Elements of Information Processing in Hippocampal Neuronal Activity: Space, Time, and Memory

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Abstract The earliest studies on the firing properties of hippocampal neurons revealed coding of both spatial and non-spatial dimensions of experience. Since then, distinct lines of investigation have elaborated these findings to provide compelling evidence that the hippocampal neurons represent the events we remember within spatial as well as temporal frameworks. This characterization suggests that neural networks in the hippocampus underlie a "memory space" that organizes the features of memory dependent on hippocampal function.

A comprehensive understanding of the hippocampus requires identifying the nature of information encoded by its information processing elements combined with interpretation of the overall network representations that underlie cognitive and memory functions. Here I will attempt an overview of our knowledge about information processing by hippocampal neurons and networks. This will not be a comprehensive review—there have been several recent collections that survey the firing properties of hippocampal neurons in behaving animals and humans (Hartley et al. 2013; Mizumori 2007; Derdikman and Knierim 2014). Rather, here I will provide examples of the broad variety of hippocampal coding properties and attempt a synthesis of what these findings tell us about single neuron and network coding mechanisms that underlie memory representations.

Ancient History: The Early Studies on Firing Patterns of Hippocampal Neurons in Behaving Animals

In the early 1970s, several investigators adopted newly developed methods using single sharp electrodes or bundles of small-diameter flexible wires to record the activity of principal neurons in the hippocampus. Their studies pre-dated the advent of digitized recordings and computerized data analysis, and so depended on human

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observation to correlate auditory artifacts of neuronal spiking with ongoing behavior or simple automated averaging of spiking over time to compute firing rates time-locked to specific stimuli. These papers identified both spatial and non-spatial correlates of hippocampal neural activity that we still struggle to reconcile today.

The first of these publications was a short communication by O’Keefe and Dostrovsky (1971) that described the firing properties of neurons recorded from the dorsal hippocampus in rats using sharp electrodes as they moved through or were positioned within an open field environment. They focused on the activity patterns of eight hippocampal neurons that fired solely or maximally when a rat was in a particular part of the open field. The activity of most of these cells was also dependent on specific sensory stimuli (e.g. a tactile or visual stimulus) and the direction of orientation within the environment. The more extensive follow-up study by O’Keefe (1976) described many more hippocampal cells whose activity was dependent on spatial location and emphasized a distinction between “place cells” that fired when the rat occupied or ran past a particular location and “misplace cells” whose spatially specific activity depended on exploratory sniffing, usually when the rat did not find an expected object at the location. So, while these firing patterns were immediately interpreted as supporting the idea that hippocampal neurons map space, the data were equally clear that hippocampal neuronal firing patterns also encoded specific stimuli, behaviors, and cognitive states.

Quite independently, and around the same time, James Olds and his colleagues recorded from single neurons using fine wire electrodes positioned in various brain areas. They established an approach to identifying “learning centers” in the rat brain defined as areas where neurons developed short-latency responses time locked to stimuli (tones) as animals were classically conditioned to expect food delivery following the tones (Olds et al. 1972). Using this paradigm they identified neuronal responses to the conditioned tone observed throughout the hippocampus (Segal and Olds 1972). In these studies no effort was employed to control or determine the location of the animal within the small conditioning chamber. However, typically the neurons did not respond to the tones or reward delivery during a preliminary pseudo-conditioning session, suggesting that the stimulus-driven responses depended specifically on the learned association and not solely other aspects of sensory experience, behavior, or location.

In 1973 James Ranck published an extensive analysis of hippocampal neuron firing patterns observed in rats performing a variety of behaviors in an open field, including eating, drinking, grooming, being held, bar pressing, and sleeping. He observed correlations between neural activity and ongoing behavior in almost all hippocampal neurons, and reported that no two principal cells had the identical behavioral correlate. Four main types emerged from his analysis: “approach-consummate cells” that fired during the approach to and consumption of food, “approach-consummate mismatch cells” that fired similarly during approach and also during exploration of a missing water bottle (like O’Keefe’s misplace cells), “appetitive cells” that fired during orienting movements and approach but not consummatory behavior, and “motion-punctuate cells” that fired at the end of orienting movements or change in direction of movement. No effort was made to control for spatial location in this study, and Ranck acknowledged that, “perhaps spatial characteristics are the entire basis of firing in these cells" (Ranck 1973). However, the distinctions between the different behavioral correlates of these cell types seems unlikely explained purely by differences in where the behaviors occurred.

Finally, Theodore Berger, Richard Thompson, and their colleagues recorded multi-units and single neurons in the hippocampus of rabbits undergoing tone-cued classical eye-blink conditioning (Berger et al. 1976, 1983). They reported the emergence of tone-evoked conditioned responses of hippocampal neurons that paralleled both success in learning across trials and the time course of the conditioned eye-blink within trials. In these studies position within space was strictly controlled in that the animals were immobilized within a restraining device throughout learning. Thus the learning and behavioral correlates of conditioned eye-blinks cannot be attributed to spatial coding.

In many ways these early observations already provided insights into the broad scope of information that is encoded by hippocampal neural activity patterns that are evident in current studies. Place is a major determinant of the firing patterns of hippocampal neurons in animals that freely move through the environment. This property of hippocampal neurons was recognized in the awarding of the 2015 Nobel Prize to O'Keefe, who discovered the spatial firing patterns of hippocampal neurons. However, differences in spatial location do not account fully for firing patterns of many neurons, such as the misplace/mismatch neurons of O'Keefe and Ranck suggestive of additional correlates of cognitive and memory function. In addition, the coding of specific sensory stimuli was implicated in O'Keefe's original study and more systematically in Olds and colleagues' observations on conditioned neural responses. And, just as Ranck's observations are strongly suggestive that specific actions (e.g., approach behavior) seem to play some role, the findings of conditioned eye-blink related responses by Berger & Thompson strongly indicate that learned actions are encoded by hippocampal neurons in immobilized animals where location cannot explain the neural firing patterns.

