

Time (and space) in the hippocampus

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There is considerable recent evidence that, in addition to its representation of space, the hippocampus also represents the temporal organization of memories. Time plays a central role in episodic memory, and studies have identified the hippocampus as playing an essential role in the temporal organization of memories in humans and animals. Temporal organization is supported by a gradually changing temporal context signal in the hippocampus, and this changing context signal involves ‘time cells’ in the hippocampus that code sequential moments in temporally organized experiences. Finally, hippocampal temporal context representations involve mechanisms in intrinsic circuitry and oscillatory patterns throughout hippocampal subfields and depend on inputs from parahippocampal cortical areas as well as a widespread temporal processing system in the neocortex.

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Introduction

There is considerable evidence of a special role for the hippocampal system in representing the spatial organization of events. It is commonly viewed that hippocampal neurons fire associated with the location of an animal in its spatial environment (place cells), and these are complemented by neurons in neighboring areas that fire associated with location, head direction, speed of movement, and boundaries. These discoveries have led to a widely held view that the hippocampus and interconnected neighboring areas compose a brain system that maps space and guides spatial navigation [1,2], heralded as ‘the brain’s GPS’ in the announcement of the Nobel Prize for Physiology or Medicine for 2014. While new discoveries have confirmed that the hippocampus does indeed create maps of space and where important events occur [3,4] and these maps surely serve navigation to

desired goals, the scope of hippocampal function in memory goes well beyond organizing memories in space [5,6].

An additional dimension mapped within the hippocampal system is time. Since Aristotle [7] it has been recognized that we recall experiences as organized in time, and Tulving [8] focused on temporal organization in his original characterization of episodic memories. Vargha-Khadem [9] identified a key role for the hippocampus in episodic memory, and many studies since have explored aspects of temporal organization in memory processing within the hippocampal system (see recent reviews in [10–12]). Here I will highlight recent discoveries on the role of the hippocampal system in the temporal organization of memory in humans and animals, the neural coding mechanisms that support this role within the hippocampus, and the larger brain system that supports the temporal organization of memories.

Recent evidence on the critical role of the hippocampus in memory for temporal organization

New experiments have reinforced the idea that the hippocampus is essential to the temporal organization of memories. Dede *et al.* [13•] led normal individuals and participants with damage to the hippocampus in a tour of the campus of the University of California, San Diego, and subsequently inquired about their memories of the experience. Subjects with hippocampal damage recalled fewer memories for episodic details than normal controls, including significant decrements in memory for the objects that were seen and events that occurred at each location, as well as details about the places where the events occurred. Remarkably, in contrast to accurate memory for the order of the sequential events in control subjects, the order in which patients with hippocampal damage recalled the events was statistically unrelated to the order in which they occurred. This strikingly severe deficit in memory for order with partially preserved ability to remember the events themselves parallels an earlier report that selective hippocampal damage in rats impairs memory for the order of odor stimuli studied in sequence contrasted with preserved memory for the appearance of items in the lists [14].

Allen *et al.* [15] strengthened the commonalities between memory for temporal organization between humans and animals by evaluating performance of human participants and rats on a task where subjects learned two sequences of objects (pictures for humans, odors for rats), then were probed with altered sequences to identify specific types of out-of-sequence events, including items that were

repeated, items presented early, and items that taken from the other sequence but presented in the same ordinal position. Humans and rats performed equally well on this task and both easily identified items that were repeated regardless of ordinal position. Humans and animals also equally identified items presented early in the sequence, and performed better if the item appeared multiple ordinal positions early over one position early. Also both humans and rats equally identified items from the other list regardless of ordinal position, but less well than they identified repeats, suggesting that humans and rats represent both the inter-item associations and item-ordinal position associations. These findings strongly suggest fundamental similarities in the representation of temporal organization across species.

The hippocampus supports temporal organization by a representation of a gradually changing temporal context

How does the hippocampus represent temporal organization? An influential theory that guides research in this area is the ‘Temporal Context Memory’ hypothesis, in which it is argued that the brain maintains representations of events and composes a leaky integration of recent experience that at any instant contains a record of the current and immediately past events and gradually weaker information about more temporally remote events [16]. As time moves on, the representation is most influenced by the next current event and the record of more increasingly distant events weakens. Within this perspective, the temporal context of an event is defined as a period of time surrounding each event that includes representations of the sequence of temporally neighboring events. Recent work has extended this theory as a unified framework that accounts for the spatial and temporal organization of memories in the hippocampus [17,18] and extends to roles of temporal organization in other brain regions [19*].

