Episodic memory: Neuronal codes for what, where, and when

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Abstract

Episodic memory is defined as the ability to recall events in a spatiotemporal context. Formation of such memories is critically dependent on the hippocampal formation and its inputs from the entorhinal cortex. To be able to support the formation of episodic memories, entorhinal cortex and hippocampal formation should contain a neuronal code that follows several requirements. First, the code should include information about position of the agent ("where"), sequence of events ("when"), and the content of the experience itself ("what"). Second, the code should arise instantly thereby being able to support memory formation of one-shot experiences. For successful encoding and to avoid interference between memories during recall, variations in location, time, or in content of experience should result in unique ensemble activity. Finally, the code should capture several different resolutions of experience so that the necessary details relevant for future memory-based predictions will be stored. We review how neuronal codes in entorhinal cortex and hippocampus follow these requirements and argue that during formation of episodic memories entorhinal cortex provides hippocampus with instant information about ongoing experience. Such information originates from (a) spatially modulated neurons in medial entorhinal cortex, including grid cells, which provide a stable and universal positional metric of the environment; (b) a continuously varying signal in lateral entorhinal cortex providing a code for the temporal progression of events; and (c) entorhinal neurons coding the content of experiences exemplified by object-coding and odor-selective neurons. During formation of episodic memories, information from these systems are thought to be encoded as unique sequential ensemble activity in hippocampus, thereby encoding associations between the content of an event and its spatial and temporal contexts. Upon exposure to parts of the encoded stimuli, activity in these ensembles can be reinstated, leading to reactivation of the encoded activity pattern and memory recollection.

KEYWORDS
allocentric, cognitive map, egocentric, pattern completion, pattern separation, place cell, time cell

1 | INTRODUCTION

In December 2017, a group of neuroscientists gathered in Tucson to celebrate one of the giants in neuroscience, Lynn Nadel (Figure 1). We celebrated his 75th birthday and his achievements, and the 40 years anniversary of his book "The Cognitive Map" (O'Keefe & Nadel, 1978). The ability to form episodic memories of such occasions is critically dependent on a set of interconnected brain areas including...
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encoding and retrieval of such memories (Burgess, Maguire, & O'Keefe, 2002; Hayes, Ryan, Schnyer, & Nadel, 2004; Nadel, Campbell, & Ryan, 2007; Squire et al., 1992). Even though the subjective attributes of episodic memories are not accessible in animals, there are now several experimental models where episodic-like memory can be studied in nonhumans. For example, Clayton and Dickinson (1998) showed that food caching scrub jays were able to preferentially search for fresh perishable food before searching for nonperishable food. Thus, the jays demonstrated that they knew "what" was stored "where" and "when," meeting the criteria for episodic-like memory as described by Tulving (1983). Likewise are rats able to integrate "what" and "where" information to retrieve the order of events ("when"), an ability which is lost after lesions to hippocampus, thus mimicking the amnesic syndrome first reported by Scoville and Milner in 1957 (Ergorul & Eichenbaum, 2004; Fortin, Wright, & Eichenbaum, 2004).

Scoville and Milner's reports on anterograde amnesia after removal of the hippocampal and surrounding cortical areas bolstered an interest in revealing the neural mechanisms underlying such functions. One major advance in understanding these memory circuits came with the discovery of hippocampal cells with spatial correlates and the idea that these neurons called "place-cells" were suggested to be parts of a cognitive map of space (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978). The key idea was that place cells with neighboring place fields were suggested to be linked together so that an ensemble of place cells constitute a memory system for related locations. Extensions of the cognitive map theory have been suggested to serve the basis for several other higher mental functions. One of these was the addition of a temporal dimension to the spatial codes which would result in a memory system for episodes. Such spatiotemporal maps would not only represent spatial locations (i.e., Location A is next to Location B), but also of temporal relationships (i.e., I was at Location A first, then I moved to Location B). Thus, it could be suggested that hippocampus would provide a spatiotemporal scaffold, or a coordinate system, onto which experience could be mapped and thus serve as a neural substrate for episodic memories. Implicit in these ideas and extended by others was the suggestion that episodic memories are encoded into unique activity patterns in hippocampal ensembles and/or in unique sets of neurons (Hebb, 1949; Josselyn, Kohler, & Frankland, 2015; Leutgeb et al., 2005).

As these ideas were published, several steps have been made toward a more complete insight of how episodic memories are formed and retrieved. One of these steps is the acknowledgment that a key to understanding hippocampal functions is to understand the inputs it receives from entorhinal cortex, where the majority of the cortical inputs to the system originates (Cappaert, Van Strien, & Witter, 2015). A milestone in the understanding of the functional correlates of single cells in entorhinal cortex was the remarkable discovery of grid cells and the following findings of a conglomerate of spatially modulated neurons in the medial entorhinal cortex (MEC) (Moser, Moser, & McNaughton, 2017). These different functional cell types suggested that hippocampal place cells interacted with a spatial system in MEC and that an understanding of entorhinal–hippocampal interactions is a key to the understanding of hippocampal functions.

By now, it is still not fully understood how entorhinal–hippocampal circuits contribute to encoding and recollection of episodic memories and how these memories are coded by neural activity in these circuits. However, several requirements for what an episodic memory code should look like can be made; first, the code should include not only spatial information ("where"), but also information about sequences of episodes ("when") and the content of the experience itself ("what"), so that these elements can be associated and integrated and recollected as a whole when the system is presented to a partial retrieval cue. Second, to avoid interference between similar episodes the circuits should be able to produce unique activity patterns for unique episodes. Experiences that vary in the spatial and/or temporal context in which they were acquired should result in activity patterns with minimal overlap so that similar memories are not interfering with each other during encoding or recall. Third, the code should arise instantly, supporting memory formation of one-shot experiences. Finally, the code should be able to capture relevant scales of experience, that is, different resolutions of experience should be included in the code. For instance, the memory of a single event can be used differently; in some settings it might be useful to retrieve unique and detailed features of past experiences. In other situations, it could be more useful to retrieve commonalities between memories of the past and ongoing experience. To achieve such flexibility in the retrieval process, important details and coarse-scale features of the experience should be encoded into memory in parallel.