Subsequent work on hippocampal neuron firing patterns in behaving animals and humans has expanded in four main directions. First, many studies have explored the spatial firing properties of hippocampal neurons, identifying cues that control, as well as other factors that modulate, spatial firing patterns. Second, many other studies have explored how learning of non-spatial information or actions is encoded by hippocampal neurons, along with or independent of spatial information. Third, recent evidence has indicated that hippocampal neurons encode time much like they encode space, suggesting a parallel dimension for mapping experiences. Fourth, another new direction involves explorations of how hippocampal neuronal ensembles integrate representations of multiple related experiences into networks of memories (also called "schemas"). These directions will be examined in turn. As you read this review, note that, while the coding of position in space has received the greatest attention in this literature, there is considerable evidence that position coding is often subordinate to other abstract features (the "context") of a behavioral task, and the finding of robust temporal coding indicates that space may be only one of the dimensions employed by hippocampal networks to organize memories.

Spatial Coding by Hippocampal Neurons

As can been deduced from the early observations, a mixture of spatial and non-spatial parameters influences hippocampal neural activity. In particular, it is clear that non-spatial events must be considered because of the findings on classical eyelid conditioning that show coding of learned behavior when space is held constant. Thus, when animals are freely moving in space, it might be that overt or subtle distinctions in ongoing perception, behavior, or cognition are confounded with, and drive the observation of position correlates of hippocampal neurons.

This issue was addressed by Olton et al. (1978) who identified clear place fields of hippocampal neurons in rats performing a task where they traversed the arms of an 8-arm radial maze and were required to remember visited arms. Despite the behavioral sequence being identical on all maze arms, many hippocampal neurons fired as the animal ran through particular locations on only one or a few of the arms, thus distinguishing the spatial correlate on some arms from the absence of activity during matched behavior on all arms. Another way the issue was addressed employed a clever behavioral paradigm created by Muller and colleagues (1987) that involved recording from hippocampal neurons as rats foraged for small bits of food dropped within an open field. The aim of this approach was to control for potential behavioral influences by testing whether a position correlate would emerge in a situation where foraging behavior is constant over all locations in the environment, thereby experimentally “subtracting” its influence. The results were striking: many hippocampal neurons had clear-cut place fields during random foraging in an open field. The observation of strong position coding when behavior is constant, involving either continuous foraging throughout a two-dimensional open field or identical movement sequences through linear tracks or mazes, have been replicated many times.

Variants of these linear maze and open field paradigms have been employed to characterize the sensory cues that determine position coding by hippocampal neurons. These findings can be summarized as follows. Nearly all of our information on hippocampal neuronal firing patterns comes from data on CA1 and CA3 pyramidal cells in the dorsal hippocampus of rats and to some degree in mice, monkeys, and humans (see Muller 1996; Eichenbaum et al. 1999, for more detailed reviews). As the animal explores or merely traverses a large environment, one can readily correlate dramatic increases in a cell’s firing rate when the rat arrives at a particular location, called the “place field”, and these cells are called “place cells”. From a baseline of less than 1 spikes/s, the firing rate can exceed 100 Hz, although during some passes through the place field the cell may not fire at all. Typically a large fraction of cells, perhaps 40–75%, have place fields in any environment, although the low baseline firing rates may let many cells without place fields go undetected. Place fields vary in size from quite small to half the size of an environment and are dispersed throughout the environment, although they may be concentrated at areas of particular salience such as where rewards occur (e.g., Hollup et al. 2001; McKenzie et al. 2013). In most of the environments used to date, most hippocampal cells have only one or two place fields, although in large environments they can have many place fields (Rich et al. 2014).

Sensory Cues That Govern the Spatial Firing Patterns of Place Cells Many studies have focused on identifying the environmental cues that drive spatially specific activity. O'Keefe (1979) defined place cells as neurons whose activity is not dependent on any particular stimulus, but rather reflects the presence and topography of multiple environmental cues. Several studies have shown that a variety of visual and nonvisual cues can determine the location of place fields (e.g., Hill and Best 1981; Muller et al. 1987; Save et al. 2000; Gener et al. 2013; but see Cressant et al. 1997). O'Keefe and Conway (1978) performed the first study where multiple spatial cues were provided and then manipulated to determine which cues controlled spatial representations, and found that some cells were controlled by only one or two of the cues and others by any subset of the cues. More recent studies indicate that place cells are driven by relatively few relatively proximal cues. O'Keefe and Burgess (1996) showed that the shape and locus of most place fields within a simple rectangular chamber are determined by the dimensions of, and spatial relations between, only a few nearby walls of the environment (see also Hetherington and Shapiro 1997). Several other studies have shown that place cells can encode subsets of the spatial cues and that these representations are independent of the spatial representations of other cells in the same environment. Shapiro, Tanila, and colleagues (Shapiro et al. 1997; Tanila et al. 1997a, b, c) and Knierim (2002) examined the responses of hippocampal cells to systematic manipulations of a large set of spatial cues, including both distant cues outside a maze and proximal cues on the floors of maze arms. Different place cells encoded individual proximal and distant stimuli, combinations of proximal or distant stimuli, or relations between proximal and distant cues. The place fields of some cells were fully controlled by as little as a single cue within a very complex environment, and most cells were controlled by different subsets of the controlled cues. More recently Leutgeb et al. (2005) examined firing patterns of hippocampal neurons as rats explored multiple small environments (boxes) within multiple large environments (rooms) and reported that whether or not place cells fire and the locations of place fields depend on distant ("global") cues that lie outside of the small environment, whereas the firing rate, but not location of place fields depends on proximal cues (called "rate coding"). However, when distant cues are minimized, place fields can be entirely determined by local cues (Young et al. 1994; Hetherington and Shapiro 1997).

Not Necessarily Location Per Se: Length and Distance Place fields do not necessarily represent specific locations but rather can reflect continuous spatial dimensions of length and distance. O'Keefe and Burgess (1996) recorded from rats as they foraged in rectangular chambers whose walls varied in length. They found that place fields stretch along a wall of an environment that is elongated, indicating that when environmental cues are continuously variable, place cells represent spatial dimensions continuously. Gothard et al. (1996a, b) found that when a particularly salient cue or enclosure within an open field is moved repeatedly and randomly, the spatial firing patterns of some cells become tied to that cue. When rats were trained to shuttle between a mobile starting box and a goal location defined by landmarks in an open field, some cells fired relative to the static environmental cues, whereas others fired relative to a landmark-defined goal site, or in relation to the start box. When rats were trained to shuttle between a movable start-end box and goal site on a linear track, the anchor of the spatial representation of many cells switched between these two cues, depending on which was closer. Under these conditions the majority of the activated hippocampal cells did not exhibit location-specific activity that was associated with fixed environmental cues. Instead, their activity could be characterized as "spatial" only to the extent that they fired at specific distances from a particular stimulus or goal. Distance coding has also been observed in rats running on a treadmill where external spatial cues signaling motion are absent (Kraus et al. 2013) and in a task where spatial cues are variable and distance provides salient information about location (Ravassard et al. 2013; Aghajan et al. 2015).

