

Time cells in the hippocampus: a new dimension for mapping memories

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Abstract | Recent studies have revealed the existence of hippocampal neurons that fire at successive moments in temporally structured experiences. Several studies have shown that such temporal coding is not attributable to external events, specific behaviours or spatial dimensions of an experience. Instead, these cells represent the flow of time in specific memories and have therefore been dubbed ‘time cells’. The firing properties of time cells parallel those of hippocampal place cells; time cells thus provide an additional dimension that is integrated with spatial mapping. The robust representation of both time and space in the hippocampus suggests a fundamental mechanism for organizing the elements of experience into coherent memories.

If I asked you to recall what you did when you woke up today, you might say that you got out of bed, showered and dressed, walked the dog, then sipped coffee and read the newspaper. Central to retelling this experience is remembering the order of events that composed the episode. The idea that recollection is temporally organized dates back at least to Aristotle and was described as the fundamental organizing dimension of episodic memory, as introduced by Tulving¹. Interest in the temporal dimension of episodic memory is increasing², as is a focus on mechanisms for encoding temporal relations among events in both simple and complex forms of associative learning³.

A large literature of studies in animals and humans has shown that the hippocampus plays a critical part in the organization of memories in time. A recent review summarized evidence from human and animal studies that used various physiological and behavioural approaches, and concluded that the hippocampus is essential to memory of the order of sequential events — even when it is not required for remembering specific events themselves — across a broad range of behavioural paradigms⁴. BOX 1 lists studies showing that damage to the hippocampus impairs memory of the temporal order of events in humans and animals, and that the hippocampus is activated in humans during encoding and recall of a sequence of events. Notably, the importance of temporal organization in hippocampal function extends even to simple conditioning and associative memory performance. For example, in classical trace conditioning (which is known to depend on the hippocampus) a tone is associated — across a temporal gap — with a shock, and the duration of the gap is a central component of the memory representation⁵.

Correspondingly, neurophysiological studies on classical conditioning have revealed that many hippocampal pyramidal neurons fire at specific moments that are timed to the conditioned response^{6,7}. Also, in an experiment in which rats learned to associate the durations of different time intervals with particular stimuli, the hippocampus was essential for discriminating close temporal differences, suggesting a role in temporal pattern separation⁸. These findings indicate a strong link between the hippocampus and temporal dimensions of memory.

What is the fundamental mechanism for temporal representation within the hippocampal circuitry? As a point of reference for addressing this question, it is generally thought that the mechanism for spatial representation in the hippocampus involves place cells, which are the principal neurons of the hippocampus that fire when an animal occupies a particular location in an environment⁹. In striking similarity, recent evidence shows that there are also hippocampal ‘time cells’ that fire when an animal is at a particular moment in a temporally structured experience, encoding scalar time and controlled by temporal dimensions of the experience (FIG. 1). Could time cells be the key to understanding how memories are temporally organized? Here I evaluate this hypothesis, discussing first the evidence for the existence of hippocampal time cells, their characteristics and their role in memory. Then I assess the similarities between time cells and place cells, and discuss how representations of time and space cooperate to organize the contents of memories. Finally, I consider the possible sources of temporal information in the hippocampus, as well as the possible mechanisms by which time cells may arise within the hippocampus.

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Box 1 | Studies reporting hippocampal involvement in the temporal organization of memories

Damage to the hippocampus in humans results in impairments in:

- Reproducing the order of words in a list⁷⁷
- Recalling and recognizing the order of words and word pairs⁷⁸
- Remembering the order of objects visited in a virtual environment⁷⁹
- Deferred imitation of action sequences^{80,81}
- Retrieval of the order of presented objects⁸²

Damage to the hippocampus in rodents results in impairments in:

- Memory for once-presented odour sequences^{83,84}
- Disambiguation of overlapping odour sequences⁸⁵
- Preferential exploration of earlier-presented odours in familiar sequences⁸⁶
- Memory for the order of odours presented in different places⁸⁷
- Preferential exploration of the earlier-presented object in a set of objects that had been presented once before⁷⁴
- Memory for stimulus associations across a temporal gap^{73,74}
- Memory for the order of once-presented odour pairings⁸⁸
- Memory for the duration between presented odours⁸
- Serial reaction-time sequence learning⁸⁹
- Anticipatory selection of maze arms experienced in sequence⁹⁰
- Flexible expression of body-turn sequences in a maze⁹¹

Activation of the hippocampus in humans occurs during:

- Encoding of overlapping face sequences⁹²
- Remembering the order of objects visited in a virtual environment⁹³
- Reconstruction of the order of scenes in a movie clip⁹⁴
- Retrieval of overlapping and non-overlapping face sequences⁹⁵
- Viewing of items out of order in a familiar sequence⁹⁶

- Encoding of word triplets predicting memory success⁹⁷
- Encoding during increased demand to bridge a temporal gap between stimuli⁹⁸
- Serial reaction-time sequence learning⁹⁹
- Disambiguation of overlapping routes through a virtual maze¹⁰⁰
- Successful retrieval of coarse temporal order¹⁰¹
- Similar coding of consistently successive experienced objects¹⁰²
- Successful retrieval of the temporal positions of objects in learned sequences⁵⁹
- Differentiation of temporal context during successful sequence retrieval¹⁰³
- Similar coding of neighbouring objects predicting successful order memory¹⁰⁴

Temporal coding by hippocampal neurons occurs during:

- Encoding of once-presented odour sequences in rats¹²
- Long periods between repeated experiences in rats^{12–15}
- Wheel running during the delay in maze alternation in rats¹⁶
- Inter-trial intervals as rats learn a place reversal task¹⁷
- Delay periods between paired-associate stimuli in rats¹⁸
- Delay periods between sequentially presented stimuli in immobilized monkeys²²
- Treadmill running at different speeds during the delay in maze alternation in rats¹⁹
- Delay periods in delayed non-match to sample in immobilized rats²⁰
- Trace eyelid conditioning in immobilized mice²¹
- Memory for sequential events in movie clips in humans^{23–25}

Time cells

The earliest evidence of the representation of time by hippocampal neurons came from studies revealing that CA1 principal cells exhibit temporal coding in freely moving rats performing tasks that involve remembering sequences of events. These findings generated considerable interest but were initially criticized as being confounded by effects of variations in the animal's location across time and of distance travelled over time, so that the apparent temporal coding could reflect spatial rather than temporal dimensions of the animal's experience^{10,11}. More recent studies have addressed these concerns by tightly controlling the animal's location and movement. In addition, recent studies have found evidence of temporal representation by hippocampal neurons in non-human primates and humans. The brief descriptions of these experiments below provide an overview of the characteristics of temporal coding by the hippocampus (see BOX 1 for a summary).