In this paper, we review electrophysiological data recorded in rodents, shedding light on how the neural code in the entorhinal–hippocampal circuit fulfills these requirements of an episodic memory system.
2 | IMMEDIATE AND UNIVERSAL MAPS OF SPACE IN ENTORHINAL CORTEX AND UNIQUE MAPS IN HIPPOCAMPUS

Entorhinal cortex is one of the key areas in the brain contributing to spatial computations. The discovery of the grid cell paved the way for this new insight and initiated a range of new discoveries of other functional cell types contributing to the positional system of the rodent brain (Hafting, Fyhn, Molden, Moser, & Moser, 2005; Kropff & Treves, 2008; Sargolini et al., 2006; Solstad, Boccara, Kropff, Moser, & Moser, 2008) and of related activity patterns in other species such as humans (Doeller, Barry, & Burgess, 2010; Jacobs, Kahana, Ekstrom, Mollison, & Fried, 2010; Reagh & Yassa, 2014). Let us briefly review electrophysiological recordings of each specific cell type below, to illustrate the diversity of functions provided by the MEC.

First, the grid cell is characterized by activity fields distributed in a pattern of hexagons in which the smallest unit formed by the vertices is triangles tiling the entire environment (Figure 2a). Each grid cell has a slight offset, a different phase, from other grid cells so that a small population of grid cells covers all positions within an environment (Hafting et al., 2005). The activity fields are stably anchored to the environment so that grid cells constitute a metric and a coordinate system of space. How can a biological system provide such a precise coordinate system while the animal is freely moving? Models of grid cell formation suggest that grid cells are organized in continuous attractor networks where information about both the heading direction of the animal and fine-tuned speed information are needed to continuously update the locus of activity while the animal moves (Burak & Fiete, 2009; Couey et al., 2013; Fuhs & Touretzky, 2006; McNaughton, Battaglia, Jensen, Moser, & Moser, 2006). Indeed, MEC was found to contain cells signaling the head direction of the animal similar to the ones discovered by Ranck and Taube in the dorsal presubiculum over a decade earlier (Sargolini et al., 2006; Taube, Muller, & Ranck, 1990). Later, grid cells and head direction cells were found to be weakly correlated to the speed of the animal (Hinman, Brandon, Climer, Chapman, & Hasselmo, 2016; Wills, Barry, & Cacucci, 2012). In addition, a population of cells with a linear relationship to the speed of the animal was discovered (Kropff, Carmichael, Moser, & Moser, 2015). In the latter population, firing rate increases neatly in parallel to an increase in the animal’s speed. A substantial proportion of these speed cells are fast-spiking, likely parvalbumin-positive interneurons (Ye, Witter, Moser, & Moser, 2018). Accordingly, the precise firing of both grid cells and speed cells is lost when parvalbumin interneuron activity is blocked (whereas other functional cell types such as the head direction cells are intact) (Miao, Cao, Moser, & Moser, 2017). Likewise, the grid signal is impaired when head-direction signals are disrupted (Winter, Clark, & Taube, 2015). These findings support the idea that the precise location of the activity fields of grid cells is a result of integration of head-direction signals and continuous information of the speed of the animal (McNaughton et al., 2006). A positional system based on path integration mechanisms is likely to accumulate errors over time and therefore needs to be reanchored at regular intervals (Hafting et al., 2005; McNaughton et al., 2006), for instance, when the animal is perceiving familiar environmental cues such as borders or landmarks (Campbell et al., 2018; Hardcastle, Ganguli, & Giocomo, 2015). In line with these ideas, border cells signaling positions close to boundaries such as walls have been identified in MEC and likely play a role for anchoring the activity of spatially modulated cells to the boundaries of an environment (Solstad et al., 2008). Hence, grid cells are likely a result of integration of self-motion signals continuously corrected for by environmental cues. Accordingly, when an animal is placed in an environment, grid cells instantly display their characteristic tessellating grid pattern and are thus meeting the requirement for a spatial code supporting memory formation of one-shot episodes.

The different groups of spatially modulated neurons are universal across environments. In navigating rats, a grid cell in one environment is always a grid cell in other environments. However, grid cells rotate and shift the grid location, that is, reanchor their x-y coordinates and orientation between environments. Grid cells with similar spacing between their grid fields maintain coherent spatial relationships to each other in all environments, so that two cells will keep their spatial offset between their firing fields in all environments (Fyhn, Hafting, Treves, Moser, & Moser, 2007; Hafting et al., 2005; Stensola et al., 2012). Similar coherencies also hold for head direction cells and border cells, so that if the environment is rotated 90°, all cells will show similar rotation of their head direction or border preference (Boccara et al., 2010; Sargolini et al., 2006; Solstad et al., 2008). Next, speed cells recorded in one environment can be used to decode the speed of the animal in another environment, thus speed cells maintain their linear firing relationship to speed across environments (Kropff et al., 2015). Accordingly, the networks of spatially modulated neurons in MEC provide an immediate, universal, and robust code for all environments.