Place Cells Encode Both the Similarities and Differences Between Environments That Share Spatial Features Several studies have shown that place cells are not linked together to form a cohesive map of the environment. Tanila et al. (1997b) found that ensembles of simultaneously recorded place cells changed their firing patterns independently associated with distinct subsets of the cues, indicating that the spatial representation was not cohesive but instead coded for spatial cues that were common to and distinct in multiple environments. In several cases where two cells had overlapping place fields associated with one configuration of the cues, each cell responded differently when the same cues were rearranged. This finding shows that each cell was controlled by a different subset of the cues at the same time, and that their differential encodings are not due to shifts between two different spatial "reference frames" used by all cells at different times (Gothard et al. 1996b). Skaggs and McNaughton (1998) confirmed this finding by recording from a large number of place cells simultaneously in rats foraging randomly in two identical enclosures, between which they could move freely. Each hippocampal ensemble contained cells that had similar place fields and others that had distinct spatial firing patterns between the two enclosures. In this situation, some cells encoded the physical cues, whereas the activity of others at the same time reflected the knowledge that the two environments were distinct.

Spatial Representations Are Context Dependent One view of place cells is that they compose a representation of the context in which specific events occur. What constitutes a "context", as opposed to a set of individual cues is not clear, and whether its domain includes spatial and temporal, as well as other aspects of the situation in which events occur is also not clear. The data suggests that all aspects of the background context in which specific events occur and when places are occupied can dramatically affect hippocampal neural activity. For example, the spatial firing patterns, and the extent to which firing is dependent on spatial orientation, are dramatically different when a rat forages randomly or produces repeated paths as it traverses the identical environment (Markus et al. 1995). Similarly, when different starting points in a radial maze determined the locations of goals, the firing patterns of place cells changed dramatically (Smith and Mizumori 2006). Notably, some places cells fire similarly in the two situational contexts whereas others change dramatically—showing that the hippocampus represents both the commonalities and differences in the two context-defined situations.

Seemingly subtle changes in environmental cues can also produce dramatic changes in the spatial firing patterns of hippocampal neurons. For example, changes in the background color or background odor of an environment can dramatically change the spatial firing patterns of individual hippocampal neurons (Anderson and Jeffrey 2003). Notably, again some cells do not change for each contextual shift, whereas others do. What cues and the extent of situational change that causes changes in firing patterns is not clear, but several studies have examined the dynamics of firing pattern changes when cues are gradually altered. When the shape of an environment is gradually altered (Wills et al. 2005), or critical cues are gradually changed (Rotenberg and Muller 1997), most place cells do not alter their firing patterns initially, but at some level of change, dramatically alter their firing patterns. This sudden switch of firing patterns when a threshold of cue alteration is passed suggests an attractor state dynamic (not unlike that of many other brain areas) in which the contextual representation switches from pattern completion to pattern separation. Area CA3 demonstrates a particularly sharp discrimination gradient in making this switch (Leutgeb et al. 2004; Lee et al. 2004). It appears that hippocampal cell assemblies can rapidly switch between spatial representations as animals perform different tasks within the same environment (Fenton et al. 1998; Jackson and Redish 2007).

Spatial firing patterns can also dramatically change when the affective association of a constant spatial environment is altered. Several studies have reported major alternations in hippocampal spatial representations of previously neutral environments when a rat is shocked in the environment, thus altering the meaning of the environment to evoke fear (Moita et al. 2004; Wang et al. 2012) or vice versa (Wang et al. 2015).

Several other recent studies have focused on changes in context defined by the behavioral demands of a task. In several of these studies, rats alternate routes that involve left and right turns through a T-maze where they traverse a part of the maze that is common to both routes. In this and similar tasks, many hippocampal neurons have distinct firing patterns, even when the rat traverses the common maze area depending on whether the rat is performing a left-turn or right-turn trial (Wood et al. 2000; Frank et al. 2000; Ferbinteanu and Shapiro 2003; Ainge et al. 2007; Bower et al. 2005; Lee et al. 2006; Griffin et al. 2007; reviewed in Shapiro et al. 2006). Importantly, some cells fire similarly as the rat performs both routes, indicating the hippocampus represents both the distinct paths and the common elements among them. Furthermore, the distinct firing patterns of place cells predict success in the alternation task (Robitsek et al. 2013). Also, the same pattern of findings occurs when the choice of different goals is guided by motivational context (hunger or thirst), indicating that the distinctions in firing patterns are not due to the accumulated movements (i.e., path integration) prior to the overlapping segment of the maze, but rather to the cognitive state associated with different routes through the maze (Kennedy and Shapiro 2009). A recent extension on these findings showed that, when the alternation task is separated into distinct sample and choice phases, most hippocampal neurons have different spatial firing patterns in the distinct trial phases, and within that, some cells also differentiate the two routes within each phase (Griffin et al. 2007). These data are consistent with other findings discussed above showing that different cognitive states within a single overall behavioral task are represented distinctly and linked by representations of their common features by hippocampal neurons.

Finally, new findings suggest that the ventral hippocampus, not examined in the studies described above, may represent large scale space that constitutes a meaningful spatial “context”. Kjelstrup et al. (2008) compared the sizes of place fields in the dorsal and ventral hippocampus and found that place fields become larger as one records along the dorsal to ventral portions of the hippocampus. More recently, Komorowski et al. (2013) also recorded along this axis as rats performed a task where they were required to employ their current spatial context (one of two chambers) to remember which of two objects contained a reward, and found that ventral hippocampal neurons had large place fields, many of which filled most of all of one of the contexts. However, these fields never bridged between contexts in animals successfully performing the task, suggesting that ventral hippocampal networks code for representations of spatial and meaningful contexts.

