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A unified view of theta-phase coding in the entorhinal–hippocampal system

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The discovery of theta-rhythm-dependent firing of rodent hippocampal neurons highlighted the functional significance of temporal encoding in hippocampal memory. However, earlier theoretical studies on this topic seem divergent and experimental implications are invariably complicated. To obtain a unified understanding of neural dynamics in the hippocampal memory, we here review recent developments in computational models and experimental discoveries on the ‘theta-phase precession’ of hippocampal place cells and entorhinal grid cells. We identify a theoretical hypothesis that is well supported by experimental facts; this model reveals a significant contribution of theta-phase coding to the on-line real-time operation of episodic events, through highly parallel representation of spatiotemporal information.

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Current Opinion in Neurobiology 2007, **17**:197–204

This review comes from a themed issue on
Cognitive neuroscience
Edited by Keiji Tanaka and Takeo Watanabe

Available online 26th March 2007

0959-4388/\$ – see front matter

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DOI [10.1016/j.conb.2007.03.007](https://doi.org/10.1016/j.conb.2007.03.007)

Introduction

The hippocampus in human and animals is crucial for episodic memory (memory of experienced events within spatiotemporal contexts) [1–3]. Although it is generally accepted that the hippocampus is concerned with formation of associative memories of novel experiences through synaptic plasticity, it is so far unknown how episodes that have spatiotemporal contexts are represented at the neural population level.

The hippocampus is also known to possess networks that exhibit a variety of dynamics. One of the most well known

dynamics is the ‘theta rhythm’ — regular oscillation of the local field potential (LFP) at frequencies of 4–12 Hz [4] — which has been observed in rodents during voluntary behaviors. The timing of hippocampal neuronal firing is not simply modulated by the LFP; it also exhibits gradual advancement in oscillation phase relative to LFP theta oscillation along the behavioral sequence, as shown in Figure 1 [5]. This ‘theta-phase precession’ is prominent in hippocampal neurons of freely running rats. Theta-phase precession was observed first in the hippocampal area CA1 [5], next in the dentate gyrus [6,7] and finally in the CA3 region [8] (briefly reported also in [5]). Recently, the superficial layer of the entorhinal cortex has been reported to demonstrate the unique property of environmental-position-dependent firing, in terms of ‘grid cells’ [9] and theta-phase precession [10[•],11[•]].

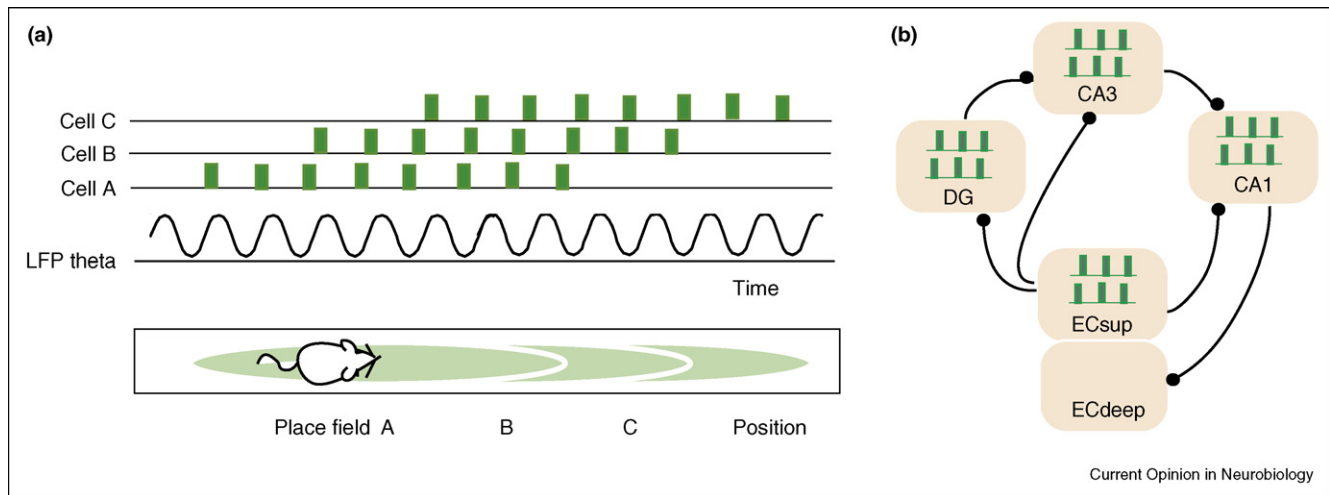
Thus, it is now clear that theta-phase precession is not a localized neural event but distributes over the entorhinal–hippocampal network. Because synaptic plasticity is sensitive to dynamics that occur in a timescale near to the oscillation period of the theta rhythm [12–14], it is of great interest whether these neural dynamics are essential for the memory function of the hippocampus. Several theoretical models have been proposed for the neural mechanism of theta-phase precession in a single cell or in a small neural population, but these have not been conclusive. To understand the memory function of the hippocampus on the basis of its complex dynamics, a unified view, from a single-cell dynamics to network dynamics, is needed. This will require an integrative approach.