2.1 | Entorhinal cortex and hippocampus represent space at multiple resolutions

Spatial cells in entorhinal cortex and hippocampus display different sizes of their place fields. These differently “sized” spatial-selective cells are distributed topographically throughout the long axis of entorhinal cortex and hippocampus; cells with smaller fields located most dorsally, whereas more broadly tuned cells are located in more ventral parts. In essence, grid cells, head direction cells and place cells with wider tuning curves are located in more ventral portions of entorhinal cortex and hippocampus (Barry, Hayman, Burgess, & Jeffery, 2007; Brun et al., 2008; Giocomo et al., 2014; Hafting et al., 2005; Killian, Jutras, & Buffalo, 2012; Kjelstrup et al., 2008; Stensola et al., 2012). Compared to dorsally recorded neurons, more ventrally recorded grid cells display larger field widths and a near 10-fold increase in interpeak distance and ventrally recorded place cells in hippocampus display a field width up to 10 m when recorded in large environments. Intriguingly, these data are paralleled with data obtained from humans; increased activity in anterior hippocampus is related to processing and retrieval of large-scale locations, whereas activity in posterior hippocampus is related to processing and retrieval of fine-
grained details of the environment and associated cues (Evensmoen et al., 2013; Evensmoen et al., 2015; Nadel, Hoscheidt, & Ryan, 2013). Thus, the spatial signal in MEC and hippocampus show a clear topography. This observation indicates that the more dorsal/posterior parts are more involved in processing details of space, whereas ventral/anterior parts are more involved in representing global spatial layouts. In the context of episodic memory, such a parallel multi-scale representation of an environment is important mainly because the spatial code captures several relevant scales which episodes could be associated to (Erdem & Hasselmo, 2014; Marchette, Ryan, & Epstein, 2017). Dorsal/posterior portions of rodent/primate hippocampus contain a narrow-meshed coordinate system that captures details of an environment, whereas ventral/anterior hippocampus contains a wide-meshed coordinate system that captures larger spaces such as whole environments (Komorowski et al., 2013; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). Thus, the memory of an event can be generalized to large spaces.
and whole environments due to the large-sized place fields that covers large areas. On the other hand, events happening at two nearby locations can be separated due to neurons with small-sized place fields.

2.2 | Unique maps in hippocampus

MEC contains spatially modulated cells providing coherent and always active universal maps. These maps are different from those formed by hippocampal place cells (O'Keefe & Conway, 1978; O'Keefe & Dostrovsky, 1971; O'Keefe & Burgess, 1998). Place cells turn on/off in different environments or if active in multiple environments the place fields are not located in comparable locations (Figure 2c). Thus, place cells provide statistically independent ensemble activity in separate environments. This phenomenon, commonly referred to as global remapping, has been suggested to reduce the risk for memory interference (Alme et al., 2014; Leutgeb et al., 2005; Muller & Kubie, 1987), as each environment has its distinct signature map which is recollected within a theta cycle (Jezeek, Henriksen, Treves, Moser, & Moser, 2011). Thus, the environment-specific ensemble activity in hippocampus provides a unique internal map of space and therefore offers a neural substrate which could associate events to a unique location.

How can a universal coherent map, including grid cells with repetitive and symmetrical activity patterns contribute to the formation of unique ensemble activity patterns of place cells in the downstream structure hippocampus? It turns out that grid cells are organized in distinct modules (Figure 2a), where each module contains grid cells with similar spacing between their firing fields and a similar orientation of the grid pattern relative to the environment (Gu et al., 2018; Stensola et al., 2012). If these modules orient and anchor independently to landmarks, a linear summation of grid cells from different modules would, in different environments, create unique ensemble activity in the hippocampus (Fyhn et al., 2007; McNaughton et al., 2006; Solstad, Moser, & Einevoll, 2006; Stensola et al., 2012). Just as each of the wheels on a combination lock can be turned independently from each other and thereby make thousands of unique combinations, a few differently sized grid modules, each with independent anchoring to the environment would be sufficient to create unique ensemble activity for a large number of environments in the downstream structure hippocampus (Figure 2b). Converging inputs from multiple independent grid modules provide a potential mechanism for remapping of hippocampal ensemble activity, thus forming unique ensemble activity of place cells in each environment (global remapping) (Monaco & Abbott, 2011; Solstad et al., 2006; Sreenivasan & Fiete, 2011; Stemmler, Mathis, & Herz, 2015). It should also be noted that place cells receive inputs from all classes of spatially modulated neurons in MEC (Ye et al., 2018; Zhang et al., 2013) and place cells have been reported to be responsive to environmental cues such as borders or objects (Deshmukh & Knierim, 2013; O'Keefe & Burgess, 1996). These observations clearly indicate that also other functionally defined cell groups may contribute to the generation of unique place cell ensemble activity in hippocampus. It has been suggested that the formation of unique ensemble activity is the neural substrate of episodic memories and that the formation of such ensembles is dependent on long-term potentiation. This idea is supported by experiments where plasticity in hippocampal synapses were saturated by high-frequency stimulations (Brun, Ytterbo, Morris, Moser, & Moser, 2001); in well-trained rats such stimulations deteriorated performance in a spatial memory task, suggesting that memory retrieval is dependent on the pattern of synaptic weights in these ensembles.

Taken together, entorhinal–hippocampal circuitry fulfills the requirements of a system supporting the spatial component of episodic memories. First, the spatial code in entorhinal cortex and hippocampus appears immediately after introduction to a novel environment and covers relevant scales of space, thereby providing an instant, universal metric which could be used for one-shot encoding of episodes. Next, the spatial code in hippocampus is unique in different environments, thus providing environment-specific maps which events can be associated with. The unique hippocampal maps are possibly achieved by combining multiple independent scales of space in MEC. Thus, MEC constitutes a perfect system for generating hippocampal cognitive maps in which objects, landmarks, and events can be mapped into.