Where the Rat “Thinks” It Is Notably, the spatial activity patterns of place cells may be more determined by where the rat may “think” it is rather than being explicitly driven by spatial cues. This possibility is consistent with the observation that the spatial firing patterns of place cells can persist even when all of the spatial cues are removed or the room is darkened (O’Keefe and Speakman 1987; Muller and Kubie 1987; Quirk et al. 1990), although the selectivity of spatial firing may be degraded in the dark (Markus et al. 1994). Also, the findings discussed above showing that place cells form categorical representations even in circumstances of ambiguous spatial cues (Skaggs and McNaughton 1998) or continuously changing spatial cues (Leutgeb et al. 2004), indicates that the animal’s perspective on where it is can dominate over the actual spatial cues. Also, when a rat is first introduced into a new environment, place cells may continue firing associated with the cues of a former highly experienced environment, and then suddenly “re-map” after successive exposures (Bostock et al. 1991; see also Sharp et al. 1990). In a direct test of whether the animal’s conception of its location can govern place cell activity, O’Keefe and Speakman (1987) tested rats in a task where they had to remember where removed spatial cues had been. They found that errors in their choice behavior predicted shifts of their hippocampal place fields, suggesting that these codings were determined by the orientation of the maze remembered by the rat, thus providing a compelling link between hippocampal spatial coding and spatial memory but also showing that place cells reflect an internal representation of space rather than a representation that depends on external cues.

Direction of Movement Influences Place Cells When Movements Through Space Are Meaningfully Directional According to O'Keefe (1979) true place cells fire whenever an animal is in the place field, regardless of its orientation or ongoing behavior. However, the only situation where large numbers of true place cells are observed is when animals forage by random walk through an environment, where behavior is held constant and the meaning of movement directions is homogeneous. However, in contrast to this open field foraging, in virtually any situation where movement directions are meaningfully different, distinct movement directions influence spatially specific activity. For example, in the radial maze task where animals regularly perform runs outward on each maze arm to obtain a reward, and then return to the central platform to initiate the next choice, outward and inward arm movements reflect meaningfully distinct behavioral episodes that occur repetitively. Correspondingly, hippocampal neurons reflect the relevant "directional structure" imposed by this protocol, and almost all place cells fire only during outward or inward journeys (McNaughton et al. 1983), and directionality is also observed when animals perform the same task in an open field, indicating that directionality is not due to the constraints of location by walls of the arms on a radial maze (Weiner et al. 1989). Similarly, place cells are activated selectively during distinct approach and return episodes and from variable goal and start locations in open fields and linear tracks. Furthermore, Muller et al. (1994) showed that the same place cells that are non-directional during random foraging are highly directional in a radial maze. Most impressively, Markus et al. (1995) directly compared the directionality of place cells under different task demands, and found that place cells that were non-directional when rats foraged randomly in an open field, were directional when they systematically visited a small number of reward locations. Taken together, these findings emphasize that place cells exhibit movement-related firing patterns whenever particular movements are associated with meaningfully different events. Also, directionality of place fields is obtained only following experience in directional movements (Navratilova et al. 2012).

Conclusions About Spatial Coding in Hippocampal Neurons The phenomenon of place cells in freely moving animals is highly robust and observed both in situations where the hippocampus is necessary for memory performance (e.g., the radial maze) and where it is not (foraging for food in an open field). A broad variety of individual spatial and non-spatial cues and cognitive states can drive or strongly influence place cells, so they do not provide a simple cohesive map of coordinate locations within a space defined by geometric relations among spatial cues as O'Keefe (1979) originally envisioned. On the other hand, perhaps the most straightforward explanation of place cells is that they reflect where an animal "thinks" it is in space as well as where it "thinks" it is going. This view is consistent with the notion that the hippocampal representation of space is "cognitive" as opposed to stimulus driven. A critical remaining question is whether the function of this cognitive map of space is dedicated to navigation, as some have suggested (McNaughton et al. 1996, 2006; Moser et al. 2008; Hartley et al. 2013) or whether the purpose of the map is to represent where events occur in spatial context, as has been suggested by recent studies on humans and animals (Eichenbaum et al. 2007; Davachi 2006; Diana et al. 2007). Much of the evidence that place cells are components of a dedicated spatial mapping system rest on the observation that hippocampal cells (and other cells in neighboring regions) can encode spatial parameters (location, head direction, borders, distance traveled; Hartley et al. 2013), but these findings may well just reflect the relevant dimensions of specific experiences that are dominated by spatial dimensions and lack non-spatial stimuli and behavioral demands. Deciding between these views rests instead on the extent to which hippocampal neurons encode specific stimuli, behavioral actions, and non-spatial cognitive events that fall outside the domain of spatial navigation and instead are consistent with a spatial framework for memories.

Representation of Stimuli, Behavioral Actions, and Cognitive States Independent of, or Along With Position

The Berger & Thompson studies described above indicate that hippocampal neurons can have clear learning and behavioral correlates in animals entirely restrained within a specific location. However, it may well be that space still plays a role even in this highly controlled task, because the same behavior related firing pattern may depend upon the location where conditioning occurs, as does the behavior in this kind of classical conditioning (Penick and Solomon 1991). To address this possibility, many studies employed learning and memory tasks where *explicitly distinct* sensory or behavioral events occur in multiple positions in an environment, with the aim of distinguishing the extent to which firing patterns are dependent on the nature of the event, on where it occurs, or both. These studies have revealed that hippocampal neuronal firing patterns distinguish both the different events and the positions and spatial contexts where they occur.

Sensory Driven Responses Many studies in rodents, monkeys, and humans have described hippocampal neuronal activity associated with a very broad range of non-spatial stimuli and behavioral events. In rodents, many studies have observed robust activation of hippocampal neurons associated with visual, tactile, olfactory, and auditory cues in several learning and memory paradigms (reviewed in Eichenbaum et al. 1999; Eichenbaum 2004). These findings join with many other reports of robust activation of hippocampal neurons associated with combinations of specific stimuli, match/non-match stimulus comparisons, and the locations of these events in animals performing discrimination and recognition memory tasks (Eichenbaum et al. 1987; Wood et al. 1999; Wiebe and Staubli 1999; Deadwyler et al. 1995; Otto and Eichenbaum 1992; Hampson et al. 1993; Wible et al. 1986). The extent to which non-spatial and spatial cues are represented depends on the context of behavioral demands. For example, in the same environment with the same olfactory cues, hippocampal neurons strongly encode location when rewards are associated with the location of the cue, but fire associated with the odors when the odor identity is associated with reward (Muzzio et al. 2009). Similarly, Lee and

Kim (2010) reported that hippocampal neuronal activity shifted from spatially determined to stimulus determined as learning about the stimuli developed. In addition, hippocampal neurons signal learned behavioral actions. Lenck-Santini et al. (2008) described hippocampal neurons that fire during learned "jump" avoidance responses, reminiscent of Ranck's (1973) pioneering descriptions of a variety of behavioral correlates of hippocampal neurons in rats and the findings on conditioned eye-blink related responses described by Berger et al. (1976), a finding extended in recent studies on classical eye-blink conditioning (Hattori et al. 2015; McEchron and Disterhoft 1997).