Initial evidence of a gradually changing temporal context signal in the hippocampus was reported in a study where hippocampal neurons were recorded in rats performing a task where they were presented with unique sequences of five odors and then subsequently presented with two of the odors and rewarded for selecting the one had occurred earlier in the study phase [20]. The pattern of activity of a hippocampal neuron ensemble changed gradually across periods of time around the sampling of each odor, and the strength of this change predicted memory performance in the subsequent probe test of memory for their order, such that significant changes in activity patterns across the odor sampling events predicted accurate memory whereas the absence of a changing temporal pattern predicted memory errors. These findings suggested that the hippocampal neuronal activity patterns provided an evolving temporal context signal that supports encoding of memories for the order of odor presentations. The firing patterns of the same hippocampal neurons also differed at distinct locations

where the odor stimuli were presented, but the differences in hippocampal spatial representations of these events were equivalent on correct trials and error trials and therefore did not predict the accuracy of memory performance. Thus, in a task where temporal organization was important and memory for location was not, a hippocampal temporal context signal predicted accurate memory.

A more recent study of hippocampal neuronal activity patterns in rats extended these results [21]. In this experiment rats were tested as described above in the Allen *et al.* [15] protocol where rats are initially trained on two odor sequences and then later presented with altered sequences where they are required to identify out-of-sequence items. This study reported a population of hippocampal neurons with reliable, distinct patterns for each trained sequence, thus composing signals that differentiated the repeated temporal contexts that defined each of the two sequences. The study also found individual neurons that fired associated with specific odors in particular ordinal positions as well as neurons that coded specific out-of-sequence probes. Furthermore, the temporal context representations could be decoded into a network organization in the form of a representational hierarchy in which the hippocampal ensemble initially categorized sequence elements as in-sequence or out-of-sequence, thus showing that temporal context was the predominant predictor of trial classifications. In addition, context coding was a strong predictor of accurate memory performance.

Another recent study identified a very slowly changing temporal context representation in the hippocampus that binds related memories over a period of hours [22*]. The activity of a large population of hippocampal neurons was monitored in mice exposed to one environmental context, then a week later to two other distinct environmental contexts separated by five hours. The population of neurons representing contexts separated by a five hours involved significant overlap in the neurons activated, but there was little overlap of the activated population for the contexts experienced seven days apart. Subsequently, the behavioral significance of the overlap in activated populations for temporally proximal contexts was demonstrated by showing that later pairing of shock with the final context resulted in fear of that context and the context that was experienced five hours earlier but not the context experienced a week earlier. This experiment revealed that a slowly changing population representation of temporal context, previously observed in hippocampal ensemble recordings in animals without behavioral assessments [20,23–25], supports the linkage of events occurring over hours and the separation of memories for events occurring over days.

Another recent study examined hippocampal temporal context signals in humans associated with experiences

that occurred over a month and over distances of 30 km in the Columbus, Ohio area that were recorded with a smartphone ‘lifelogging’ system [26•]. During subsequent recall of those experiences, fMRI patterns in the hippocampus showed gradients of similarity associated with temporal and spatial distance between events such that the multivoxel patterns were more similar for events that occurred closer in time or location. These findings extended earlier observations of a gradient of representational similarity associated with temporal distance between events experienced over short intervals in humans [27,28].

‘Time cells’ underlie the representations of temporal context

The above-described studies demonstrated that a continuously changing neuronal ensemble representation in the hippocampus constitutes a temporal context signal that supports the temporal organization of memories. The cellular mechanism of this temporal context signal has been revealed in additional experiments where stimuli and behavioral events are held constant over a fixed period, and these temporally-defined events are repeated while recording the activity of multiple neurons. These experiments have identified reliable activations of single hippocampal neurons at specific sequential moments, and these neurons are called ‘time cells’ (Figure 1; for review see Eichenbaum [11]). In an early study that involved this

