Phase precession: a neural code underlying episodic memory?

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Abstract

In the hippocampal formation, the sequential activation of place-specific cells represents a conceptual model for the spatio-temporal events that assemble episodic memories. The imprinting of behavioral sequences in hippocampal networks might be achieved via spike-timing-dependent plasticity and *phase precession* of the spiking activity of neurons. It is unclear, however, whether phase precession plays an active role by enabling sequence learning via synaptic plasticity or whether phase precession passively reflects retrieval dynamics. Here we examine these possibilities in the context of potential mechanisms generating phase precession. Knowledge of these mechanisms would allow to selectively alter phase precession and test its role in episodic memory. We finally review the few successful approaches to degrade phase precession and the resulting impact on behavior.

Keywords: phase precession, hippocampal formation, sequence learning, episodic-memory formation, temporal compression, spike-timing-dependent plasticity

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The hippocampal formation is a notable structure in the mammalian brain implicated in episodic memory and navigation [1]. While rats, mice, bats, or humans are exploring a given environment, cells in their hippocampal formation code for space by firing in restricted regions of the environment, the cells' firing fields [2] (see also [3, 4] for cells with non-spatial firing fields). Spatio-temporal events constitute episodic memories, and remembering the sequential ordering of these events is important. Thus, the neural encoding of sequences of firing fields in the awake state and their subsequent replay [5] are thought to be a substrate for episodic memory acquisition and consolidation. It is not clear, however, how such firing-field sequences are formed.

A basic understanding of the neurobiology of sequence learning requires knowledge about rules of synaptic plasticity, whose outcome critically depends on the correlated activity of neurons. Therefore, knowledge about the neural representation of sensory information is required. While recent experiments have revealed in great detail the dependence of the induction of long-term plasticity in the hippocampus on the millisecond timing of pre- and postsynaptic spikes [6] (for a review see, e.g., [7]), much less is known about how such millisecond timing in hippocampal neurons is related to sensory input. In other words, do hippocampal networks exhibit an appropriate neuron-correlation code [8] where the millisecond-timing of action potentials (with respect to the theta rhythm) carries information about sensory input?

Hippocampal *phase precession* [9] is a potential candidate for a code that supports the learning of behavioral sequences [10]. Phase precession means that within the firing fields of place-specific cells in the hippocampus, there is a systematic advancement of spike phases relative to the ongoing extracellular theta oscillation (4–12 Hz) (Fig. 1 *A*). If two cells with overlapping place fields show phase precession, the temporal separation between spikes in the overlap region is typically in the order of milliseconds. The order and the small interval between pre- and postsynaptic spikes is well suited for asymmetric spike-timing-dependent plasticity (STDP) rules, which can modulate the connection strength between these cells to facilitate sequence formation. However, despite consider-

able recent efforts in modeling and analyzing phase precession, there is to date no clear answer to whether the brain actually uses this code.

In what follows, we review the possible functions of phase precession in light of their hypothesized mechanisms of generation and the evidence supporting them. We then review a few studies that have assessed the behavioral impact of interfering with phase precession. We conclude with a few open questions for future research in the field of phase precession.

What are the possible functions of phase precession?

Phase precession has typically been studied in the rodent hippocampal formation while the animal navigates in a one- or two-dimensional environment [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20], but phase precession has also been observed outside the hippocampal formation [21], and in a variety of contexts including running on a wheel [3] or treadmill [22], jumping [23], virtual reality [24, 25, 26], and during fixation [27]. Recent evidence indicates phase precession also in the human hippocampus [28].

Here, we first review three classic hypotheses on the functional relevance of phase precession: (1) phase coding (e.g., [9, 29]), (2) enabling synaptic plasticity (e.g., [10]), and (3) sequence retrieval and prediction (e.g., [30]). It is important to note that these three hypotheses are not mutually exclusive but rather suggest distinct computations that could be carried out in the brain to support episodic memory; moreover, the three hypotheses might even be interrelated.