3 | POPULATION ACTIVITY IN ENTORHINAL CORTEX AND HIPPOCAMPUS VARY WITH TIME

Episodic memories are organized not only in space but also in time. Encoding “when” an experience happened relative to other events is essential for successful retrieval. In humans, this ability is dependent on an intact hippocampus (Dede, Frascino, Wixted, & Squire, 2016; Mayes et al., 2001) which shows increased activity when subjects recall the temporal order of events (Kalm, Davis, & Norris, 2013; Lehn et al., 2009). Hippocampal-lesioned rats are similarly impaired in determining the duration of an event or the sequence of events (Fortin, Agster, & Eichenbaum, 2002; Jacobs, Allen, Nguyen, & Fortin, 2013). The introduction of a temporal gap between a conditioned and unconditioned stimulus or within a spatial working memory task changes the task from being insensitive to become sensitive to hippocampal lesions (Ainge, van der Meer, Langston, & Wood, 2007; Jacobs et al., 2013; McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998). Likewise, inactivation of entorhinal neurons in rodents also disturbs time perception (Robinson et al., 2017; Suh, Rivest, Nakashiba, Tominaga, & Tonegawa, 2011). These observations suggest an important role for the hippocampus and entorhinal cortex in sorting and tagging events which are separated in time.

How does hippocampus code the temporal relationship of events? Electrophysiological recordings have revealed that hippocampal neurons are organized into ensembles where the activity of individual cells can be temporally organized. For instance, sequences of place cells are compressed within theta cycles so that place cells coding passed or upcoming locations are active during the same theta cycle. Importantly, the order of active cells during each of these cycles reflects the order each of the place fields are visited (O'Keefe & Recce, 1993; Skaggs, McNaughton, Wilson, & Barnes, 1996). This phenomenon commonly referred to as “phase precession” is also present in cells representing
nonspatial features of experience (Lenck-Santini, Fenton, & Muller, 2008; Pastalkova, Itskov, Amarasingham, & Buzsaki, 2008; Terada, Sakurai, Nakahara, & Fujisawa, 2017) suggesting that chunking neuronal activity into temporally ordered ensembles is a fundamental organization principle of hippocampus (Jensen & Lisman, 1996; Skaggs & McNaughton, 1996).

In addition to organizing neural ensembles into sequences within a theta cycle, hippocampal neurons also code for temporal progression within episodes. "Time cells" have receptive fields for a specific duration from an event (ranging from 0 to 20 s in experiments; Figure 3a). The activity of time cells tile an interval such as time elapsed during running on a linear track, in a running wheel or time of a delay within a working memory task (Gill, Mizumori, & Smith, 2011; Itskov, Curto, Pastalkova, & Buzsaki, 2011; Kraus et al., 2013; MacDonald, Carrow, Place, & Eichenbaum, 2013; Pastalkova et al., 2008; Redish, Rosenzweig, Bohanick, McNaughton, & Barnes, 2000; Salz et al., 2016), and is suggested to code for the temporal organization of an episode. Importantly, these time cell sequences develop and stabilize in parallel with learning, suggesting a link between the formation of time cell ensembles and memory (Modi, Dhawale, & Bhalla, 2014).

**FIGURE 3**  Time codes in hippocampus and entorhinal cortex. (a) Time cells in hippocampus tile a time interval within an episode when a rat runs on a treadmill. Each row represents the normalized firing rate of one neuron (blue, no firing; red, peak firing of that neuron) and the neurons are sorted by their peak firing time. Adapted from Kraus, Robinson, White, Eichenbaum, and Hasselmo (2013). (b) Stability of location specific activity of place cells in CA1 (red), CA2 (green), and CA3 (blue) was measured as population vector correlations between pairs of recordings. The black error bars report the mean ± SEM for pair-wise comparisons at each time interval. Over time the population activity of CA2 (green) and CA1 neurons (red) decrease as a function of elapsed time between recording sessions. Adapted from Mankin, Diehl, Sparks, Leutgeb, and Leutgeb (2015). (c) Temporal codes in lateral entorhinal cortex. Top: experimental design; Animals ran 12 times 250 s trials in boxes with either black or white walls. Bottom: example general linear model fits for cells with selectivity for trial time (Cells 5 and 7) or session time (Cell 6), with the observed firing rate shown in grey, and predicted firing rate in blue, suggesting that the passage of time is encoded in firing rates of individual cells. (d) Two-dimensional projections of neural population responses during the experiment depicted in “a”. Axes correspond to the first two linear discriminants (LD1 and LD2; arbitrary units). The wall color of each trial is indicated by a shade of green (black walls) or purple (white walls) with progression of shade from dark to light indicating the progression of trials. Population responses showed a progression corresponding to the temporal order of the experiment. (e) Left: comparison of decoding accuracy for trial identity when the rat is either engaged in alternating left/right laps on a figure eight maze or during the 12 black/white trials-experiment (BW) depicted in “c”. Decoding accuracy for trial identity is higher during free foraging in BW than in the figure eight maze (p < .0001). Right: same as left, but for time epochs within a trial. Decoding of trial time is higher in the figure eight maze than in BW (p < 10^-10). Grey-dotted lines indicate chance levels. c–e adapted from (Tsao et al., 2018) [Color figure can be viewed at wileyonlinelibrary.com]
Intriguingly, time cells share many features with place cells. Activity of time cells, like activity of place cells, differentiates memory-based decisions by modulating their rate (Gill et al., 2011; Pastalkova et al., 2008). Like place cells, in which the place fields are reorganized after changes in the spatial layout, the receptive fields of time cells are reorganized if the duration of the mapped interval is changed (Kraus et al., 2013; MacDonald et al., 2011; MacDonald et al., 2013; Pastalkova et al., 2008). Thus, as distinct place cell ensembles are active during exploration of different environments (‘remapping’), distinct ensembles of time cells are active during delay periods initiated by different conditions (‘retiming’). These findings are paralleled by experiments in humans; during recall of sequences, hippocampus display activity patterns that are specific to unique sequences, thus resembling the retiming phenomena of time cells in rodents (Hsieh, Gruber, Jenkins, & Ranganath, 2014; Thavabalasingam, O’Neil, Tay, Nestor, & Lee, 2019). Importantly, retiming in both humans and rodents develops with acquisition and supports the role of hippocampus in separating different memories also in time (Gill et al., 2011; Kalm et al., 2013).

