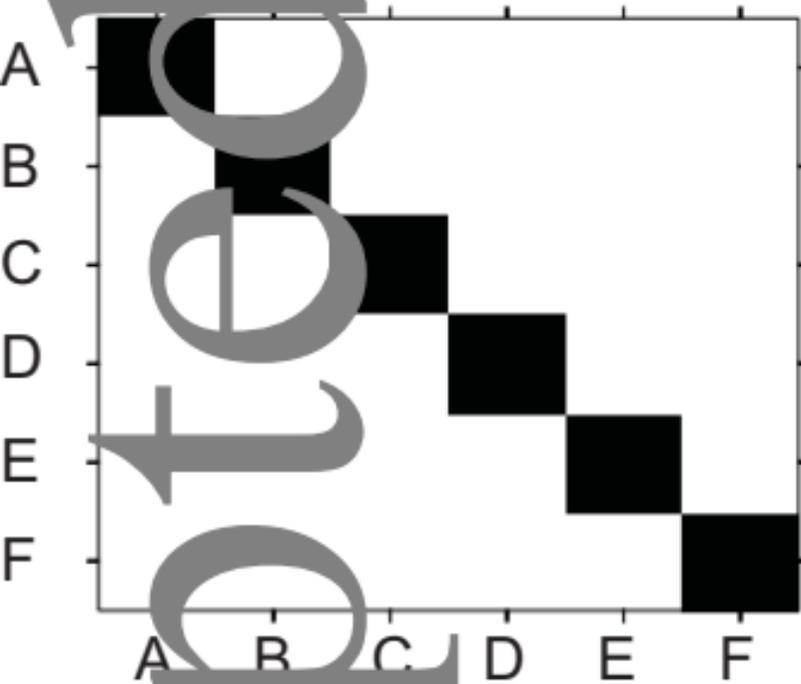
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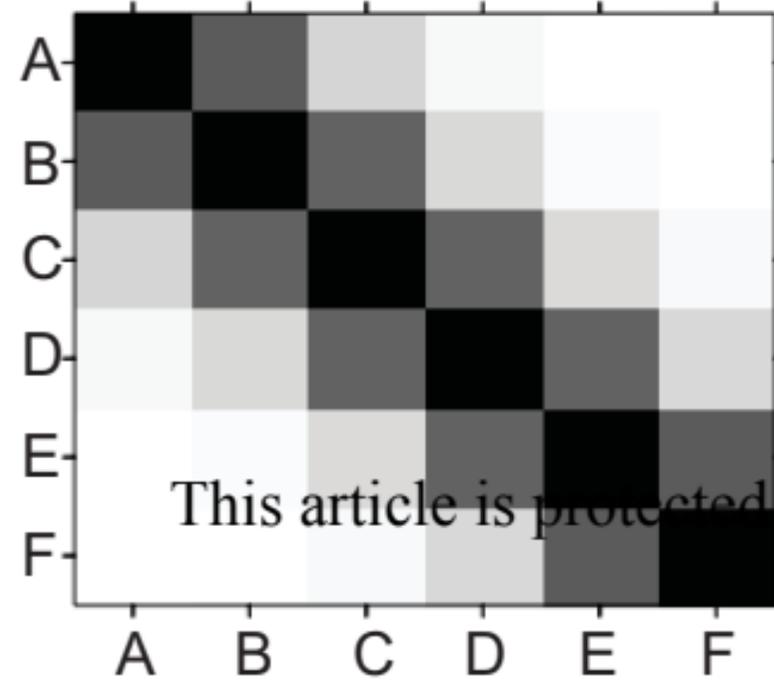
A. Howard et al. (2005):