Early evidence from freely moving animals performing memory tasks. The first direct evidence for temporal coding by hippocampal neurons emerged in an experiment in which ensembles of CA1 principal neurons were recorded in rats performing a task that required memory for the order of a sequence of odour stimuli. In the encoding phase of each trial, several odours were presented in sequence (each followed by a reward) at

alternate sides of the enclosure. In the test phase of each trial, two odours were presented and the rat had to remember which one had occurred earlier in the preceding encoding phase¹² (FIG. 2A). The pattern of activity of a CA1 neuron ensemble changed gradually across the encoding phase of a trial, and the strength of this change predicted memory performance in the subsequent test phase. This suggested that the activity pattern of the CA1 ensemble provided an evolving temporal context in the encoding of the memory of the odour presentations. The firing patterns of the same hippocampal ensemble also varied with the locations at which the odours were presented, but the differences in spatial representations were equivalent in correct trials and error trials, and therefore did not predict the accuracy of the memory performance. Notably, gradually changing patterns of hippocampal ensemble activity reflecting temporal contexts have been shown to cover periods of seconds and minutes¹², hours to days¹³, and weeks^{14,15}.

In the experiment discussed above¹², each odour sequence occurred only once, and it was therefore not possible to determine whether the firing patterns observed in each trial were reliably associated with the specific odour sequence of that trial. A subsequent study¹⁶ recorded from single CA1 neurons in rats performing a spatial alternation task in a T-maze. Here, the rats repeatedly alternated between left turns and right turns, and trials were separated by a fixed period

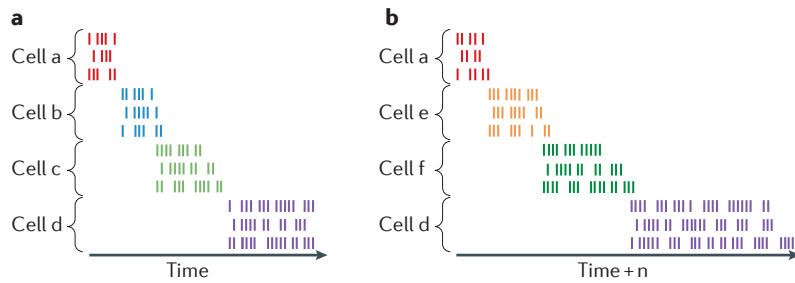


Figure 1 | Key features of time-cell firing sequences. **a** | A raster display of spiking activity from idealized, simultaneously recorded time cells (each shown in a different colour). For each cell, activity is shown as a raster of spikes for three example trials in which the cell fires for a brief period at approximately the same moment in each trial, with later-firing time cells being active for longer periods (indicating scalar coding of time). **b** | In the same recording session, when the time period is elongated (time + n), the cells shown at the top and bottom fire at the same moment relative to the beginning and end of the period, respectively (indicating that their activity is bound to those temporal boundaries), whereas the cells shown in the middle in part **a** have ceased firing and new cells (note the new colours in part **b**) fire to fill in the period, reflecting ‘re-timing’ in these cells to represent the altered temporal dimension. These characteristics parallel those of place cells, which typically fire at adjacent locations in space and, when critical spatial cues are altered, either remain bound to cues still present or ‘re-map’ to reflect the altered spatial dimensions.

of wheel running (FIG. 2B). This study showed that many neurons fired 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 mostly in the same location (that is, in the running wheel) and performing the same behaviour (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.

Another study¹⁷ examined the 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.

Another recent study¹⁸ examined whether CA1 neurons also fired at specific moments in a non-spatial task. In this task, rats learned to associate each of two visually distinct objects with one of two cups of scented sand (FIG. 3A). In each trial, rats approached and sampled one of the two objects and, after a fixed delay, were exposed to one of the two odour cups. If the odour 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 — filling out the

entire period. The 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 analysis was used to distinguish activity patterns associated with the animal’s location, speed and head direction during the delay period from activity patterns associated with the time elapsed. Although these spatial and behavioural 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 (that is, they ‘re-timed’) when the delay was increased. This happened even though the behaviour and locations of the animal during the initial period did not change (FIG. 3A; also see FIG. 1b), indicating that the firing patterns of these cells reflected the passage of time rather than variations in behaviour or place. Because these neurons fired at specific moments in a fixed period — much like place cells fire at specific locations in a fixed space — these neurons were dubbed ‘time cells’ in this study. Importantly, the authors¹⁸ observed that cells firing later in the delay period were active for longer durations (that is, they had larger ‘time-fields’) (FIG. 1), a phenomenon that was also observed in other studies^{19,20} (discussed below). This pattern suggests a scalar coding of time, which parallels a hallmark property of time judgements in humans and animals, as discussed below.

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.

Temporal versus other dimensions of experience encoded by hippocampal neural activity. In all of the studies described so far, the rats could move freely during the periods when time-related activity was observed. Even though the neural activity patterns associated with elapsed time could be distinguished from the activity patterns associated with different locations, there was still the possibility that the apparent time-related activity was confounded by effects of the distance that the animal travelled during the recording periods. One study specifically addressed this possibility¹⁹. Here, rats performed a spatial alternation task in a maze. In between alternations, the animals ran on a treadmill placed in the segment overlapping the two paths through the maze (FIG. 3B; also see [Supplementary information S1 \(movie\)](#)). The authors varied the treadmill speed randomly on each trial, so that the effects of elapsed time and distance travelled on neural activity could be disentangled. A general linear model analysis that considered head position, time and distance revealed that the activity of over 80% of the neurons that were active during treadmill running was modulated by elapsed time. Position had little influence, but distance travelled was also strongly encoded in the activity of many neurons. The firing patterns of some neurons signalled only time or only distance, but the activity of most cells was influenced to differing degrees by both variables, indicating that most of these cells encoded both time and distance.