In this review, we propose a theoretical hypothesis for hippocampal network dynamics and then use it to associate events observed in various experimental conditions in the entorhinal–hippocampal system, so that the hippocampal memory function can be understood on the basis of theta-phase precession.

A fundamental property of theta-phase precession and its relevance to associative memory formation

According to the cognitive map theory [15], some hippocampal cells in rodents have preferred positions, and the firing rates of these cells increase when the animal runs through those positions. Cells that have preferred positions are called place cells, and their preferred positions are called place fields. It takes roughly a few seconds (i.e.

Figure 1



Theta-phase precession in the hippocampus. **(a)** Theta-phase precession in rat hippocampal neurons [5,6]. Cells A, B and C fire at individual place fields as the rat runs on the platform. The spikes or spike bursts start at a specific phase relative to the local field potential (LFP) oscillation (theta) and gradually advance during running. **(b)** To date, theta-phase precession has been reported in the dentate gyrus (DG), CA3, CA1 and the superficial layers of the entorhinal cortex (ECsup), but not in the deep layers of the entorhinal cortex (ECdeep).

several or ~ 10 theta cycles) for each place cell to complete its firing in a place field, and a given position in the environmental space is represented more precisely by the firing rates of place cells in a population that have overlapping place fields. O'Keefe and Recce [5] analyzed the relative timing between place-cell spikes and LFP theta oscillations. They found that spike timing in the theta cycle was not fixed but gradually changed as the animal traversed the place field: the phase of spike firing relative to LFP theta gradually advances. The total amount of phase shift is up to one cycle (one cycle at maximum or less than one cycle). This firing with phase advancement is called 'theta-phase precession'.

When two place cells that have overlapping place fields are recorded, the phase difference of their firing is kept constant during one-way running behavior [6]. Thus, in a population of place cells that demonstrate phase precession, their firing is temporally coordinated in each theta cycle. The place cell that has early onset fires at advanced phase of each theta cycle, whereas the place cell that has late onset fires at late phase. The resultant firing sequence of place cells in each theta cycle then describes the place sequence of the running behavior. Because it takes several seconds for the animal to run through several place fields, the place-cell firing sequence within each theta cycle (125 ms in the case of 8 Hz) repeatedly represents the behavioral sequence in a compressed way along the temporal axis.

However, the timescale of the compressed sequence is also in the range of synaptic plasticity that adheres to the

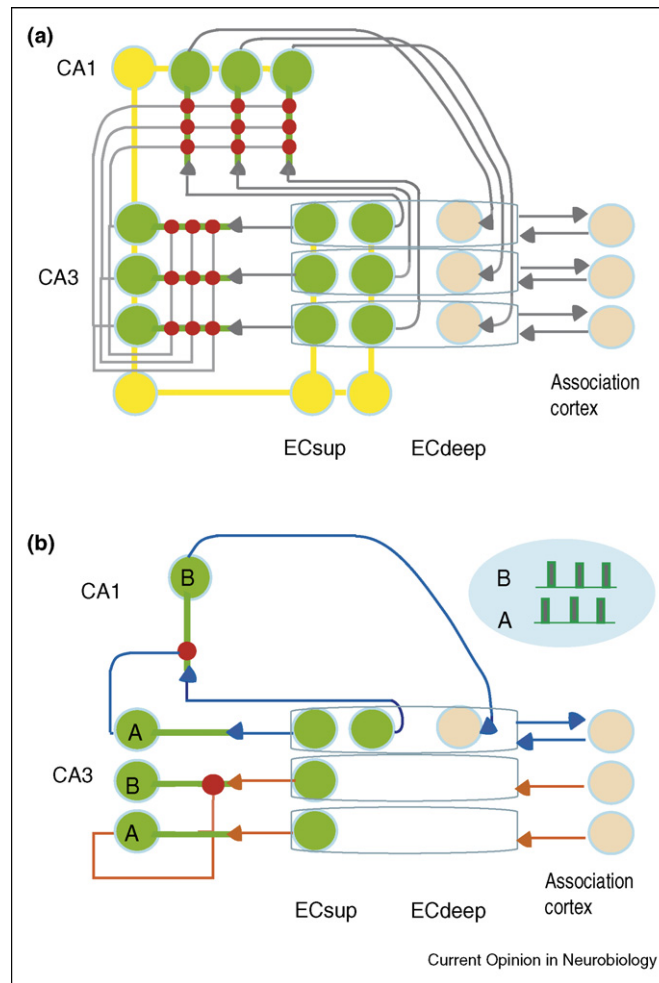
Hebb rule. Quantitative analyses have reported that the asymmetric Hebb rule applies in hippocampal pyramidal cells; according to this rule, long-term potentiation (LTP) and long-term depression (LTD) depend on the time difference between presynaptic and postsynaptic cell activities [12–14]. The optimum condition for LTP is given by the time difference by which the presynaptic cell fires before the postsynaptic cells within 0–50 ms.