As grid cells in MEC are thought to contribute to place cell formation in hippocampus, sequence-related activity in the form of time cells in hippocampus has been shown to rely on MEC activity. Inactivation of the latter neurons result in a degradation of time cells in hippocampus (Robinson et al., 2017). Accordingly, a large set of MEC neurons, including grid cells, have been shown to code for time similarly to time cells in hippocampus (Heys & Dombeck, 2018; Kraus et al., 2015). Taken together, these findings suggest that features of time cell activity in hippocampus and MEC share many features with place and grid cell activity, suggesting shared mechanisms for the generation of place and time cell codes in hippocampus.

While time cells in hippocampus keep track of the temporal progression within an event, hippocampal ensembles also keep track of time at longer timescales by a slow drift of their population activity over time (Figure 3b) (Folkerts, Rutishauser, & Howard, 2018; Howard, Viskontas, Shankar, & Fried, 2012; Manns, Howard, & Eichenbaum, 2007; Mau et al., 2018; Ziv et al., 2013). This phenomenon is particularly prominent in Cornu Ammonis (CA)2, and to some extent in other hippocampal and parahippocampal areas such as CA1 and MEC (Diehl, Hon, Leutgeb, & Leutgeb, 2019; Mankin et al., 2015). In these areas, the population of neurons display a variable degree of stability; some neurons maintain their receptive field and firing rate whereas other neurons vary their firing rates and/or shift their receptive field. This mix of stable and unstable codes results in population activity that slowly drifts over hours, so that two events happening close in time are represented by more similar ensemble activity compared to two events happening at distant time points. This phenomenon is in accordance with the hypothesis that temporal relationships of episodes are encoded by gradually changing representations in CA2 and CA1 so that the duration of an episode or durations between episodes can be read out by the dissimilarity of ensemble activity (Figure 3b) (Mankin et al., 2015). These ideas are supported by experimental evidence; if rats or humans sample a sequence of stimuli and afterwards have to decide which of two of the stimuli were sampled most recently, there is a significant difference between error and success trials; during correct trials the change of population activity is larger compared to in error trials (Jenkins & Ranganath, 2016; Manns et al., 2007). Next, functional magnetic resonance imaging (fMRI) patterns of activity is more similar for pairs of stimuli which is remembered as being close in time (Ezzyat & Davachi, 2014). Together, these studies suggest that continuously changing population activity is involved in coding passage of time.

An unstable and drifting signal might seem counterintuitive in the context of a system used for providing cognitive maps. A cognitive map should remain stable across the same exposure to sensory stimuli, which is partly not the case for place cells in some regions of the hippocampus (Mankin et al., 2012; Mankin et al., 2015). In an episodic memory context, a mix of stable and unstable activity patterns might be necessary to map temporal relations of experiences. Continuously varying ensemble activity would implicate that memorable events experienced at two different time points are allocated to partly different population activity, where time-dependent unique activity patterns provide a temporal context for specific time points (Cai et al., 2016; Howard & Kahana, 2002). The idea is that neurons that stably represent prominent features of the experience are associated with neurons providing a temporal tag for that experience and together they form a unique representation of a particular experience. These ideas are supported from experiments in rodents. It is now established that episodic memories, such as the memory of being foot-shocked, are partly allocated to hippocampal neurons that transiently express c-fos during encoding, and that memory retrieval can be elicited by experimentally inducing activity in these cells (Liu et al., 2012). Interestingly, the same neurons display greater drift compared to c-fos negative cells (Tanaka et al., 2018), suggesting a link between drifting cells and their role in providing unique ensemble activity during encoding of one-shot episodic memories. How could such a system function during natural memory recall? When the subject is exposed to a retrieval cue, cells which stably represent features common to the retrieval cue and the encoded experience would lead to pattern completion processes in hippocampus which would reinstate the activity pattern at encoding, including the associated neuronal temporal context (Howard, Fotedar, Datey, & Hasselmo, 2005). Data from single-cell recordings and fMRI in humans suggest that this is the case; during successful recall, hippocampal ensemble activity reinstates the activity pattern that was present during encoding (Folkerts et al., 2018). Next activity patterns for two events that are remembered as close in time are more similar compared to two events that are remembered to be separated by a longer time interval on timescales ranging from minutes to months, suggesting that the temporal context had drifted between encoding of the two events and that the temporal context is retrieved during recall (Deecke, Bellmund, Navarro Schroder, & Doeller, 2016; Nielson, Smith, Sreekumar, Dennis, & Sederberg, 2015). Thus, two similar episodes experienced at the same place could be separated by a temporally varying signal and encoded onto distinct ensemble activity (Figure 5).
Together these studies suggest that signals varying over time are essential for allocating memories of one-shot experiences into unique activity patterns.