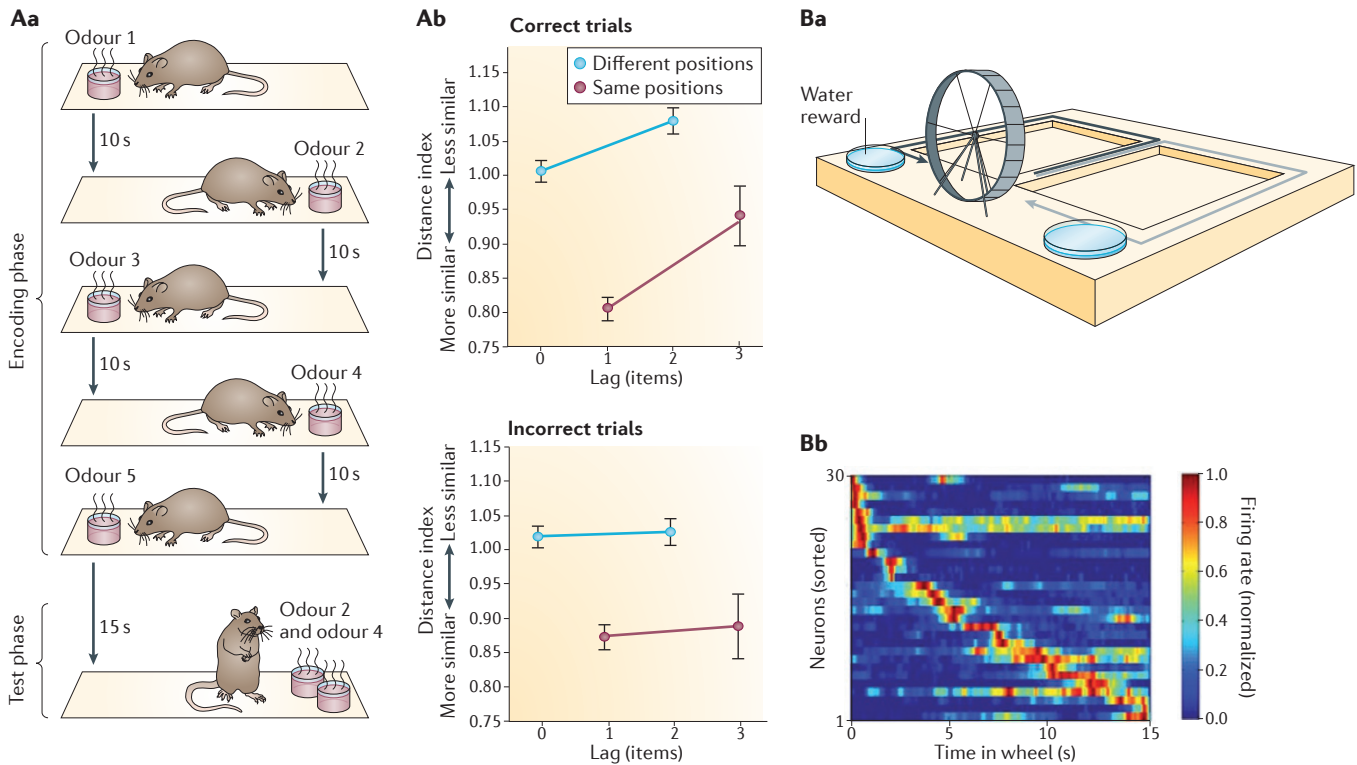


Figure 2 | Early discoveries on temporal coding by hippocampal neurons. **Aa** | Design of an odour sequence memory task. In the encoding phase of each trial, rats sampled a sequence of five odours, which were presented at alternating positions on a platform. In the test phase at the end of each trial, they were presented with two odours and had to judge which of the two had been presented earlier. **Ab** | Recordings from CA1 neural ensembles made during the test phase revealed that an index of distance (or dissimilarity) between periods surrounding odour representations in neural populations was larger for odours that had been sampled further apart (that is, they were separated by a larger number of intervening items) than for odours sampled close together (smaller lag) — but only on trials in which the order judgement was correct and not on error trials, regardless of whether the odours appeared at the same or different positions. By contrast, the distance between population representations of positions in space did not differentiate correct trials and errors. Error bars indicate the standard error of the mean for the variability across sessions. **Ba** | Design of a spatial alternation T-maze task. Rats travelled along two paths in a T-maze (indicated by black and grey arrows) in alternation, and in between they ran in a running wheel. **Bb** | The ensemble firing-rate plot shows the normalized firing rates of 30 neurons during the wheel running period (each row shows the activity of one neuron). The plot reveals that different hippocampal neurons fired at different times during wheel running, and that together, the neurons' firing covered the entire period. These two studies revealed the existence of representations of a gradually changing temporal context signal in two very different memory tasks: one in which animals encoded unique sequences of odours and another in which they repeatedly ran on a running wheel in between memory judgements. Part **A** reprinted from *Neuron*, 56, Manns, J. R., Howard, M. W. and Eichenbaum, H. Gradual changes in hippocampal activity support remembering the order of events, 530–540, © (2007), with permission from Elsevier. Part **Bb** from Pastalkova, E., Itskov, V., Amarasingham, A., and Buzsáki, G. Internally generated cell assembly sequences in the rat hippocampus. *Science* 321, 1322–1327 (2008). Reprinted with permission from AAAS.

Further evidence supporting the existence of temporal signals that are independent of place or distance has come from recent studies of time cells in head-fixed animals in which the animal's location and behaviour were kept constant and movement was eliminated. For example, in one study²⁰, rats performed an odour-cued delayed matching-to-sample task in which each trial began with the presentation of one of multiple sample odours for 1 s. Following a fixed delay, a test odour was presented. In order to receive a reward, the animal had to respond only to the test odour that matched the sample on that trial (FIG. 4A). In these rats, approximately 30% of hippocampal cells encoded successive moments during the 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 in mice undergoing classical conditioning²¹. On each trial, mice heard a brief tone that was followed, after a temporal gap, by an air puff to the eye (FIG. 4B). During acquisition of the conditioned eye-blink response, CA1 cells developed time-locked firing sequences throughout the trial, including during the temporal gap.

Together, these observations provide compelling evidence that the principal cells of hippocampal area CA1 encode the temporal structure of events in remembered experiences independently of any effects of location and movement on neuronal activity.