However, we suggest that hypothesis (2) is more related to cellular models of phase precession generation, while hypothesis (3) is more consistent with network models. Understanding the mechanisms of phase precession generation is of utmost importance because only then can we interfere with phase precession to elucidate its functional relevance. Unfortunately, unraveling the mechanisms behind phase precession has proven challenging [31], although a combination of network, cellular, and inheritance mechanisms are likely to be involved (see [32, 33, 34] for a discussion of models). Nevertheless, recent experimental re-

sults have considerably extended our understanding of the properties of phase precession and provided further constraints on potential generating mechanisms [35, 36, 37, 38, 39, 15, 40, 41, 42, 43, 44, 45, 46, 25, 24].

(1) Phase coding: a hallmark of phase precession

Phase precession was initially defined in terms of the correlation of action potentials' theta phase and position or time within the firing field, which immediately also suggested the existence of a phase code [9]. More precisely, the phase-coding hypothesis states that the theta phase complements the information provided by the coarse place-selectivity at the level of the trial-averaged firing rate [47, 48, 49]. Indeed, phase information can be used to reconstruct more precisely the current location of an animal beyond the rate within a place field [29, 50]. With phase information at hand, it is possible to disambiguate entry and exit through a place field, even if the animal engages in backward travel [43].

Phase precession can also code for behaviorally relevant variables beyond position such as a goal location. When rats navigated a T-maze during a spatial alternation task, cells in the ventral striatum ramped their firing activity and exhibited phase precession towards reward locations [51]. The anticipatory activity of the phase-precessing ramp cells could underlie the learning of place-reward associations [21]. It is thus possible that phase precession in the ventral striatum is inherited from the hippocampus [51, 32, 33]. Thus, the theta phase provides additional information beyond the firing rate although the relationship between phase, firing rate, and position might be complex [43].

(2) Enabling synaptic plasticity: cellular models for phase precession and temporal compression

Cellular models explain phase precession as arising from the dynamics within a single cell, which causes the cell to reach firing threshold at earlier phases as the animal crosses the cell's firing field (e.g., [9, 52, 12, 11, 53]; for review

see, e.g., [54]). Importantly, no particular synaptic connectivity is assumed for cellular models.

If phase precession is an emergent property of single cells, it could be used for the encoding of behavioral sequences. Through temporal compression, behavioral sequences experienced by the animal, for example, place-field sequences, they are represented within a theta cycle (see Box 1 for a detailed definition of temporal compression). Because of temporal compression, and given a set of overlapping place fields (Fig. 1 *B*), the spikes from the corresponding place cells are separated by a few tens of milliseconds: a time scale appropriate for the induction of LTP or LTD (or STDP, if the synaptic-weight change additionally depends on exact pre-postsynaptic timing) [10, 55, 56]. Thus, by means of phase precession, asymmetric connections between place cells that allow for a rapid encoding of sequences can be formed.

Only a few studies have explored the relationship between place-cell firing patterns and the plasticity of hippocampal cells. For example, place fields in the CA1 region of the hippocampus expand asymmetrically after repeated exposures to familiar tracks [57, 58], and this expansion is abolished with NMDA-receptor antagonists [59, 45, 46].

In an *in vitro* study, Isaac and colleagues [60] injected natural, that is, physiological spike trains into two connected CA3-CA1 cells. The degree of LTP was dependent on the degree of temporal overlap between the two spike trains, which mimics the spatial overlap during place-field traversals. Synaptic weights between place cells could thus be used to encode spatial distance [61]. It was intriguing that only LTP was observed, regardless of the relative ordering between pre- and postsynaptic spikes (see also [62]). Similarly, STDP at CA3-CA3 synapses *in vitro* showed a symmetric dependence on spike timing [6].

The studies described above suggest that plasticity results from experience as well as from the typical firing patterns found in the hippocampus *in vivo* during place-field traversals. It is not clear yet, however, whether the temporal structure of the spiking activity, as dictated by phase precession, has any bearing on the synaptic associations between place cells.