Consistent with these findings in rodents, a large fraction of hippocampal neurons in head-fixed monkeys fire robustly associated with learned associations between specific visual stimuli and eye-movement responses (Wirth et al. 2003). Similarly, a large fraction of hippocampal neurons in monkeys respond to visual stimuli modulated by their familiarity in the naturalistic recognition task described above (Jutras and Buffalo 2010). Furthermore, multiple studies have reported that hippocampal neurons in humans also respond to visual stimuli and their responses are modulated by familiarity in recognition tasks (Fried et al. 1997) and distinguish the stimuli that are recalled from those forgotten (Rutishauser et al. 2008). Hippocampal neuronal responses also predict memory for learned verbal paired associates (Cameron et al. 2007). Human hippocampal neurons exhibit sparse and distributed coding of individual remembered stimuli (Wixted et al. 2014) and rapidly develop as humans learn associations between objects and locations (Ison et al. 2015), and many hippocampal neurons generalize across closely related stimuli (Quiroga et al. 2005; Krieman et al. 2000a) and fire while the subject is imagining a cued stimulus (Krieman et al. 2000b). These studies provide strong evidence that many hippocampal neurons fire associated with specific stimuli and actions when space is held constant (e.g. eye-blink conditioning) and are driven by conditioned stimuli when the animal is immobile (Olds et al. 1972; the studies in monkeys and humans).

Conjoint Sensory-Behavioral and Spatial Responses Several other studies have shown that hippocampal neurons conjoin sensory-behavioral events and positions where they occur. The most striking of these studies also involve tracking learning about sensory stimuli and related conditioned behavioral responses. These studies show that hippocampal neuronal activation that occurs during the exploration of specific objects is embedded within the spatial firing patterns (place fields) of those neurons. For example, following tone-cued fear conditioning, hippocampal neurons come to be driven by the conditioned tone stimulus when the animal is within the place field of that neuron (Moita et al. 2003; Wang et al. 2012). Also, in rats performing a variant of the novel object exploration task, hippocampal neurons fired associated with specific objects and their familiarity embedded within the spatial firing patterns (place fields) of these neurons (Manns and Eichenbaum 2009). In rats performing a context-guided object-reward association task, hippocampal neurons fire when animals sample specific objects within particular locations and spatial contexts. In this experiment, the spatial specificity of responses occurred early and the object related activity paralleled learning to respond to different objects in only one context (Komorowski et al. 2009). Similarly, after training on somatosensory or auditory discrimination tasks, hippocampal neurons encode tactile and auditory cues along with the locations where they were experienced and rewarded (Itskov et al. 2011, 2012; Vinnik et al. 2012). This combination of studies clarifies that position-related firing precedes the adoption of stimulus or action specificity and suggests that the hippocampal network constitutes a spatial framework onto which memories of stimuli are incorporated. This conclusion is consistent with a large literature that positions the hippocampus as convergence site for streams of information processing about objects and space (reviewed in Davachi 2006; Eichenbaum et al. 2007), and suggests the mechanism for coding objects and events in space is conjunctive object and place coding by single hippocampal neurons.

Conclusions About Non-spatial Coding in Hippocampal Neurons There is considerable evidence that a broad range of specific significant stimuli can drive hippocampal neuronal activity and that hippocampal neurons fire associated with specific learned behaviors. At the same time, however, whenever these sensory and behavioral events occur in multiple locations, these activity patterns differ across locations. Thus, sensory-behavioral responses of hippocampal neurons are embedded within a spatial framework of hippocampal representation.

Time as an Additional Framework for Encoding Memories

There is considerable recent evidence that the hippocampus is involved in representing the flow of events in time, in parallel to its representation of the organization of events in space (Eichenbaum 2013, 2014), and indeed it has been suggested that bridging between successive events to link them in time may be a fundamental function of hippocampal circuitry (Rawlins 1985; Levy 1989; Wallenstein et al. 1998; Howard et al. 2014). Consistent with this idea, hippocampal lesions impair memory for the order of sequences of events (Fortin et al. 2002; Kesner et al. 2002) and ensemble activity patterns of CA1 neurons gradually change while rats sample sequences of odors, and this signal of continuously evolving temporal context predicted success in remembering the odor sequence (Manns et al. 2007). These findings, and more discussed below, suggest that temporal coding by the hippocampus is not merely representing the passage of time, but supports representation of the order of events in experiences, which can be used to guide subsequent behavior.

Several studies have now identified hippocampal principal neurons that fire at a particular moments in time of a temporally structured event, composing temporal maps of specific experiences. Across these studies, the location of the animal is held constant or firing patterns associated with elapsed time are distinguished from those associated with spatial and behavioral variables, and the firing patterns of these cells are dependent on the critical temporal parameters that characterize the task. Because these properties parallel those of place cells in coding locations in spatially structured experiences, we called these neurons "time cells" (MacDonald et al.

2011), even though these neurons are the same cells that exhibit spatial firing specificity in other circumstances.

Time cells have now been observed in several experiments. Pastalkova et al. (2008) recorded from single CA1 neurons as rats performed a spatial T-maze task where alternating left-turns and right-turns, and trials were separated by a fixed period of wheel running. They were the first to report that hippocampal neurons fire reliably at specific moments during wheel running and the entire period of each wheel run was filled by a sequence of brief neuronal activations. Importantly, the firing sequences differed between trials in which the rat subsequently turned left or right—even though the rat was largely in the same location (that is, in the running wheel) and performing the same behavior (that is, running)—but they were consistent between left-turn trials and consistent between right-turn trials, suggesting that a sequence was linked to the content of the trial. Subsequently, Kraus et al. (2013) also observed time cells in rats running in place on a treadmill in between trials on a T-maze, and showed that these cells are influenced independently and conjunctively by elapsed time and distance traveled on the treadmill (Fig. 1).