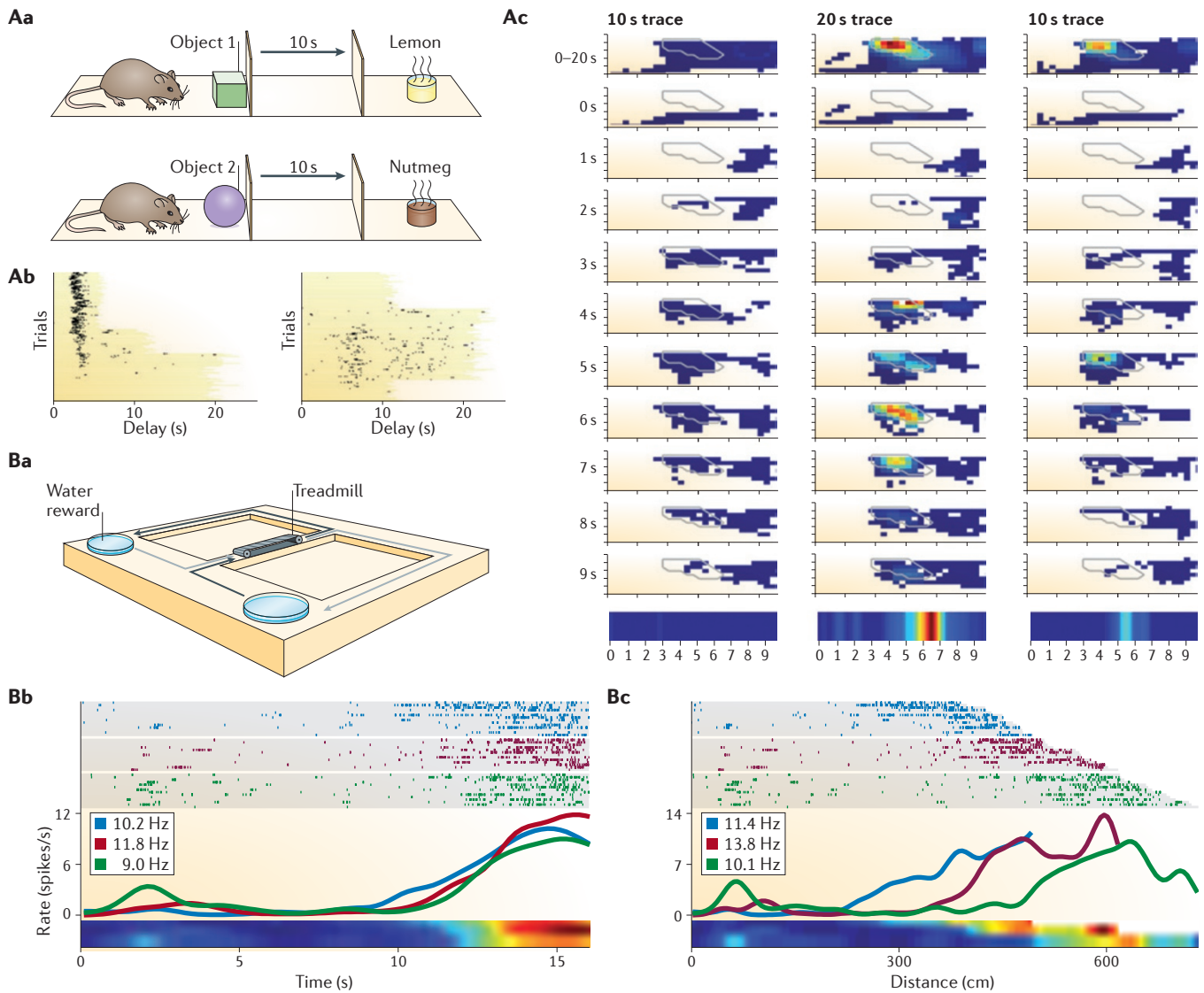


Figure 3 | Time coding and spatial coding. **Aa** | Design of a non-spatial task in which time cells were observed. Rats learned to associate each of two visually distinct objects with one of two cups of scented sand (for example, the green block was associated with the lemon-scented cup and the purple sphere was associated with the nutmeg-scented cup). In each trial, rats approached and sampled one of the two objects and, after a fixed (10 s or 20 s) delay, were exposed to one of the two odours. If the odour matched the object (for example, lemon odour following a green block), the rat had to dig in the scented sand to retrieve a reward. If the odour did not match the object (not shown), no reward was available in the odour cup and the rat did not dig. **Ab** | Two examples of cells that ‘re-timed’. On the left, a cell that progressively lost its time field as the delay was elongated from 5 s, to 10 s, to 20 s. On the right, a cell that did not fire when the delay period was 10 s but that did fire (at about $t = 6-7$ s) when the delay period was 20 s. **Ac** | The spatial activity pattern (place field) of the cell whose raster plot is shown on the right in part **Ab**. Activity is plotted for the entire delay period (top) and for the first ten successive seconds of the delay period in each trial block. Note that the cell fired at a particular location but only during the sixth to seventh second of the 20 s delay period (middle column) and not in trials with a 10 s delay period (left and right column; also see the normalized firing rates over time in the trace at the bottom). **Ba** | Design of a spatial alternation task. Rats ran on a treadmill in between alternating left turns and right turns on a T-maze (paths indicated by black and grey arrows). **Bb,Bc** | The firing patterns of a hippocampal neuron shown in raster plots (top), firing rate histograms (middle) and normalized firing rate (bottom) across a range of treadmill speeds. When firing is plotted according to time elapsed (**Bb**), the cell fired at about 14 s into treadmill running regardless of speed. Plotting the same data according to distance travelled (**Bc**) reveals that the cell fired at different distances depending upon speed. These experiments showed that hippocampal neurons can encode time and space conjointly (**A**) or can encode time only and not spatial dimensions (**B**). Parts **Ab** and **Ac** reprinted from *Neuron*, **71**, MacDonald, C. J., Lepage, K. Q., Eden, U. T. and Eichenbaum, H. Hippocampal ‘time cells’ bridge the gap in memory for discontinuous events, 737–749, © (2011), with permission from Elsevier. Parts **Bb** and **Bc** reprinted from *Neuron*, **78**, Kraus, B. J., Robinson II, R. J., White, J. A., Eichenbaum, H. and Hasselmo, M. E. Hippocampal ‘time cells’: Time versus path integration, 1090–1101, © (2013), with permission from Elsevier.