Sequential firing of different cells during learned time intervals and continuously drifting population representations are pronounced temporal signals in the hippocampus. However, both of these temporal representations may partly fulfill the requirements for a temporal code supporting the encoding of episodic memories. Time-cell sequences develop with learning and therefore does not fulfill the requirement of an instantaneous time signal needed to capture one-shot episodes. The drifting representations of CA2 and CA1 arise spontaneously as required; however, the temporal drift occurs on the scales of hours that is not necessarily sufficient to capture the details of a typical episode. Recent electrophysiological studies in rodents and fMRI studies in humans suggest that a likely source of temporal information is found in the lateral entorhinal cortex (LEC) (Bellmund, Deuker, & Doeller, 2018; Montchal, Reagh, & Yassa, 2019; Tsao et al., 2018). We recorded LEC neurons while rats were freely foraging in an arena for 12 trials each lasting about 4 min (Figure 3c). In such a setup, we hypothesized that the rat would treat each of the 12 visits to the arena as distinct episodes and would serve as a reference frame for putative temporal representations. Interestingly, about 20% of the recorded neurons in LEC displayed ramping activity through the experiment (Figure 3c). As a new trial was initiated, neurons started out with a certain firing rate and from then on displayed a tendency to either increase or decrease their firing rates as time passed by. These ramping cells displayed two important features. First, the change in firing rates displayed a wide range of time constants as some cells ramped up/down faster than others. Such a feature has been proposed to be sufficient for the formation of cells responsive at certain time intervals, like time cells observed in hippocampus and MEC (Howard et al., 2014; Kraus et al., 2015; MacDonald et al., 2011). Secondly, ramping cells were reset by different “landmark” events. Some cells reset when the animal was moved from the holding pot and into the arena, whereas others did not reset to events related to our experimental design. These observations suggest that different cells had different triggers for resetting of their ramping activity. Population activity of LEC cells could thereby provide a unique tag for any time point in the experiment. Time epochs ranging from seconds, minutes, and possible also hours could be decoded from LEC population activity (Figure 3d).

Intriguingly, the temporal signal in LEC is dependent on ongoing experience. While rats were running on a figure eight maze, where the nature of the task result in repetitive behavior, neural activity could be used to decode time across the experiment (i.e., different laps) far less accurately, whereas the ability to decode time within each of the laps improved (Figure 3e). Consequently, activity from the recorded cells could not be used to differentiate early laps from late laps, but could instead be used to differentiate events at very short time scales. Thus, the temporal signal in LEC changed when the animal was engaged in different tasks. During free exploration, LEC population activity continuously changed, whereas activity was anchored to temporal landmarks when engaged in the structured and repetitive tasks. This difference is presumably linked to changes in inputs from higher order sensory areas, areas devoted represent behavioral and internal states of the animal, and/or inputs from hippocampus which likely is more structured and repetitive during the memory task (Tsao, 2017; Tsao et al., 2018). These observations imply that LEC derives time directly from the structure of ongoing experience. Just as the spatially modulated cells in MEC are continuously updated by self-motion signals and reset by environmental cues, the flow of experience moves and resets population activity in LEC, suggesting a strong link between “what” a subject experiences and the encoding of temporal information (“when”).

These features make the temporal signal in LEC particularly well suited for coding “episodic time”; the order of events within experience. It arises spontaneously and covers the temporal granularities expected of a code supporting encoding of episodic memories. These findings are paralleled by reports from human fMRI studies reporting that activity patterns in entorhinal cortex, including its lateral part, continuously change during encoding of an experience and that the amounts of change during encoding is related to later recalled duration of the same experience (Bellmund et al., 2018; Lositsky et al., 2016). Even though it is currently not known how the temporal signals in the entorhinal–hippocampal circuits are related, it is tempting to suggest that both the formation of time cell sequences and the drifting activity in hippocampus could be driven by the temporal signals in LEC which covers both of these scales. Thus, it could be hypothesized that the temporal code in LEC, driven by the continuous flow of experience, could elicit sequential activity patterns in hippocampus covering multiple temporal scales.

ENTORHINAL CORTEX FILLS MEMORIES WITH CONTENT

Our memories are populated with content such as sensory cues, objects, and emotions. In experimental settings, content of an experience is often operationalized by presenting objects or sensory stimuli while relating neuronal responses to these stimuli. How does neuronal activity in entorhinal cortex represent such stimuli? Cells in the entorhinal cortex of monkeys and in rat and human LEC are preferably active when the animal encounters objects or cues (Deshmuk & Knierim, 2011; Kreiman, Koch, & Fried, 2000; Neunuebel, Yoganarasimha, Rao, & Knierim, 2013; Quiroga, Reddy, Kreiman, Koch, & Fried, 2005; Reagh et al., 2018; Reagh & Yassa, 2014; Suzuki, Miller, & Desimone, 1997). More specifically, a population of rat LEC neurons is active when the animal is in close vicinity of objects (Deshmukh & Knierim, 2011) and a small proportion of LEC neurons signals where objects have previously been localized (Tsao, Moser, & Moser, 2013). The presence of these “trace cells” suggest that LEC codes object information within a spatial framework and that object-place associations exist already at the level of LEC.

There exists even more complex object-related activity patterns in entorhinal cortex. Although a subset of LEC cells code the direction to landmarks referenced to the animals head (egocentric) (Wang et al., 2018), object-vector cells in MEC signal the direction and distance to the object referenced to a global environmental bound axis irrespective of the head direction of the animal (allocentric) (Høydal,
Skytøen, Andersson, Moser, & Moser, 2019). Thus, as an object is moved, the firing field moves with the object so that the vectorial relationship between the object and the firing field is maintained. Intriguingly, the activity pattern of object-vector cells is instant and universal; similar to the other spatially modulated cells in MEC. Object-vector cells appear immediately after the animal is introduced to the environment and show generalized responses to all objects independent of their identity. Thus object-vector cells conjunctively signal the presence of objects and the position of the animal relative to objects. In more realistic environments filled with multiple objects, the combined activity of multiple object-vector cells with different directional and distance preferences could potentially signal the spatial arrangement of objects in an environment. In an environment with multiple objects there will, for each spatial constellation of objects, be a unique combination of active object-vector cells in any position the animal occupies, likely supporting the ability to use object constellations to find hidden food (Collett, Cartwright, & Smith, 1986). Thus, single object-vector cells signal the position of the animal relative to any object whereas an ensemble of object-vector cells may signal the position of the animal relative to a specific spatial configuration of objects. These findings are likely related to findings in humans; a subset of cells in human entorhinal cortex display selectivity to specific scenes filled with landmarks (Mormann et al., 2017).