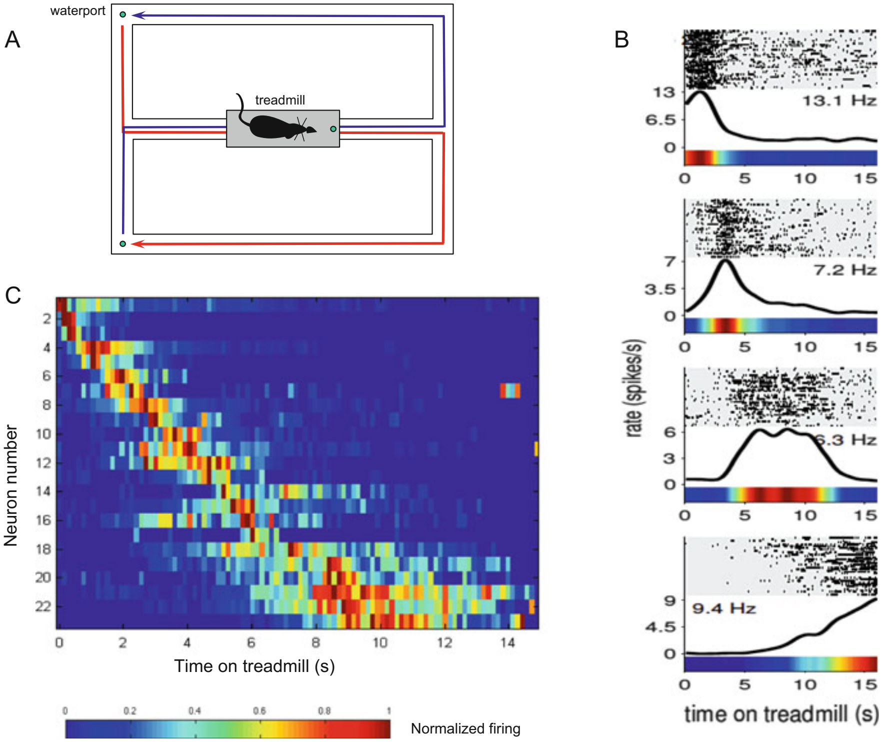

Fig. 1 Hippocampal neurons encode the flow of time while a rat runs in place. (**a**) Spatial alternation task in which on each trial the rat runs in place on a treadmill for 15 s. (**b**) Raster display, histogram, and heat plot of the time related firing pattern of four hippocampal neurons that fire at different moments during treadmill running. (**c**) Normalized firing rates of 23 hippocampal neurons over the course of treadmill running period. Adapted from Kraus et al. (2013)

Another study (Gill et al. 2011) examined activity patterns of CA1 neurons in rats performing a place-reversal task. In the first half of each daily session, trials began at any of three arms of a plus-maze and the rats had to go to the remaining arm to obtain a reward; in the second half of the session, another arm became the ‘reward arm’ and trials started from any of the other three arms. In between trials, rats were placed on a small platform outside the maze for several seconds. During the course of training, time-specific firing patterns emerged during the inter-trial periods, and the firing sequences differed between the two sessions. The rats could move freely during the delay, but cells that had reliable place fields were excluded from the analysis, indicating that the measured activity patterns encoded time rather than place.

In another study MacDonald et al. (2011) examined whether CA1 neurons also fired at specific moments in a non-spatial task where rats learned to associate each of two visually distinct objects with one of two cups of scented sand (Fig. 2a). On each trial, rats approached and sampled one of the two objects and, after a fixed delay, were exposed to one of the two odor cups. If the odor matched the object, the rat had to dig in the sand to retrieve a buried reward. During the delay period, individual neurons fired at successive moments that fill out the entire period, and firing patterns differed depending on which object the rats had to remember and were consistent between trials in which the same object had to be remembered. Extensive general linear model (GLM) analysis was used to distinguish activity patterns associated with the animal’s location, speed and head direction during the delay period from the time elapsed. Although these spatial and behavioral parameters contributed to the activity patterns of many of the recorded cells, the analysis also revealed a contribution of time that was independent of these variables. Furthermore, the firing patterns of many of these neurons changed (i.e. they ‘re-timed’) when the delay was increased. This happened even though the behavior and locations of the animal during the initial period did not change, indicating that the firing patterns of these cells reflected the passage of time rather than variations in behavior or place. Importantly, the cells firing later in the delay period were active for longer durations (i.e. had larger “time-fields”; also see Kraus et al. 2013, Fig. 1; MacDonald et al. 2013). This pattern suggests a scalar coding of time, which parallels a hallmark property of time judgments in humans and animals (Howard and Eichenbaum 2013). Each of these studies provided evidence for the existence of an evolving temporal signal that takes the form of a succession of briefly firing neurons.

Further evidence supporting the existence of temporal signals that are independent of place or distance has come from recent studies showing time cells in head-fixed animals in which the animal’s location and behavior were kept constant and movement was eliminated. For example, in one study (MacDonald et al. 2013) rats performed an odor-cued delayed matching to sample task in which each trial began with the presentation of one of multiple sample odors for 1 s. Following a fixed delay, a test odor was presented. In order to receive a reward, the animal had to respond only to the test odor that matched the sample on that trial. We found that approximately 30 % of hippocampal cells encoded specific moments during the