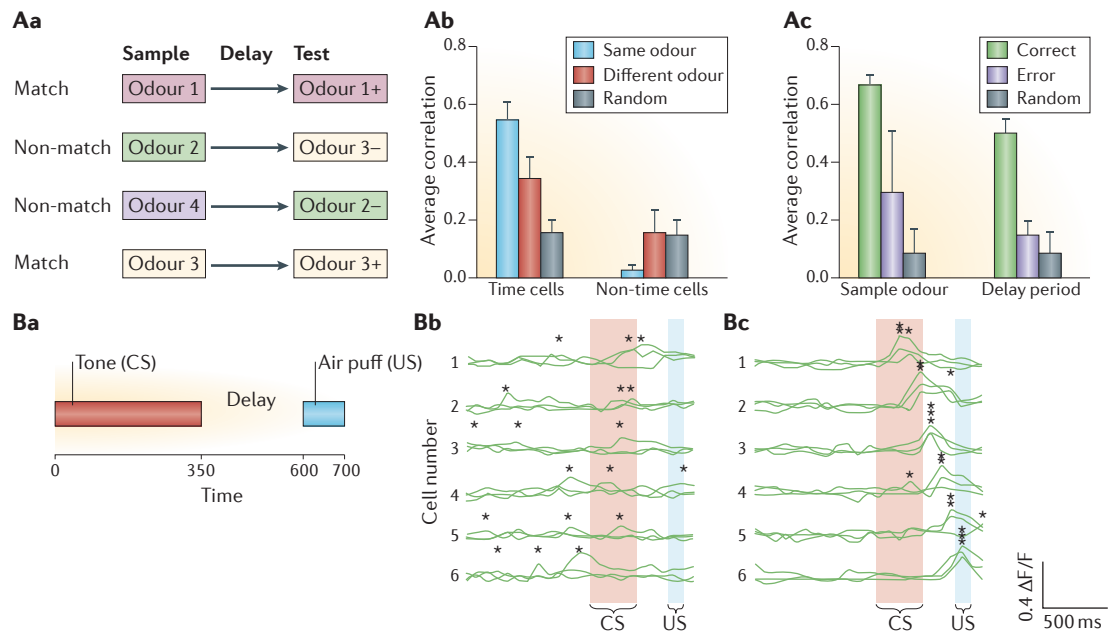


Figure 4 | Time cells have a role in memory. **Aa** | Design of an example series of trials used in immobilized (head-fixed) rats performing an odour-cued delayed matching-to-sample task. Each trial began with the presentation of one of up to four sample odours for 1 s. Following a 2–5 s delay, a test odour was presented. In ‘match’ trials (that is, when the test odour was the same as the sample odour), the rat could respond to the test odour to receive a reward (indicated by ‘+’). In ‘non-match’ trials (that is, when the test odour differed from the sample odour), no reward was available (indicated by ‘-’). Match and non-match trials were presented in a random order. **Ab** | Population vectors during the delay period for time cells were well correlated between trials that began with the same sample odour, and were less strongly correlated (but still above that of control (random) conditions) between trials with different sample odours; cells that were not temporally modulated did not code for different sample odours. Error bars indicate the standard error of the mean. **Ac** | Population vectors were similar between trials with the same sample when the match/non-match judgement was subsequently correct during both the sample period and the ensuing delay, but these correlations were reduced on error trials. Error bars indicate the standard error of the mean. **Ba** | Mice were given trace classical conditioning; in each trial, a 350 ms tone (the conditioned stimulus (CS); red bar) was followed by a 250 ms delay period, then a 100 ms air puff (the unconditioned stimulus (US); blue bar). **Bb, Bc** | Calcium signals ($\Delta F/F$) in six example CA1 neurons (activity patterns on three example trials are shown for each neuron) from the same mouse before (**Bb**) and after (**Bc**) learning show the emergence of successive timing signals (* indicates the peak signal for each cell). Specifically, after conditioning, the timing of the CS (red bar), the delay and the US (blue bar) periods are encoded by the firing sequence of the six neurons. Part **A** is adapted with permission from REF. 20, Society for Neuroscience. Part **B** is adapted with permission from REF. 21, eLife Sciences.

Time cells in other species. There is also evidence of temporal coding by hippocampal neurons in monkeys and humans. For example, one study examined temporal modulation of hippocampal firing patterns in head-fixed monkeys performing a temporal-order memory task²². On each trial the monkey was shown two objects, separated by brief delay. When the animal was subsequently presented with an array of three objects composed of the same two objects and one other object, it had to identify the two previously encountered objects in the correct sequence in order to receive a reward. The firing rate of many hippocampal neurons increased or decreased during the delay between the two object presentations, such that the firing pattern of the whole ensemble consistently signalled the passage of time during the delay periods. Notably, only few hippocampal neurons encoded object identity. The proportion of cells encoding time decreased from entorhinal cortex to perirhinal cortex to inferotemporal cortex (upstream of the hippocampus), whereas the proportion of cells encoding object identity increased.

Other studies have involved recording of single-neuron activity in humans viewing video clips. These studies showed gradually changing patterns of activity of neurons in the medial temporal lobe that were repeated when specific clips were remembered²³ or when specific memories were cued²⁴. Also, the firing sequences of neurons in the hippocampus (but not in any other medial temporal areas) became more similar with repeated viewings of a particular clip segment — that is, while a memory of the clip was being formed²⁵. Although these slowly changing activity patterns more closely resemble the gradually evolving time signal in the study by Manns *et al.*¹² than the sequences of punctate time-cell activations in the above-described studies on rodents, these observations clearly demonstrate that temporal coding by neuronal activity related to memory also occurs in the human hippocampus.

The findings discussed in this section indicate that temporal coding by hippocampal neurons is prevalent across species and a broad range of memory paradigms.

In each experiment, temporal coding was characterized by a gradual change in the activity of the neuronal population over time. Most prominent in some of the studies were individual neurons — called ‘time cells’ — that fired for brief periods consistently at successive moments within distinct repeated experiences. Several of these experiments provided compelling evidence that hippocampal neurons signal elapsed time independent of place, distance travelled and movement (FIG. 4), although these dimensions can also be encoded by the same neurons (FIG. 3).

The role of time cells in memory

Some of the studies discussed above have linked the temporal coding patterns of hippocampal neurons to memory performance, providing compelling evidence that the hippocampus creates a temporal organization of memories. Temporal coding has been linked to memory performance in three ways: first, temporal coding develops as animals acquire temporally structured memories; second, distinct temporal codes are associated with specific memories; and third, temporal coding predicts accurate memory judgements about individual events.

With regard to the development of temporal coding with learning, memory-specific firing sequences of time cells during wheel running were observed only after rats had been trained to remember particular paths through a maze and not during wheel running outside the memory task¹⁶. Furthermore, memory-specific time-cell firing sequences developed only over the course of learning a hippocampus-dependent place-reversal task and not during random runs on the same maze¹⁷. Moreover, in head-fixed mice undergoing classical trace eye-blink conditioning, reliable time-cell firing sequences appeared only after the conditioned response was established²¹ (FIG. 4B).

With regard to the specificity of memory coding, in several studies in which specific memories were repeated, distinct temporal codes were observed. For example, different consistent firing sequences of time cells during wheel running were observed that preceded the memory-specific judgements that rats subsequently made in a spatial alternation task¹⁶. Also, in head-fixed rats performing an odour-cued delayed matching-to-sample task, the time-cell firing sequences observed during the delay period following each odour cue involved both neurons that were specific to the preceding sample odour and neurons that were common to all of the odour memories (and that therefore probably represented the common temporal structure of all trials)²⁰ (FIG. 4A). Moreover, in humans, neurons in the hippocampal region that fired in sequence as subjects watched individual video clips ‘replayed’ these sequential firing patterns as subjects mentally recalled the same individual clips²³.

With regard to the accuracy of memory, the appearance of specific firing sequences predicts subsequent accurate memory judgements in individual trials. In an early study on temporal coding, successful memory for sequences of events that were presented only once was associated with a gradually changing firing pattern within a hippocampal neuronal population¹² (FIG. 2A). Also, during performance of the odour-cued delayed

matching-to-sample task, odour-specific time-cell firing sequences both during the sample period and during the delay of a particular trial predicted subsequent memory success on that trial²⁰ (FIG. 4A). These studies show that time-cell sequences can reflect both unique memories and common elements between memories, and suggest that these patterns drive accurate memory performance. Finally, earlier studies have shown that neural ensemble activity in the hippocampus evolves over time during the delay in a recognition memory task, and the decay of these patterns predicts memory errors²⁶.

Time cells and place cells

Time cells are the same neurons as place cells. One line of evidence supporting this conclusion is that, in freely moving animals, time cells are activated only when the animal is in a particular location (FIG. 3A). In rats performing a spatial alternation task including running on a treadmill between alternations¹⁹, time-specific firing could be identified when rats were running on the treadmill, and place-specific firing patterns could be identified when rats traversed other segments of the maze. Both time cells and place cells were observed within the same population of simultaneously recorded cells. Indeed, some of the same neurons that fired at particular moments in time (that is, time cells) on the treadmill also fired when the rat passed through specific locations on the maze outside the treadmill, showing that these cells also function as place cells (see Supplementary information S1 (movie)).