### Similarity in Model Representations

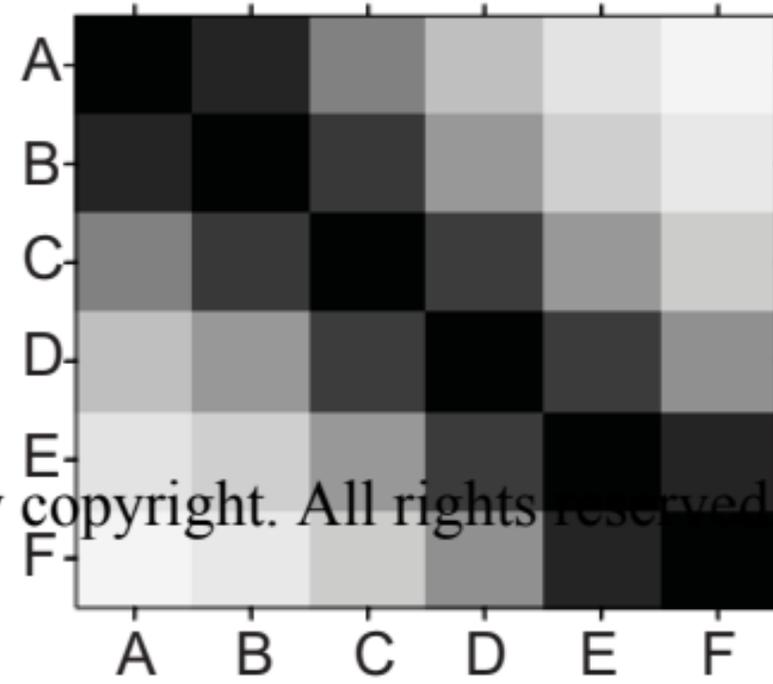
Before Learning



One Trial

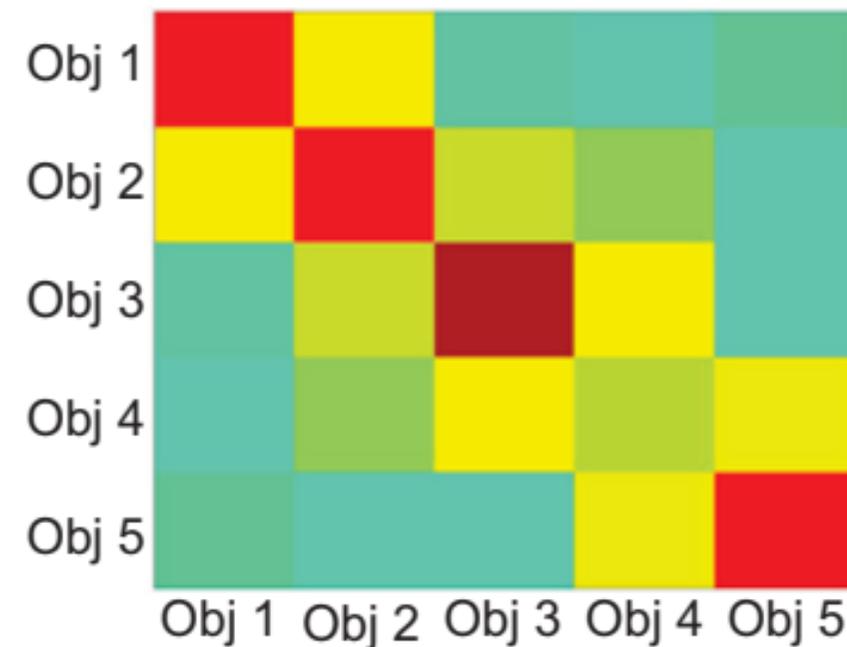


Five Trials



B. Hsieh et al. (2014):