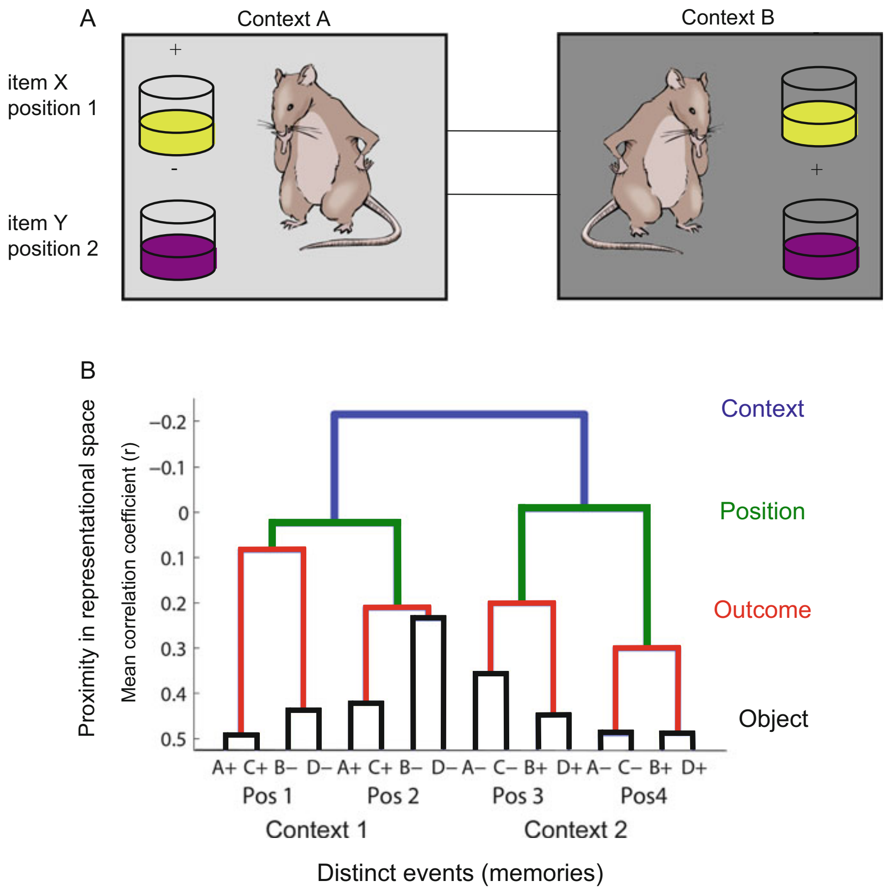

Fig. 2 Context-guided object memory task. (**a**) Rats enter either of two spatial contexts (A and B) in which they are presented with the same two object stimuli (X and Y) in either of the two positions shown. In Context A, object X contains a reward whereas in Context B, object Y contains a reward. (**b**) Dendrogram illustrating the relationships between representations of each type of event (x-axis) as linked (y-axis) by specific task dimensions (*right*). At the top of this schema, events that occur in different contexts are widely separated in representational space, indicated by anti-correlation between events that occur in different contexts, putting context as the highest superordinate dimension. Within each context-based network, events are then separated by positions within a context, i.e., positions are subordinate to contexts. Next, within positions, events are separated by different reward associations, i.e., reward association is subordinate to position. Finally, closest together in this schema are events that involve different objects that have the same reward association in the same location and context, i.e., object identity is subordinate to reward values. Adapted from McKenzie et al. (2014)

delay. Another study in head-fixed animals used two-photon calcium imaging to investigate the evolution of firing patterns among large ensembles of hippocampal neurons as mice underwent classical conditioning (Modi et al. 2014). On each trial, mice heard a brief tone that was followed, after a temporal gap, by an air-puff to the eye. During acquisition of the conditioned eye-blink response, CA1 cells developed time-locked firing sequences throughout the trial, including during the temporal gap.

Conclusions About Temporal Coding by Hippocampal Neurons Time cells have been observed in a range of behavioral conditions, including during delay periods in maze tasks in which rats alternate goals (Gill et al. 2011; Pastalkova et al. 2008; Kraus et al. 2013), bridging temporal gaps between associated non-spatial cues (MacDonald et al. 2011), during the delay period in a in non-spatial matching to sample task (MacDonald et al. 2013), and throughout trials in trace eyelid conditioning (Modi et al. 2014). Importantly, in some of these studies, the animal is immobilized and thus space plays no role in ongoing behavior or memory (MacDonald et al. 2013; Modi et al. 2014; Naya and Suzuki 2011). The findings of these studies establish a broad scope of temporally structured episodes in which the hippocampus encodes the temporal organization of specific experiences. Furthermore, some of the studies in animals have closely linked the emergence of time cell sequences to the encoding of specific memories and to subsequent memory accuracy (Gill et al. 2011; Modi et al. 2014; MacDonald et al. 2013), thus indicating a causal role of time cell firing patterns to memory performance. Also, the representation of temporally ordered sequences of events by the hippocampus extends to monkeys and humans. In monkeys, hippocampal neuronal activity signals elapsed time in a memory delay between associated objects (Naya and Suzuki 2011). In humans, hippocampal neurons fire in sequence associated with learning (Paz et al. 2010) and memory (Gelbard-Sagiv et al. 2008) of the flow of events experienced in movie clips.

Combined Spatial and Temporal Coding In addition, many studies have reported that ensembles of simultaneously recorded place cells that fire in sequential locations as animals traverse a path through a maze, subsequently also ‘replay’ the corresponding sequence of firings during ‘off-line’ periods, including sleep and quiet wakefulness when the animal is not moving through those locations (Carr et al. 2011; Karlsson & Frank 2009). Thus, spatial coding observed as rats actively run through a maze is recapitulated in temporal coded firing sequences when the rat is not moving. Disruption of these replay events impairs subsequent memory of the path (Jadhav et al. 2012). Moreover, field potentials associated with replays of sequences associated with alternative choice paths in a maze predict acquisition of learned performance (Singer et al. 2013). In addition, replay can be observed in sequential firing patterns associated with place-cell sequences that are about to occur as a rat takes a novel path in an open field (Pfeiffer and Foster 2013), and these replays converge on the target goal location (Pfeiffer and Foster 2015). The findings on replay strongly indicate a temporal coding of spatial representations relevant to memory.

The significance of prominent temporal representation as an aspect of non-spatial coding in the hippocampus is high in two ways. First, as introduced by Tulving (1983) episodic memories are defined by a temporal organization that embodies the temporal organization of events in personal experiences. We know that the hippocampus is critical to episodic memory and to memory for the temporal order of events, even when space is not relevant. Now the existence of time cells provides a mechanism by which the hippocampus organizes memories for events in time. Second, the existence of time cells offers a parallel temporal organizing mechanism to the spatial organizing mechanism offered by place cells. Therefore, the hippocampus could support representations of episodes by mapping objects and events within a framework of space and time, conferring upon those memories connections that reflect the spatial and temporal associations between distinct but related events embodied within a mapping by place and time cells (Eichenbaum 2013, 2014).

Linking Related Experiences into Memory Networks

McClelland et al. (1995) suggested that a key function of the hippocampus is to integrate new memories with the existing organization of related knowledge. Experimental evidence supporting this idea came from studies showing that rats integrate related memories and this capacity depends on the hippocampus (Dusek and Eichenbaum 1997, 1998; Bunsey and Eichenbaum 1996). More recently, Tse et al. (2007) showed that when rats learn to find specific food flavors in particular places in an open field, they develop an organized representation of the spatial relations among the objects in a particular environment and rely on the hippocampus for rapid assimilation of new flavor-place associations within the relational representation. Relating these findings to place cells, McKenzie et al. (2013) reported that hippocampal neurons encode multiple reward locations and rapidly assimilate and reorganize the overall network representation to incorporate new reward locations (see also Dupret et al. 2010).