(3) Sequence-retrieval and prediction: network models for phase precession and theta sequences

Network models explain phase precession through the concept of look-ahead: external feed-forward input activates neurons selective for the animal's current location, and internal recurrent connections propagate this neural activity to neurons representing positions ahead of the animal's trajectory (e.g., [63, 64]; for a review see, e.g., [30]). This network-level mechanism can generate phase precession in single cells through the transition between the external (feed-forward) drive and the internal (recurrent) input. Thus, network-level interactions could generate phase precession that reflects the retrieval or prediction of already encoded behavioral sequences.

According to the look-ahead property of network models of phase precession, there is a sequential representation of the path ahead of the animal. To quantify this representation, one can rank the sequentially activated place cells according to the temporal order of place cells visited. The order of the sequentially activated place cells is also preserved within one theta cycle at the level of spike times, as initially pointed out by Skaggs and colleagues [10] and later quantified by Dragoi and Buszaki [65]. To further formalize these findings, Foster and Wilson [66] introduced the concept of theta sequences: sequences of spikes from an ensemble of place cells where there is a correlation between cell order and spike time within one theta cycle (Fig. 1 *C* and 2 *A*). Thus, behavioral sequences are compressed within one theta cycle in a manner reminiscent of the temporal compression previously described. We should note that this sequential representation is not necessarily exclusive to network models but could in principle also arise from single-cell phase precession in a population of cells (see section "How are theta sequences related to phase precession?" below).

Johnson and Redish [67] and Gupta and colleagues [68] studied the relationship between theta sequences and behavior using a T-maze spatial alternation task. In [68], theta sequences represented not only paths ahead of the animal (prospective coding, see also [67]) but also paths behind (retrospective coding). Both types of coding occurred preferentially between landmarks or points of

special interest such as decision points (for prospective and retrospective coding at a single-cell level see [69]). Trajectories represented by theta sequences were also observed in a study where rats were placed on a train and were carried through a maze during forward and backward travel [43] (Fig. 2 *B*). Remarkably, theta sequences also predicted goal locations as rats performed a value-guided decision-making task [70], demonstrating a behavioral relevance beyond navigation (Fig. 2 *C*).

How are theta sequences related to phase precession?

Phase precession is a property of the spiking activity of a single cell (whatever mechanism generates it) whereas theta sequences are defined only in a population of cells. A population of phase-precessing cells with similar entry phase also shows theta sequences. Notably, phase precession can exist even if the entry phase is variable (from trial to trial and/or across cells) but theta sequences cannot.

Feng et al. [71] explored the relationship between theta sequences and phase precession and showed that theta sequences require experience whereas phase precession can be observed even in novel environments (see also [72]). For theta sequences, it is necessary that the cells involved have a similar entrance theta phase (as in Fig. 1); thus phase-locking at field entrance develops with experience to produce the theta sequence [71]. A similar dissociation between phase precession and theta sequences was found by Middleton et al. [73] who showed that silencing CA3 input to CA1 disrupts theta sequences in CA1 while sparing phase precession, which presumably was either generated *de novo* in CA1 or inherited from MEC [40, 32, 33].

It is still unresolved whether theta sequences reflect a network structure and are thus distinct from multiple single-cells' phase precession. If theta sequences are generated in a population of recurrently connected cells as dictated by network models of phase precession [64], there should be a sequential structure above and beyond what is implied from cellular models. Foster and Wilson [66] reported such excess sequential structure by showing that the disruption of theta

sequences via shuffling does not affect theta phase-position correlations. Chadwick et al. [34] challenged this conclusion by showing that applying the same shuffling procedure to an ensemble of simulated independent phase-precessing cells leads to the same result.

An important assumption of network models of phase precession is that the connectivity between place cells is asymmetric and therefore is learned. Thus phase precession may have a learning-independent and a learning-dependent component [30]. It may be possible to map these components to the findings by Feng et al.[71] who showed that phase precession develops into theta sequences as a function of experience.

In conclusion, there is evidence that theta sequences code for behaviorally relevant variables [74, 75]. However, an important issue is still unresolved: is phase precession mediating the encoding of sequences, or is phase precession the by-product of retrieving those sequences?