approach Pastalkova *et al.* [29] recorded from single hippocampal CA1 neurons as rats repeatedly alternated left-turn and right-turn paths on a T-maze, and trials were separated by a fixed period of wheel running. They observed that many neurons fired reliably at successive moments during wheel running and the entire period of each run was filled by a sequence of brief neuronal activations. Furthermore, 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 during running wheel running, indicating that the firing sequences coded information relevant to the path subsequently taken on each trial type. To resolve whether temporally selective hippocampal neuronal activation during the wheel run might have been coding distance run rather than elapsed time, Kraus *et al.* [30] recorded CA1 neurons as rats ran on a treadmill at varying speeds, thus allowing a dissociation of neural activity differentially locked to time or distance. They found that both time and distance are coded by CA1 neurons, with some neurons that fire associated only with time and some only with distance. Subsequently, the possibility of confounding spatial and temporal dimensions of hippocampal neural activity was eliminated by the observation of CA1 time cells during the delay period of a delayed matching to sample task in head-fixed rats [31]. Furthermore, this study identified distinct time-cell firing sequences associated with specific memories during the delay, and these memory specific temporally organized firing patterns predicted accurate memory performance. Importantly, the phenomenon of time cells involves activity patterns over periods of seconds in repeated events, whereas other studies discussed above [20,22•,23,24] have described a network representation of temporal context that gradually evolves over both brief and longer periods. It is not clear whether these temporal scales involve the same or distinct cellular mechanisms.

In addition, a recent study has directly compared the activity patterns of hippocampal place cells and time cells [32]. In this experiment hippocampal principle cells in CA1 and CA3 were recorded as rats either ran repeatedly in one direction or alternated paths through a continuous T-maze, thus varying the demand for remembering the immediately previous path, and during the memory delay in between trials the rats ran for a fixed period on a treadmill. Time cells were equally prevalent when memory demands were low (repeated path) or high (alternating path) during treadmill running, and place cells were equally prominent when rats traversed the maze itself when memory demands were low or high. Time cells and place cells were observed in the same population of recorded neurons and, while some cells were both time cells and place cells, the incidence of these equaled the conjoint probability of time and place coding in the populations of both cell types. These observations show that the same population of hippocampal principal

Figure 1

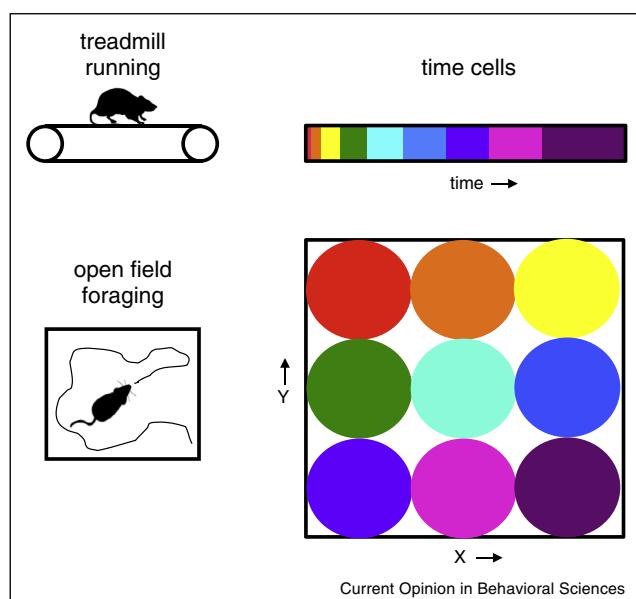


Illustration of similarities and differences between the firing patterns of time cells and place cells. Time cells (each identified with a different color) fire at successive moments during a fixed period of treadmill running, notably with larger time fields at later times. Place cells fire at adjacent locations in X and Y spatial coordinates during random walks while foraging, with equivalent sized place fields at all locations.

neurons code time and place. One major difference between time cells and place cells was observed. The resolution of place coding (size of place fields) was equivalent throughout traversal of the maze but the resolution of temporal coding during the treadmill runs decreased over the delay period (the size of time fields increased with time). Thus space is coded on a linear scale whereas time coding is nonlinear (see Figure 1; Howard and Eichenbaum [33]).

What is the origin of temporal coding in the hippocampal system?