In parallel to these findings in entorhinal cortex, a subset of hippocampal cells has been shown to signal location close to objects (Battaglia, Sutherland, & McNaughton, 2004) or distance to objects (landmark-vector cells) (Deshmukh & Knierim, 2013). Even though a limited number of such object-landmark cells have been described, the data available suggest that such responses develop over time after an object is introduced to the environment and only a minority of the objects elicit a response. The landmark-vector cells in hippocampus, in contrast to object-vector cells in MEC, seem therefore to be dependent on experience and signal the position of the animal relative to unique sets of objects. These findings suggest that the object-vector cells in MEC are likely entraining landmark-vector cells in hippocampus. Moreover, they suggest that an immediate representation of the position of an animal relative to objects is likely combined with information of object identity in hippocampus so that spatial relationships to unique landmarks can be encoded, and thus providing a possible mechanism for how events are mapped relative to identified landmarks. Together, these observations of object-responsive cells in entorhinal cortex and hippocampus could underlie the ability to use positions relative to objects, for instance to localize a hidden food storage (Collett et al., 1986).

Information from any sensory system is directed to the entorhinal–hippocampal system (Burwell & Amaral, 1998), and memory retrieval can be cued by all types of sensory stimuli. As described in Proust’s (1913) novel, the taste and smell of a Madeleine cake dipped in tea sent the main character back to his childhood where he had dipped the cake in tea at visits at his aunt’s house. How do entorhinal cortex and hippocampus interact during encoding and retrieval of such memories? In Section 4.1, we use odor processing in these areas as an example for how nonspatiotemporal variables are encoded and associated with the spatial scaffold provided by the entorhinal–hippocampal circuit. We tested the example in Proust’s novel in the lab—how can odors be encoded and used as retrieval cues for memories? Igarashi, Lu, Colgin, Moser, and Moser (2014) trained animals to use odors as retrieval cues for reward-locations while simultaneously recording cells in LEC and in the hippocampus. In these experiments, Igarashi et al. observed that the proportion of odor-selective neurons in LEC increased in parallel to the acquisition of odor–reward location associations (Figure 4). A similar development was also seen in hippocampal neurons; however, the increase of odor-selective neurons in hippocampus lagged behind the development in LEC (Figure 4b,c). In addition, Igarashi et al. observed changes in the local field potential; in naïve animals, LEC and hippocampal local field potentials were uncoupled. However, in parallel to learning and in parallel to the increasing number of odor-selective LEC neurons, hippocampus and LEC developed coherent oscillatory activity in the gamma band (20–40 Hz). Thus, the proportion of odor-selective neurons first increased in LEC, whereas the number of hippocampal odor-selective neurons increased during the emergence of gamma coupling between the two regions (Figure 4c). These findings propose that stimulus associations can occur in LEC before the hippocampus, suggesting that LEC entrains hippocampus to obtain odor–place associations, somewhat similar to the suggested relationship between object-vector cells in MEC and landmark-vector cells in hippocampus. Moreover, Igarashi et al. proposed that gamma coupling is important for such encoding likely because coherent activity in this frequency range provides presynaptic and postsynaptic activity within a time window that allows synaptic strengthening to occur (Bi & Poo, 1998). Next, they also suggest that gamma coupling is important for recollection; when coherent activity was disrupted, odor maps in both entorhinal cortex and hippocampus vanished and animals searched at the wrong site for the reward.

Taken together, the odor-based retrieval of a spatial memory and the entorhinal and hippocampal codes for objects illustrate how content of experiences are represented and integrated into memory. Entorhinal cortex provides codes for sensory cues and associations between these cues. Such associations can first be observed in LEC followed by hippocampal neurons. The observation that entorhinal neurons (Aronov, Nevers, & Tank, 2017; Keene et al., 2016; Young, Otto, Fox, & Eichenbaum, 1997) and hippocampal neurons (Ho et al., 2011; Komorowski, Manns, & Eichenbaum, 2009; Leutgeb et al., 2005) can acquire selectivity to nonspatial features of experience suggests that the findings described above can likely be generalized to how information from any sensory system is coded into episodic memory. It should still be emphasized that our knowledge of how these types of representations are generated and organized in entorhinal–hippocampal circuits are still at a nascent state compared to our knowledge and ideas of how spatial codes (and to some extent temporal codes) are generated and organized in the same circuits.

4.1 | What, where, and when signals are entangled and form unique ensembles

During an experience, the brain is constantly bombarded by massive amounts of external sensory information which potentially could be
encoded and stored into memory. The binding of sensory stimuli into a cohesive and unique episodic memory likely depends on neuronal activity in entorhinal cortex that signals temporal relationships ("when"), a spatial universal metric ("where"), and the experience itself ("what"). The spatial and temporal signals arise spontaneously as a result of changes in ongoing experience; the spatial signal is likely driven by self-motion signals and updated by environmental cues along the route (such as interactions with known landmarks). Similarly, the temporal signal found in LEC depends on the content and structure of the experience, thus suggesting that the sense of time and space are subjective and depends on how the agent is experiencing and perceiving the world.