Interfering with phase precession

Although there is no consensus on the mechanisms generating phase precession, it has been possible to alter the entorhinal-hippocampal circuitry in specific ways that resulted in abnormal phase precession. Robbe and Buzsáki [76] examined the effect of cannabinoids on the spatial coding properties of place cells in the hippocampus, as well as on memory and navigation in a spatial-alternation task: the administration of a cannabinoid agonist impaired rats in performing the delayed spatial-alternation task while leaving the place-field (i.e., rate) representation essentially intact. However, on a theta time scale, which is the time scale relevant for phase precession, there were alterations of the dynamics as measured by the sequence compression factor (Box 1). Similar results on aberrant phase precession and compression of temporal sequences were found in epileptic rats [77]. Furthermore, in [76] there was a strong correlation between the percentage of correct trials and the theta-scale sequence compression index, suggesting that the theta-scale coding was necessary to perform the task.

Wang et al. [42] found a similar dissociation between a place code and theta-time scale activity. They inactivated the medial septum of rats, and this manipulation abolished theta sequences and episode fields during wheel running and disrupted the animal's behavior in a memory task (Fig. 2 *D*), but spared the place-cell representation when the rats were navigating in a maze.

Overall, the results from the above studies suggest that it is possible to interfere with theta-time scale dynamics while sparing the place-code representation. However, it is not possible to conclude that the disruption in the sequential representation was the cause of the behavioral impairments. For example, medial-septum inactivation [42] also disrupts theta oscillations, which alone could have caused the deficits. Furthermore, the above experiments cannot distinguish between the encoding and retrieval interpretations of phase precession because the interference with this phenomenon occurred during both phases; this issue can therefore only be resolved by experiments that selectively interfere with phase precession either during encoding or retrieval.

Concluding remarks

The study of phase precession has shed light on hippocampal dynamics, on memory-related and goal-related behaviors, and on the computational roles of oscillations in cognition [78]. Whether phase precession enables sequence learning, is a signature of a retrieval process, or neither, remains an open question.

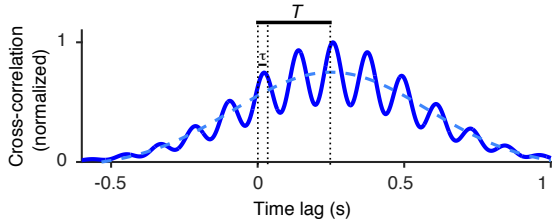
Overall, to unravel functional roles of phase precession, it should be studied in the context of hippocampus-dependent tasks (e.g. [3, 42, 70]) that allow for the isolation of internal memory or decision-making processes from other processes such as sensory-motor feedback or path integration; furthermore, phase precession should be studied in conjunction with other temporal patterns observed in the hippocampal formation that have been also linked to synaptic plasticity during memory encoding and/or retrieval, such as sharp wave-ripples and gamma oscillations in the local field potential [79, 64].

A fruitful approach towards elucidating the function of phase precession

comes from studies dissociating theta-time scale coding from behavioral-time scale coding to interfere selectively with phase precession [76, 42]. Moreover, the manipulation of phase precession at specific times with respect to a task might enable one to distinguish contributions to encoding, maintenance, and retrieval of memories. Substantial progress on this front could result from pinning down the mechanisms of phase-precession generation to selectively interfere with phase precession in different parts of the brain in search for specific deficits.

Starting from place fields and synaptic plasticity, phase precession is an appealing phenomenon to explain the formation of behavioral sequences; it remains to be quantified whether other theories that do not utilize phase precession (e.g., [80]) are also feasible. A better understanding of first, the behavioral correlates of phase precession and, second, the means to interfere with phase precession will help guide future research on hippocampal dynamics and its relationship to navigation and episodic memory.

BOX 1: Temporal compression



Temporal compression refers to the theta-time scale representation of a behavioral-time scale place-field sequence. To quantify temporal compression, one can use the cross-correlogram of a pair of phase-precessing cells with overlapping place fields (see schematic above). The time T at which the maximum of the envelope of the cross-correlogram occurs represents the separation in time of the two place-field peaks and is referred to as the behavioral time lag [65].