Additional characteristics of time cells closely paralleled the properties of place cells observed in other studies. For example, when a salient spatial cue in a familiar environment is altered, place cells either continue firing in association with the remaining spatial cues or ‘re-map’ (that is, alter the spatial firing pattern, or cease or begin firing)²⁷. Similarly, when the duration of the interval between cues in an object-odour association task is altered, some time cells maintain firing at a specific time relative to the beginning or end of the interval, whereas many other cells ‘re-time’ — that is, fire at a different moment, or cease or begin firing¹⁸ (FIGS 1b,3A). Thus, the partial reorganization of firing patterns of time cells that occurs when a critical temporal cue is altered closely parallels the partial reorganization of place cells that occurs when spatial cues are altered.

In addition, both place cells and time cells encode other relevant dimensions of experience. So, under different conditions relevant in particular behavioural paradigms, place cells can encode a range of spatial features (for example, distance and direction^{28,29}), as well as non-spatial stimuli (for example, an odour in a particular place³⁰) and action events (for example, a learned ‘jump’ escape response³¹). Similarly, as described above, in freely moving animals, time cells can also encode place, distance and ongoing behaviour^{18–20}. Thus, it may be more productive to think of hippocampal principal neurons as multidimensional, in the sense that they encode time and place along with other relevant spatial and non-spatial features of ongoing experience³².

Interactions between spatial and temporal codes

Particularly striking examples of hippocampal neurons encoding conjoint spatial and temporal dimensions of experience are evident when rats traverse routes in a maze. In this situation, space and time progress together as the rat moves through the maze, and the influences of both spatial and temporal coding can be observed. For example, 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 ‘replay’ the corresponding sequence of firings during ‘off-line’ periods, including sleep and quiet wakefulness, when the animal is not moving through those locations³³. Thus, spatial coding observed as rats actively run through a maze is recapitulated in temporally coded firing sequences when the rat is not moving. Disruption of these replay events impairs subsequent memory of the path³⁴. Moreover, replays of sequences associated with alternative choice paths in a maze predict acquisition of a learned performance³⁵. 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 field³⁶. These findings on replay strongly indicate a temporal coding of spatial representations relevant to memory.

In addition, the temporal context of an ongoing experience strongly influences place-cell activity. Thus, several studies have shown that when rats traverse the common segment of a maze that features two alternate paths, hippocampal place cells fire differentially depending on whether the animal is in the midst of following one path or the other, rather than firing in the same pattern at the common location^{37–40} (FIG. 5A). Furthermore, path-specific firing sequences predict the accuracy of memory performance; place cells exhibit path-specific firing sequences when subsequent memory choices are correct, but place cells in that sequence fire less or not at all prior to errors⁴¹ (FIG. 5B). The finding that a specific hippocampal firing sequence occurs on the overlapping segment of different routes through a maze is complemented by the report of memory-specific sequential firing patterns in the hippocampus in rats remembering overlapping sequences of odours⁴². These studies show that the broader temporal context of an entire episode strongly influences the coding of specific places and events.

A different kind of interaction between spatial and temporal coding is observed in a situation in which hippocampal neurons can use either a spatial code or a temporal code when behavioural strategies associated with these codes compete. Thus, in a maze task⁴³

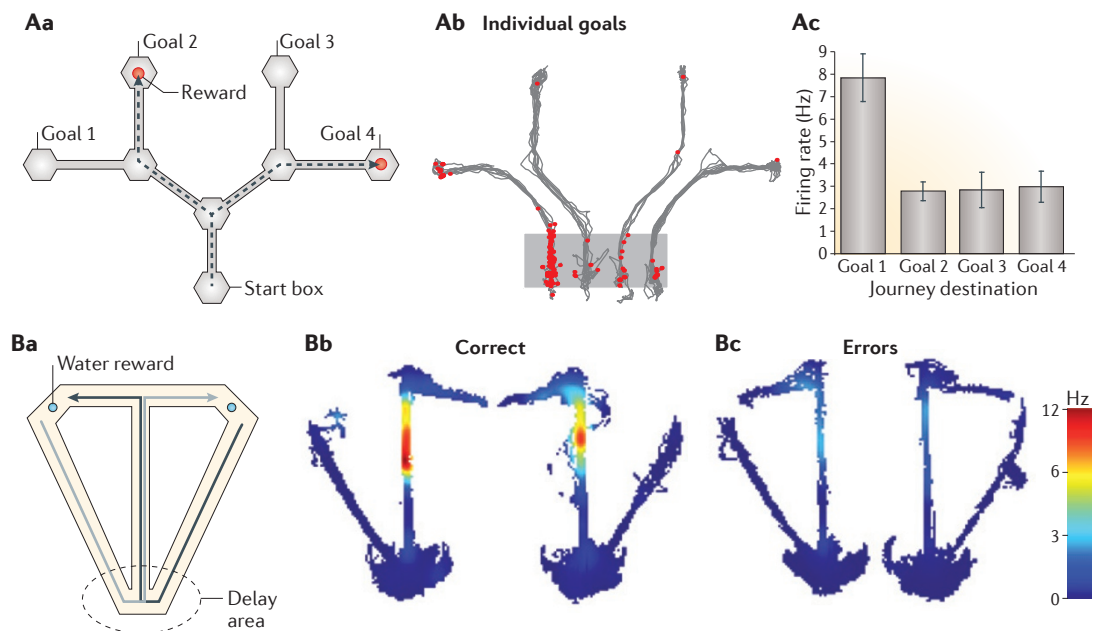


Figure 5 | The influence of temporal context on spatial coding. **Aa** | Rats were required to select one of four paths towards distinct goal boxes (two paths are shown as dashed lines). **Ab,Ac** | Plots of spikes (**Ab**) and firing rate (**Ac**) for an example cell. This cell fired maximally at the outset of the path towards goal 1, and much less so at the outset of paths towards the other three goals, even when the rat passed through the same location in all paths. Error bars indicate the standard error of the mean across trials. **Ba** | Delayed spatial alternation task in which rats alternate between left-turn (black arrow) and right-turn (grey arrow) paths at a decision point on a maze. The two paths have a common arm, and both start with a 30 s delay period at the bottom of the common arm. **Bb,Bc** | Normalized firing-rate plots of a hippocampal neuron. The plots show that this neuron fired maximally in the common maze segment on correct right-turn trials (**Bb**, left) and less so on correct left turn trials (**Bb**, right), and hardly at all on either type of error trial, regardless of the subsequent turn direction (**Bc**). In both of these experiments, the broader temporal context of the entire path through the maze determined which place cells were active at specific locations on the maze. Part **A** is adapted with permission from REF. 40, Society for Neuroscience. Part **B** reprinted from *Behavioural Brain Research*, 254, Robitsek, R. J., White, J. A. and Eichenbaum, H. Place cell activation predicts subsequent memory, 65–72, © (2013), with permission from Elsevier.

in which mice must take novel routes towards a trained goal, the path that they take is sometimes guided by the known location of the goal as defined by distant spatial cues, whereas at other times it reflects the previously learned sequence of body turns. To determine which strategy was used, trials were started from a novel location in the maze and it was observed whether the animal went to the trained goal location or made the trained sequence of body turns. Analysis of neural activity revealed that firing sequences of hippocampal neurons reflected the strategy expressed on these probe trials — that is, when the mice ran towards the learned location, which required a new sequence of body turns, the neurons fired at consistent locations in the maze. By contrast, when mice reproduced the learned sequence of body turns, which resulted in moving to a different goal location, the neurons fired at consistent steps in the sequence.