Population activity in entorhinal cortex, including the spatial signal, the temporal varying signal and signals representing sensory aspects of an experience are conveyed to hippocampus where they are stored into unique ensemble activity (Figure 5). This is likely achieved due to hippocampus’ ability to orthogonalize the pattern of activity against already encoded patterns (pattern separation) (Leutgeb, Leutgeb, Treves, Moser, & Moser, 2004), in addition to synaptic modifications due to spike-time-dependent plasticity and due to hippocampal ability to consolidate memories by its capacity to replay activity (Bi & Poo, 1998; McNaughton & Morris, 1987). The result of these processes is unique ensembles of place cell maps and time cell sequences which have been suggested to conjunctively represent a memory trace of space, time, and other aspects of experience (Hasselmo, 2009). When hippocampus is exposed to a partial or degraded input of the encoded memory trace, the hippocampal system can recollect the full memory trace through the process of pattern completion (McNaughton & Morris, 1987). Subiculum and CA1 provide outputs to the rest of cortex and have therefore been suggested to serve as indices for cortical reactivation during recall (Teyler & DiScenna, 1986). Population activity of hippocampal ensembles is therefore likely carriers of high-dimensional aspects of episodic memories that are encoded in a spatiotemporal framework.

Both the spatial and temporal codes capture multiple levels of details. Spatial codes in MEC and hippocampus display both a fine- and coarse-grained resolution of space. Comparably can the sequence of events be inferred with a precision ranging from seconds to hours. The temporal code in LEC covers these time scales. Thus, the different spatiotemporal codes are particularly suited to support formation of episodic memories; fine-grained representations could link events to the details of the local environment and to the detailed sequences of events, whereas coarse-grained representations could link events to environments and to longer episodes. These observations are paralleled with findings in humans where spatiotemporal codes are organized at multiple levels of granularity with a corresponding anatomically organization as in rodents (Marchette et al., 2017; Nadel

**FIGURE 4** Olfactory coding in lateral entorhinal cortex (LEC) and hippocampus. Adapted from Igarashi et al. (2014). (a) Rats were trained to associate two odors with two different reward locations. Responses are shown for cells with significant activity at the cue port during training of naive animals (T1) until reaching asymptotic performance (85% correct, T5). Right column contains error trials during T5. Each row shows data for one cell around the time of odor sampling (starting from white dashed line). Top: distal CA1 cells; bottom: LEC cells. Selectivity is color coded (−1 and + 1 indicate complete selectivity for banana [red] and chocolate [green], respectively). (b) Population odor selectivity was measured by correlating population activity obtained during sampling of the two different odors. Higher values indicate more odor-selective population coding. Red lines indicate 95th percentiles from shuffled distributions. Odor selectivity develops in both LEC and hippocampus in parallel to improved performance. Odor selectivity decreases during error trials (T5e) compared to during a similar number of correct trials (T5d). (c) Development of task performance, gamma coherence and selectivity in CA1 and LEC. Variables are normalized onto a scale from 0 (T1) to 1 (T5) (mean ± SEM). Odor selectivity increases faster in LEC compared to CA1 [Color figure can be viewed at wileyonlinelibrary.com]
et al., 2013; Nielson et al., 2015). Such an organization could for instance support both the ability to remember the exact location of hidden food storages and the sequence these storages were collected. Likewise, we might speculate that low spatial and temporal resolutions might lead to high interference and generalization of memories which could occur for instance during the development of phobias.

Given the entorhinal and hippocampal signals that are correlated with features of ongoing experience, what is the evidence that the same neurons actually contribute to the formation and retrieval of episodic memories? There are several lines of reports suggesting that this is the case. First of all, activity patterns elicited during sharp wave ripples during sleep and rest are similar to those that can be recorded during encoding (Jensen & Lisman, 1996; Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994). In essence, previous experiences are replayed in hippocampus, a feature that has been suggested to be an important mechanism for memory retrieval and consolidation in both hippocampus and connected extra-hippocampal structures (Ego-Stengel & Wilson, 2010; Girardeau, Benchenane, Wiener, Buzsaki, & Zugaro, 2009; Jadhav, Kemere, German, & Frank, 2012; Karlsson & Frank, 2009). Next, the same neuronal signals as was present during encoding of an experience are reinstated when humans recollect the same experience from memory (Gelbard-Sagiv, Mukamel, Harel, Malach, & Fried, 2008; Mack & Preston, 2016; Miller et al., 2013; Vaz, Inati, Brunel, & Zaghoul, 2019). Somehow comparably are sequences of neurons activated when rodents make memory-based decisions on how to get to a future goal location, as if possible paths are recruited
from memory and evaluated before a decision is made (Johnson & Redish, 2007; Pfeiffer & Foster, 2013). These findings suggest that functional correlates present during encoding are actually necessary for retrieval of the same memory.

Our understanding of encoding and retrieval of episodic memories has made considerable progress in the last decades. Much of this progress is anchored in the pioneering and thought-provoking book of O’Keefe and Nadel (1978). The idea that there exists a memory system involved in forming cognitive maps of the environments we encounter is still the foundation stone for understanding how activity in entorhinal–hippocampal circuits can underlie higher mental functions, such as episodic memories. As suggested in the book, the spatial cognitive maps could be extended to also provide cognitive "maps" for distinct episodes; spatiotemporal scaffolds in which different aspects of an event can be registered. We endorse this idea, but we would like to emphasize the role of the entorhinal cortex in this process. Here, we have reviewed data showing that entorhinal cortex provides a spatial ("where") and temporal scaffold ("when") of ongoing experience. In addition, we would like to emphasize that associations between sensory stimuli and space are already formed in LEC. We suggest that hippocampus maps these associations on top of the spatiotemporal scaffolds. Thus, we can imagine a process where entorhinal cortex presents a "movie" of ongoing experience to the hippocampus that acts as an editor of this continuous flow of information. In essence, hippocampus is able to extract and tag memorable moments of ongoing experience and consolidate them into memory. In this way, entorhinal cortex and hippocampus could contain the neural coding mechanisms that underlie our ability to form episodic memories.

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CONFLICT OF INTERESTS

The authors declare no potential conflict of interest.

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