Because the cells exhibit phase precession, the cross-correlogram also has a temporal structure at the theta-time scale. The time of the first peak (with respect to a reference at time lag 0) is called the theta time lag τ. In the case of

place fields of equal size, τ is simply the time lag within one theta cycle between the spikes of the two place cells (Fig. 1 *B* and [81]). For a given population of N cells with overlapping place fields, the quantities T_i and τ_i for $i = 1, ..., N$ cells are linearly correlated [65, 82]. Temporal compression is then quantified via the correlation coefficient (compression index) and the slope (compression factor) of the T vs. τ relationships.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Conflict of interest statement

Nothing declared.

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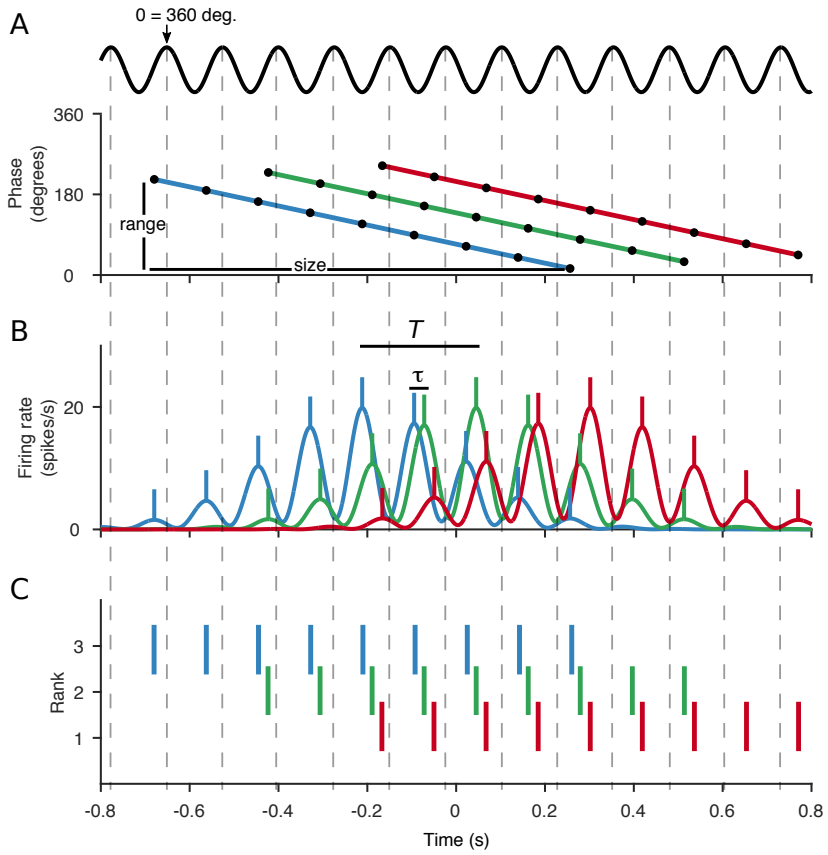

Figure 1: Sketch of phase precession, temporal compression, and theta sequences. ***A,*** Phase-time plot of spikes (black dots) of three place cells (colored lines) that exhibit phase precession within their overlapping place fields. Across theta cycles (vertical dashed lines), spikes arrive at earlier and earlier phases with respect to the theta oscillation (black curve on top). Entry phase for the three place cells is the same. ***B,*** Firing-rate activity (colored lines) of the three place cells in ***A*** illustrating temporal compression. For clarity, single spikes (vertical bars) occur preferentially at the peaks of the firing-rate curves. The symbol T denotes the separation in time between two consecutive place-field centers, and τ is the theta-time-scale separation between two spikes corresponding to two consecutive place fields within a theta cycle. ***C,*** Theta sequences allow the representation of traversed place fields at a theta time scale. Here, rank is correlated with spike time within a theta cycle, the defining feature of a theta sequence [66].