Together, these findings provide compelling evidence that hippocampal neuronal ensembles represent the sequence — that is, the temporal organization — of events in memory. This includes memories for sequences of places traversed in a maze, sequential stimuli and action sequences.

To summarize the findings on time cells, there is now substantial evidence that hippocampal neurons encode elapsed time independently of, or along with, various other spatial and non-spatial variables, just as place cells can encode location independently of, or along with, other spatial variables and non-spatial events such as specific stimuli or behaviours. Time cells are controlled by the temporal cues (the beginning and end of an episode) and the temporal structure (critical intervals) of an experience, just as place cells are controlled by the spatial cues (landmarks) and the spatial structure (shape) of the environment. Also, there is now compelling evidence that firing sequences of time cells develop with learning, are memory specific and predict the accuracy of subsequent memory across a broad variety of tasks. Finally, time cells and place cells are the same neurons, and the same neuronal ensembles can encode the temporal and spatial organization of experiences.

Origins of timing in the hippocampus

What is the source of timing signals that are used to generate time cells in the hippocampus? It is possible that temporal information generated in the cerebral cortex and other brain areas provides signals to time cells within the hippocampus (FIG. 6a). Alternatively, the time-cell phenomenon might arise from the sequential activation of firing chains that are generated locally within the hippocampal circuitry (FIG. 6b). These two possibilities are considered below.

External sources of temporal information. There is a substantial literature on time perception in humans and animals, and a large number of recent studies have sought to identify brain areas that support the brain's ability to time in different tasks^{44–47}. One prominent model suggests that the neural basis for interval timing involves interactions between multiple oscillatory

patterns in prefrontal and parietal cortical areas, resulting in unique patterns of activation at different times that are integrated in the striatum^{48,49}. Thus, possible external sources of temporal information to the hippocampus include those prefrontal and parietal areas that provide some of the major inputs to the hippocampus. Indeed, a study in rats showed that damage to the medial prefrontal area severely impaired interval timing and that neurons in the medial prefrontal cortex signalled elapsed time in a manner consistent with encoding of time on a logarithmic scale⁵⁰. Studies in monkeys performing interval-time estimation showed that neurons in the lateral parietal area signal changes in a monkey's judgements about elapsed time (relative to a standard remembered duration)^{51,52}. Furthermore, the parietal-temporal junction is activated in humans making temporal-order judgements⁵³. Interestingly, in a prefrontal-parietal-medial-temporal network, different oscillation frequencies were associated with memory for the spatial location and memory for the temporal order of events^{54,55}. These findings suggest that prefrontal areas and parietal areas that are classically considered part of the 'where' stream (that is, the visual stream for spatial processing) are also involved in the perception of time, and these areas have robust inputs to the hippocampus.

The major cortical input from the 'where' stream reaches the hippocampus via the parahippocampal cortex. This area, also known as the 'parahippocampal place area' because of its activation when humans look at scenes⁵⁶, may also signal information about temporal context. For example, different parts of the parahippocampal cortex are activated when humans view images of objects that elicit memories of temporally co-occurring items than when they view images of objects that elicit memories of spatial arrangements⁵⁷. Moreover, the level of activation in the parahippocampal cortex during the viewing of scenes depends on the recent history of scene presentations, indicating that scene coding is embedded within a representation of temporal context⁵⁸. In addition, during the retrieval of object sequences, activity patterns in the parahippocampal cortex and the perirhinal cortex were specifically associated with the temporal order of objects in sequences and with object identities, respectively, whereas those in the hippocampus encoded object identities within a temporal context⁵⁹.

Following the 'where' stream further towards the hippocampus, lesions of the medial entorhinal cortex — an area commonly associated with spatial representation — impair memory of the temporal context of recently experienced stimuli⁶⁰, and entorhinal inputs to the hippocampus are essential for bridging temporal gaps between associated events^{61,62}. Furthermore, there is recent evidence that medial entorhinal cortex neurons that fire when a rat is in particular locations in space (known as 'grid cells') also fire at particular moments during treadmill running⁶³. Combined, these findings suggest that signals about the temporal context of experience are sent via a network of cortical areas to the hippocampus, which then parses temporal context into discrete units (time fields) that represent the flow of