### fMRI pattern similarity in Right Hippocampus

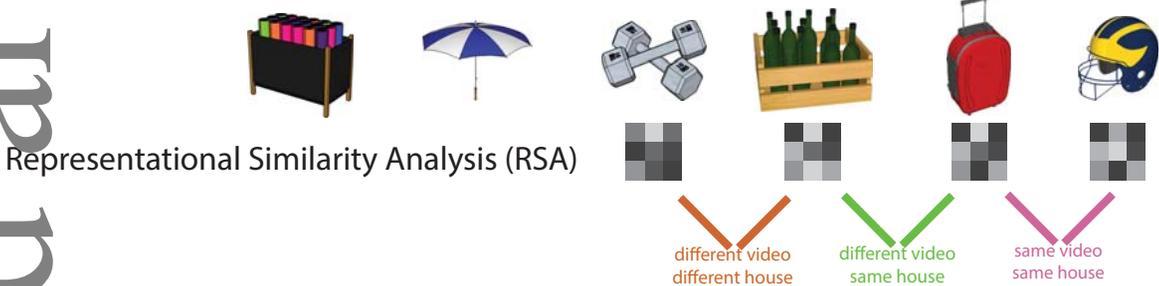


A. Dimsdale-Zucker et al. (2018) paradigm

Encoding

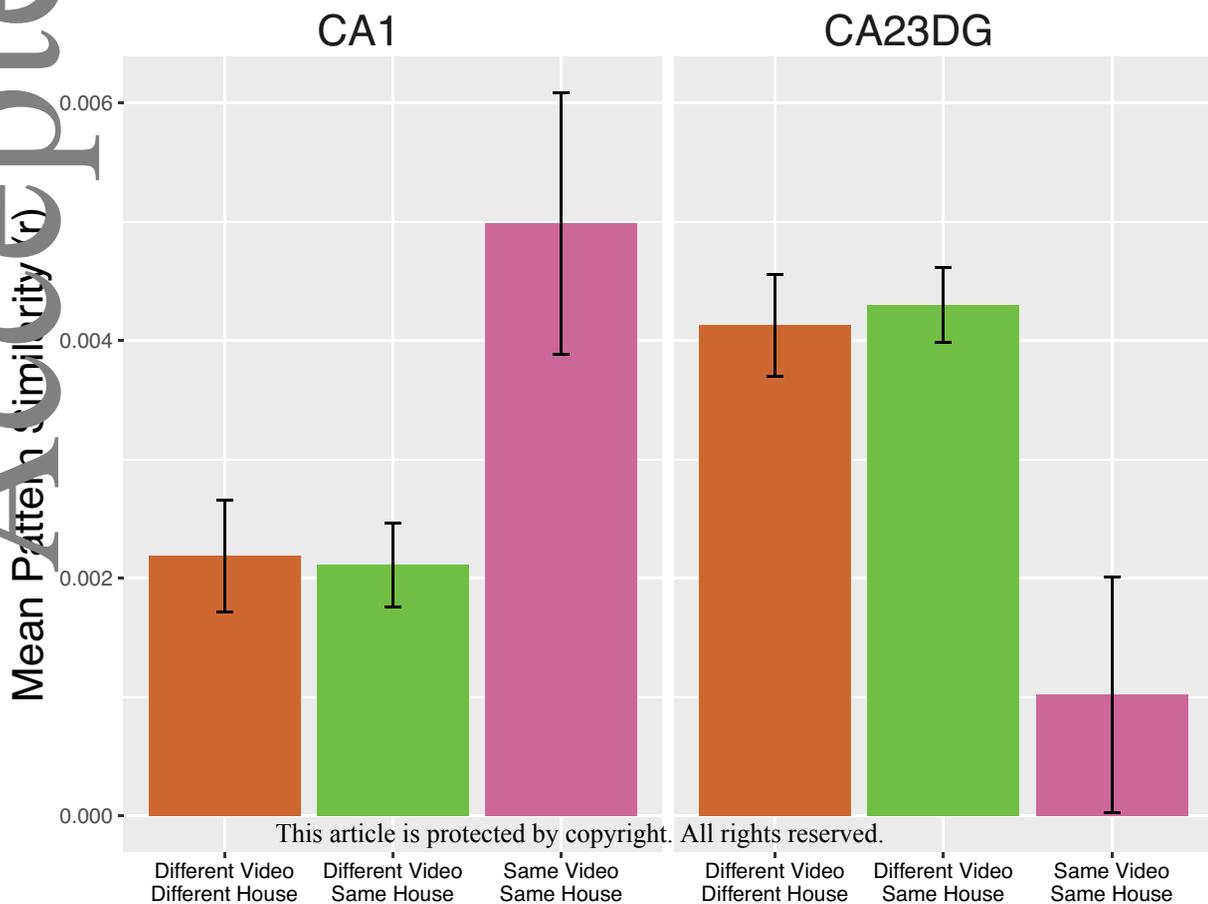


Object recognition (fMRI)