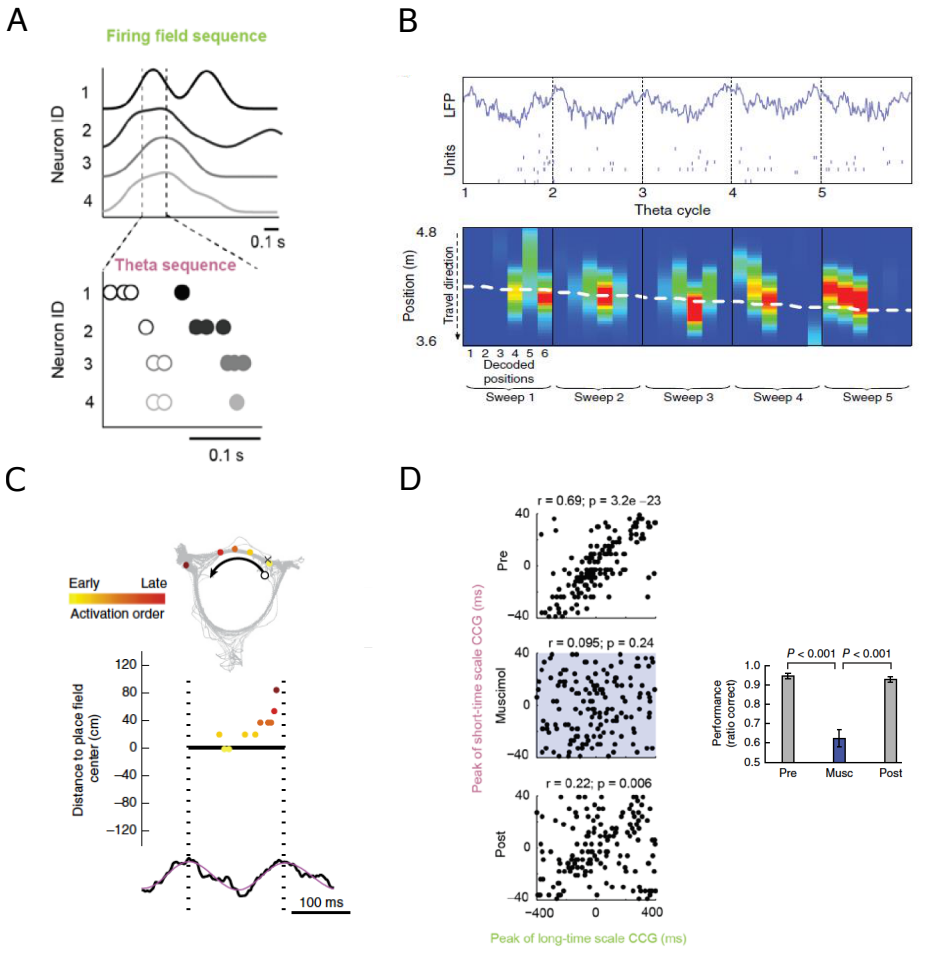

Figure 2: Examples of theta-time-scale dynamics with behavioral relevance. ***A,*** Ordered sequences of place fields (black to gray, top) are also represented by sequences of spikes within single theta cycles (empty and filled circles, bottom). ([42]; reproduced with permission from Nature Publishing Group). ***B,*** Theta sequences during backward travel ([43]; reproduced with permission from Nature Publishing Group). LFP theta oscillations and spikes of 34 simultaneously recorded CA1 pyramidal cells (top). A Bayesian decoder uses a fraction of the ongoing theta cycle, six in total, to estimate the positions ahead or behind the rat (bottom). A sweep refers to a position-reconstruction for each theta cycle and red (blue) denotes maximum (minimum) probability for the decoded position. ***C,*** Spikes within a theta cycle represent trajectories ahead of the animal and can reflect current goals ([70]; reproduced with permission from Nature Publishing Group). The 'x' marks the current position of a rat that traverses a T-maze, and colored dots correspond to cells active at points ahead of the animal on the track. The order of the dots on the track corresponds to the order of the spikes within a theta cycle. ***D,*** Left, behavioral versus theta-time scale pair-wise cross-correlation peak before (top), during (middle), and after (bottom) muscimol injection into the medial septum while rats were running on a wheel. Right, behavioral performance during a two-armed, delayed alternation memory task, which included running on a wheel during the delay.([42]; reproduced with permission from Nature Publishing Group).