In a more ambitious study, McKenzie et al. (2014) characterized hippocampal neural activity in a task where rats learned multiple context-dependent object-reward associations (Fig. 2a). Analyses of single neuron firing patterns revealed considerable variation in the types of non-spatial and spatial information encoded in hippocampal neural activity patterns, showing that hippocampal neuronal activity in complex tasks is “high-dimensional” in the sense that hippocampal neurons exhibit considerable mixed selectivity to multiple relevant non-spatial and spatial dimensions that are salient in a large range of memory tasks. In an effort to understand how these dimensions are organized in hippocampal networks, McKenzie et al. characterized the neural ensemble representations using a Representational Similarity Analysis (RSA) that compared population vectors accumulated during each type of event defined as a particular object in a specific position associated with reward or non-reward value within one of two spatial contexts. The RSA generated correlation coefficients that characterized the similarity of ensemble firing patterns among all pairs of event types. Then a hierarchical clustering analysis was used to determine the pairs of events that were most similar, then iteratively, the combined pairs of events that were most similar, and so on (Fig. 2b). This analysis revealed a hierarchy of relations among events: Events that involved the different objects of the same value were lowest in the hierarchy and embedded within specific positions. Next, events that involved different values were embedded within positions. Next, events at each position within a context were embedded within each context. Finally, representations of events across contexts were anti-correlated. Thus, hippocampal ensemble coding represented the identity of the objects, their reward assignments, the positions within a context in which they were experienced, and the context in which they occurred and networked these representations to form a systematic “map” of relations between the different types of memories.

Furthermore, after initial learning of one set of object associations, new object associations were rapidly assimilated into the relational structure that was established by initial learning. In addition, within the overall representation, items that had in common their reward associations in particular positions had strongly similar representations, even when they were never experienced together. These results suggest that, at the time of learning, new information is encoded within extant networks that stored related information, consistent with the view that new information is assimilated within networks of related memory traces to form hippocampal networks of related experiences (Eichenbaum 2004; McKenzie and Eichenbaum 2011). Similarities in hippocampal coding between familiar and novel conditions likely reflects the integration of related memories, arguably a primary purpose of memory systems in schema development and memory consolidation (McClelland et al. 1995; Tse et al. 2007). This overlapping code at the time of learning builds relational representations that can support transitive associations between separately learned experiences via of their common associations with a behaviorally relevant context (Dusek and Eichenbaum 1997; Bunsey and Eichenbaum 1996; Zeithamova et al. 2012).

The notion of relational representations that link memories in space can be readily extended to the linking of memories that are characterized by their flow in time. Thus, in studies described above where rats traverse different but overlapping routes through a T-maze, a typical finding is that some neurons represent the distinct memories that correspond to specific routes, even when rats traverse the overlapping segment of the maze, whereas other neurons fire similarly in the common segment thus providing a link between the distinct memories (Wood et al. 2000). Indeed, even in situations where animals traverse similarly structured routes in different mazes, whereas most neurons fire at distinct places in each maze, some fire similarly at positions that are functionally equivalent in the different mazes (Singer et al. 2010) or in different locations in the same maze (McKenzie et al. 2013). Thus, hippocampal networks create schemas that link spatial-temporal memories in situations where different routes have common features. Thus, the mechanism for interleaving of memories may be hippocampal neurons that encode overlapping features of multiple memories.

Conclusions: The Hippocampus as a Memory Space

The above review on hippocampal neuronal firing patterns allows me to address the following key questions: (1) What is the function of strong position coding by hippocampal neurons? And, (2) how are the various non-spatial and temporal coding properties of hippocampal neurons integrated with spatial coding?

It is remarkable that, after 40 years of research following the pioneering discoveries about hippocampal neurons in the 1970s, we have yet to reach a consensus on the nature of the hippocampal code. The early observations on hippocampal neurons in behaving animals revealed both behavioral and spatial firing properties. Each is quite apparent when the other is tightly controlled. Thus, in the studies following the early work, when behavior was held constant over locations, cells that exhibit spatial coding (place cells) are prevalent. Conversely, when space is held constant by immobilization, behavioral and temporal correlates of hippocampal activity are readily apparent in a variety of learning paradigms. Importantly, in a broad variety of testing paradigms when space, time, and sensory and behavioral events are salient, hippocampal neurons encode and integrate all of these dimensions of experience. The hundreds of studies on hippocampal neurons over these years has confirmed and extended these fundamental features of information coding by hippocampal neurons and networks. It is not too simplistic to conclude that the hippocampal network reflects all the salient events in attended experience, just as it should as indicated by its core function in memory. But how should we conceive the organization of information that supports this mirror of experience?

These properties support the notion that the hippocampus creates a "memory space" that binds in memory the elements of experiences and links memories via their common elements (Eichenbaum et al. 1999). By rapidly forming associations among any subset of its inputs, and between its inputs and reactivated relational memories, the hippocampus plays a critical role in the generation, recombination, and flexible use of information of all kinds. The representational schemes that underlie the memory space include representations of events as the relations among objects within the context in which they occur, representations of episodes as the flow of events across time, and representations that interleave events and episodes into relational networks, supporting the ability to draw novel inferences from memory (Eichenbaum 2004). This interpretation applies equally well to spatial and non-spatial domains of memory (Eichenbaum and Cohen 2014).

Considering the original definition of cognitive maps might provide progress towards a clarification of hippocampal function. According to Tolman (1948), a cognitive map is a form of mental organization of cognition, a tool for systematic organization of information across multiple domains of life. O'Keefe and Nadel (1978) interpreted the notion of a cognitive map narrowly to refer to a mental mapping of physical space and argued that the hippocampus performs spatial computations and represents geographical maps of the real world. The principals of cognitive mappings, however, can very well apply to episodic memories by viewing events as items organized in a spatial-temporal context (Butterly et al. 2012; Eichenbaum and Cohen 2014; Tavares et al. 2015). The memory space hypothesis takes the view that hippocampal networks map our location and movements within a broad range of life-spaces, supporting our ability to navigate spatial, temporal, and associational dimensions of personal experience (Eichenbaum et al. 1999; Eichenbaum 2004; see also Buzsaki and Moser 2013; Milivojevic and Doeller 2013).

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