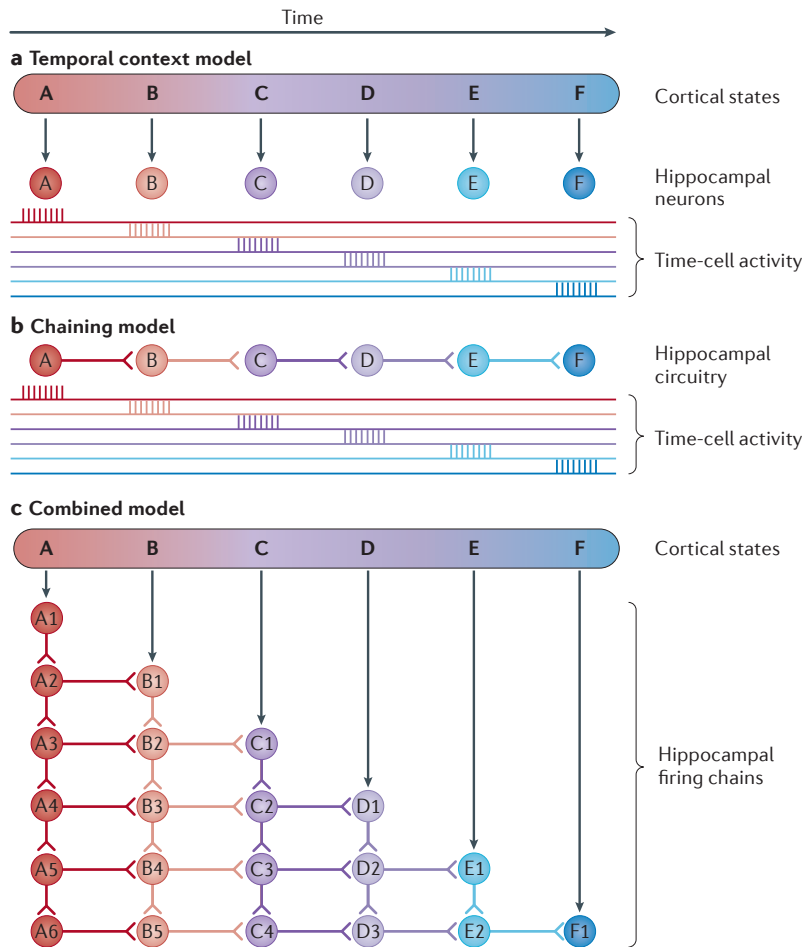


Figure 6 | Temporal context versus chaining models. **a** | In the temporal context model, each hippocampal neuron represents a unique state of cortical activity that corresponds to moments in the stream of events processed within the cortex⁶⁹. **b** | According to the chaining model, hippocampal neurons increase sequential connection strengths with repeated experiences to produce hippocampal neuron firing sequences⁶⁷. **c** | A combined model might include firing chains that are generated at successive steps as the temporal context gradually evolves, and also associations between neurons that fire at the same time across chains.

sequential events⁶⁴ (FIG. 6a). This view is consistent with a recently proposed distinction between the ability to judge temporal intervals, in which the hippocampus has a secondary role, and memory for temporal organization, in which the hippocampus is central^{65,66}.

An internal mechanism? An alternative mechanism for the time-cell phenomenon could be that the sequential activation of these cells reflects a strengthening of connections between neurons that are repeatedly activated in sequence within the hippocampus to create a firing chain (FIG. 6b). This model is consistent with the finding that when rats repeatedly run through a sequence of locations, the place fields of hippocampal neurons expand backwards from their original centre⁶⁷. This backward expansion of place fields could reflect each place cell being driven by an earlier-firing place cell through enhanced connectivity that is generated by repeated sequential activation.

Evidence for both models. Several findings suggest that a strict chaining model, composed of a single sequence of cell activations, is unlikely to be the mechanism for time cells. As discussed above¹⁸, an experimental elongation of the critical temporal dimension (specifically, the delay between object exposure and odour exposure) caused most time cells to ‘re-time’. That is, the cells changed their temporal firing patterns even during the initial part of the delay (thus creating a new temporal context representation), rather than simply adding cell activations during the extended segment of the delay (that is, elongating the firing chain). Also, distinct firing sequences disambiguate overlapping memories — experiences that contain common elements — and two studies^{16,18} have shown that such distinct temporal firing patterns are associated with different memories even though the memories share identical events. Strict firing chains cannot ‘split’ to differently encode overlapping memories, although different initial elements in a sequence could specify a distinct sequence of succeeding elements that represent overlapping events⁶⁸. In addition, firing sequences of time cells are usually scalar, so that time cells that fire later in a sequence also fire for a longer period (FIGS 1b,2b; but see REF. 16). This is inconsistent with firing chains involving uniform-duration neuronal activations but is consistent with a recent variation on the temporal context model known as the scalar temporal context model⁶⁹.

When rats perform a maze task, sequential place-cell firing patterns that occur over seconds during maze learning ‘replay’ during subsequent quiet periods, and these replays are observed in accelerated form within about 100 ms³³. Although it is easy to imagine the compression of firing chains by simply having fewer spikes per cell and the subsequent decompression as longer spike bursts, a reproduction of an externally generated representation of real-time context representations would require a more complex compression mechanism that allows decompression to reconstruct the original intervals. Furthermore, hippocampal neuronal firing sequences that can be observed prior to learning subsequently characterize the sequences of place-cell firing in maze performance⁷⁰. Conversely, firing sequences persisted in a mouse model of neurodegeneration associated with a loss of spatial sequence coding, which is consistent with the existence of temporal firing chains prior to representations of events⁷¹. These findings suggest that firing chains are preconfigured within the hippocampus and are then co-opted to provide temporal organizations of events. However, one study examining trace eye-blink conditioning reported the emergence of new temporal patterns of neuronal firings associated with learning, rather than a co-opting of existing firing chains²¹. So, internally generated firing chains within the hippocampus might provide a temporal organization for spatial coding or might be modified by sequential events to represent their temporal organization. Combining the findings that support the existence of firing chains with the observations that a broader signal that defines entire memories is needed, perhaps the most likely network mechanism involves slowly evolving

temporal context dynamics (that is, signals that spread across multiple sequential events) selecting specific firing chains that represent specific temporally organized memories⁷² (FIG. 6c).

It is important to note that studies of time cells have focused on hippocampal area CA1 because this area seems to be the most important for temporal organization⁷³. However, there is some evidence that area CA2 (but not CA3) could also be important for temporal processing, suggesting that time cells might originate within the hippocampal circuitry⁷⁴. It remains a central question whether temporal information represented within the hippocampus originates from its inputs or is generated internally, or whether a combination of mechanisms generates time cells.

Conclusions and perspective

Recent studies have revealed that in addition to place cells, which fire when rats are in a particular location in a spatially structured environment, the hippocampus contains time cells, which fire at particular moments in a temporally structured period. Place cells and time cells are the same neurons, so many of these cells encode both spatial and temporal dimensions, but the representations of place and time can be separately measured. Several recent papers, using diverse experimental approaches and multiple memory tasks, have established that temporal organization within the hippocampus occurs across animal species and humans. Furthermore, time-cell firing patterns appear during learning and can both

distinguish specific memories and predict subsequent memory performance. The temporal information from which time cells are generated might result from earlier processing in other brain areas. It could be communicated to the hippocampus via the classic ‘where’ stream, along with internal mechanisms that might generate time-cell patterns of activity. Alternatively, or in addition, time cells might be a result of internal circuitry mechanisms. Although it is unlikely that time-cell sequences reflect simple firing chains, some evidence suggests that pre-existing firing sequences are enhanced and bound to moments in the evolving temporal context of experiences.

These findings have established temporal coding as a robust and prevalent aspect of hippocampal firing patterns. This challenges the view that the fundamental function of the hippocampus is spatial mapping and navigation⁷⁵, and instead supports the notion that the hippocampus contributes to memory by organizing elements of experience in both spatial and temporal context. Finally, although both spatial and temporal coding are prevalent in the activity patterns of hippocampal neurons, and can be distinguished experimentally, it remains entirely possible that the common thread in both dimensions is ‘association by proximity’ in space or time. This would suggest that place cells and time cells are simply reflections of a basic function of the hippocampus — supporting associative networks that represent a broad range of relations among the elements of memories^{32,76}.

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This study uses multivoxel pattern analysis of functional MRI scans in humans to show that the similarity of representations across a series of events predicts the likelihood of remembering the order of those events, similar to findings in rodents based on neural ensemble firing patterns in reference 12.

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Competing interests statement

The author declares no competing interests.

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