Some studies have shown that selective lesions of area CA1 impair memory for temporal organization whereas lesions of area CA3 do not [34,35], and gradually changing spatial representations over prolonged periods are prevalent in CA1 and not CA3 [23]. On the other hand, place cells are as prevalent in CA3 as they are in CA1, and there are many similarities in the firing characteristics of time and place cells, suggesting that the entire hippocampal circuitry is involved in both temporal and spatial processing. Whether or not CA1 and CA3 have similar temporal coding properties has recently been addressed in studies on both humans and rats. Kyle *et al.* [36] used high resolution fMRI to measure activation of hippocampal subfields as humans made judgments of spatial and temporal distance between remembered events. They reported that all subfields of the hippocampus were equivalently activated associated with performance, although the patterns of activation differed for correct near and far judgments for spatial versus temporal distances. In a study on rats time cells were identified in CA3 as well as CA1 when animals run on a treadmill during the delay in between trials [32]. Time cells were equally prevalent in CA3 and CA1, were equally prevalent in variants of the maze that have low and high memory demands, and CA3 and CA1 had equal prevalence of place cells when animals traverse the maze between treadmill runs. In both areas, the resolution of temporal representations decreased with the passage of time on the treadmill, whereas there was no analogous difference in the resolution of place fields as a function of distance along the maze in either CA3 or CA1. Thus, in both humans and rats, like the representation of space, representations of time are similar throughout hippocampal circuitry.

With regard to mechanisms that support the organization of timing within hippocampal neural ensembles, recently Heusser *et al.* [37] observed that, as humans acquire sequential information in episodic memory, items in successive sequence positions are associated with greater gamma power along phases of theta cycles, consistent with Lisman's model in which order information is organized in a theta-gamma phase-amplitude coupling [38]. Correspondingly, Wang *et al.* [39[•]] reported that time cell sequences are dependent on the theta rhythm in rats during wheel running in the delay between spatial

memory trials. Notably, in contrast to the findings on time cells, the existence of place cells was not dependent on the theta rhythm. These findings suggest that theta oscillations are essential to the formation and maintenance of a self-generated temporal organization of neural ensembles that cannot be supported by external sensory inputs, but external inputs that are ever present in maze running are sufficient to support place cells.

Hippocampal time cells are also likely influenced by temporal context information provided from upstream cortical inputs, including inputs from cortical areas that neighbor the hippocampus and provide direct afferent inputs. Thus, in humans, a temporal context signal is observed in the parahippocampal cortex, which is widely known for its role in spatial context processing and is a major source of cortical input to the hippocampus [27,40]. The neural mechanisms that underlie temporal context processing in the cortex surrounding the hippocampus were revealed in a recent study of neuronal activity in the medial entorhinal cortex in rats [41[•]]. This study involved the same behavioral paradigm used to record time cells in the hippocampus [30] wherein rats ran on a treadmill for a specific period during the delay between trials in a spatial alternation task, and the same medial entorhinal cells were recorded while rats explored a large open field to identify a spatially periodic pattern of activity characteristic of 'grid cells' [42]. During treadmill running, grid cell activity was only weakly influenced by location but most grid cells and other neurons recorded from the same electrodes strongly signaled a combination of distance and time, with some signaling only distance or time. Grid cells were more sharply tuned to time and distance than non-grid cells. Many grid cells exhibited multiple firing fields during treadmill running, parallel to the periodic firing fields observed in open fields, suggesting a common mode of information processing for space and time. In addition, recent work has shown that temporary inactivation of the medial entorhinal cortex corrupts time cell sequences in the hippocampus [43]. These combined observations indicate that the medial entorhinal cortex provides an essential cortical input to the hippocampus for the representation of temporally organized experiences. Importantly, several other cortical areas process temporal as well as spatial information, and therefore many other areas could also contribute in an essential way to spatial-temporal processing within the hippocampus [44–46].

Conclusions

The mapping of time by the hippocampus complements the prominently described spatial mapping characteristics of hippocampal neural activity. Time cells underlie a gradually evolving temporal context signal that pervades hippocampal subfields and is supported by theta oscillations, and the hippocampus receives external temporal information from the neighboring medial entorhinal cortex and other cortical areas. This evidence, along with

parallel findings on spatial representation in the same system, provides an emerging understanding of how the hippocampus supports the spatial-temporal organization of experience. Finally, space and time are fundamental, easily identified and defined in experimental designs, and ever present in any behavioral situation, but they may reflect only some of a broad range of dimensions of experience mapped by the hippocampus [47–50].

Conflict of interest statement

Nothing declared.

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