Representational Similarity Analysis (RSA)

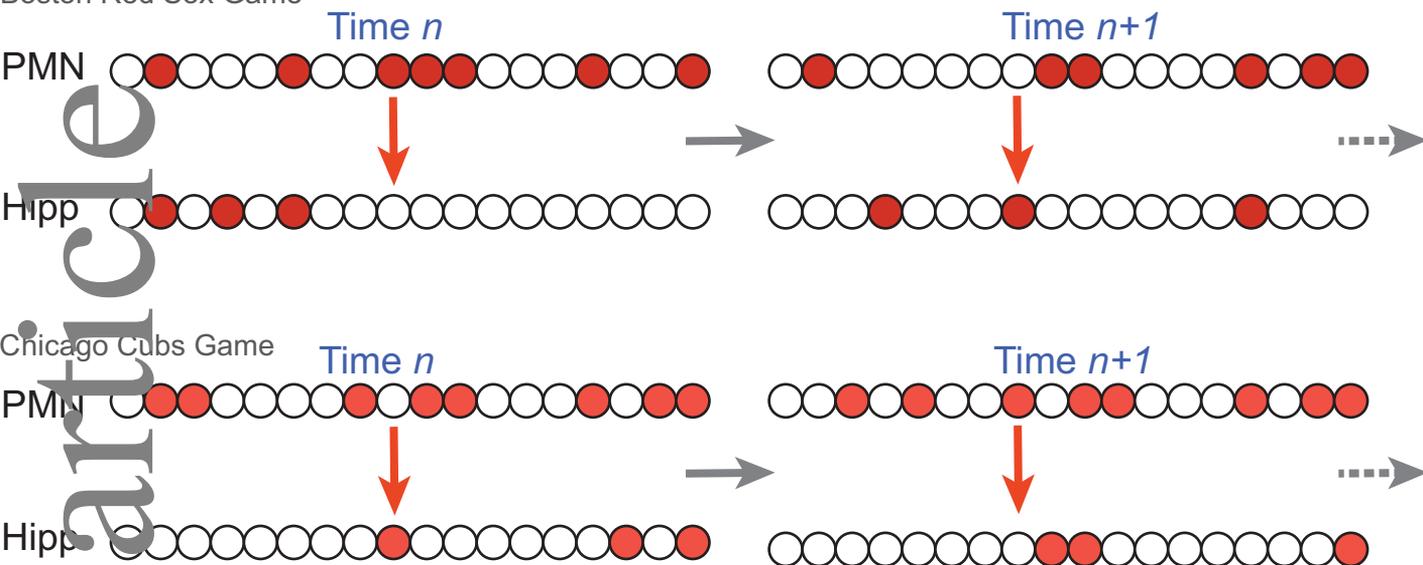
B. Activity Pattern Similarity in left Hippocampus



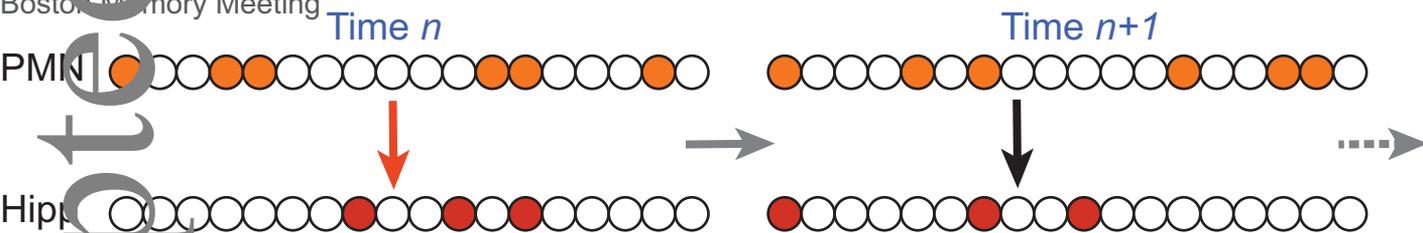
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# A. Event Encoding

Boston Red Sox Game



Boston Memory Meeting



# B. Retrieval (Pattern Completion)

Boston Red Sox Game