If cells that have recurrent connections demonstrate phase precession, then the phase difference of a given pair of cells will specify the synaptic plasticity in an asymmetric way. Although the population of active place cells continuously changes according to the running behavior in an environment, a given pair of concurrently active place cells keeps the phase difference for several theta cycles. The asymmetric connections are formed in place cells where the direction of the connection represents the temporal sequence of the running behavior.

A hypothesis for theta-phase coding in the entorhinal-hippocampal network

We propose a hippocampal network model with theta-phase precession for simple memory formation [16–18]. As shown in Figure 2a, we hypothesize that theta-phase precession is generated at the entorhinal cortex superficial layers (II and III); this hypothesis is based on the phase difference of firing phase between the dentate gyrus and CA1, suggesting transmission of phase precession along the hippocampal trisynaptic circuit [7,16,17]. This assumption is in good agreement with the observation of phase precession in the entorhinal cortex [10^{*},11^{*}] and

Figure 2



A computational model of theta-phase coding in the entorhinal–hippocampal system [16,17]. **(a)** Structure of the model and hypothesized neural dynamics. Theta-phase precession is generated at the entorhinal superficial layer (ECsup) and projected to the CA3 and the CA1, for control of memory formation. The dentate gyrus has been omitted for simplicity. **(b)** Synaptic plasticity through the asymmetric Hebb rule and theta-phase precession in the network. Orange arrows show how theta-phase precession in the entorhinal cortex is inherited by recurrent networks in the CA3 to give asymmetric connections. Cell A and cell B of both this circuit and the blue circuit are presynaptic and postsynaptic cells that create asymmetric connections in the presence of theta-phase precession (inset). Blue arrows show how the Shaffer collateral synapse is modified, depending on activity of cells in both CA3 cell the entorhinal cortex. These two processes work in unison in the on-line condition; therefore, the input at the superficial layer of the entorhinal cortex can be retrieved at the deeper layer (ECdeep) in the off-line condition. In (a) and (b), circles and arrows represent populations of neurons and their synaptic projections, respectively. Green units have theta-phase precession, yellow circles represent local field potential activity (LFP theta) at individual layers, and small red circles represent plastic connections.

is also consistent with the fact that hippocampal phase precession persists after transient intrahippocampal perturbation [19^{••}].

In the simplified network model, it is assumed that there is topographic mapping between the entorhinal cortex and CA3/CA1 at the level of neuronal populations. The theta-phase precession generated in the entorhinal cortex layers II and III is transmitted to the hippocampus associative memory networks, which demonstrate the time asymmetric Hebb rule. This network enables on-line real-time formation of memories of novel experiences as follows.

When the sensory input to the entorhinal cortex layer II is a temporal sequence, asymmetric connections for the temporal sequence are formed as a result of phase coding in the CA3 (the orange network in Figure 2b). Association between the CA3 activity and entorhinal cortex layer III input is stored in the heteroassociative memory of the CA1, as a result of on-line phase coding at presynaptic CA3 cells and postsynaptic CA1 cells (driven by the entorhinal cortex layer III) (the blue network in Figure 2b).

At the retrieval stage, the stored temporal sequence is reactivated as pattern completion in CA3, which is

followed by recall in CA1 that gives output to the deeper layer of the entorhinal cortex. Thus, the synaptic plasticity of CA3 and CA1 stores a temporal sequence. Although the storage pattern in CA3 might be modulated in the presence of input from the dentate gyrus, for the sake of separation of similar environmental input patterns, the plasticity of Schaffer collaterals in CA1 ensures that there is output to the deeper layer of the entorhinal cortex, consistent with the on-line activity of layer II. The recall sequence is replayed on a neural timescale similar to that in the on-line condition. This computational model that uses theta-phase coding would give learning the high capability offered by on-line real-time memory encoding, beyond the capability offered by a simple associative memory that uses rate coding [20–24].

Neural dynamics in the entorhinal cortex

Now let us consider the neural dynamics of entorhinal cortex neurons that generate theta-phase precession for a given position preference. Our assumption of neural dynamics in the entorhinal cortex is illustrated in Figure 3. This is based on a general principle of phase locking in coupled nonlinear oscillations [25,26]: coupled oscillations that have different natural frequencies can result in oscillations in the same frequency with constant phase differences (Figure 3a).

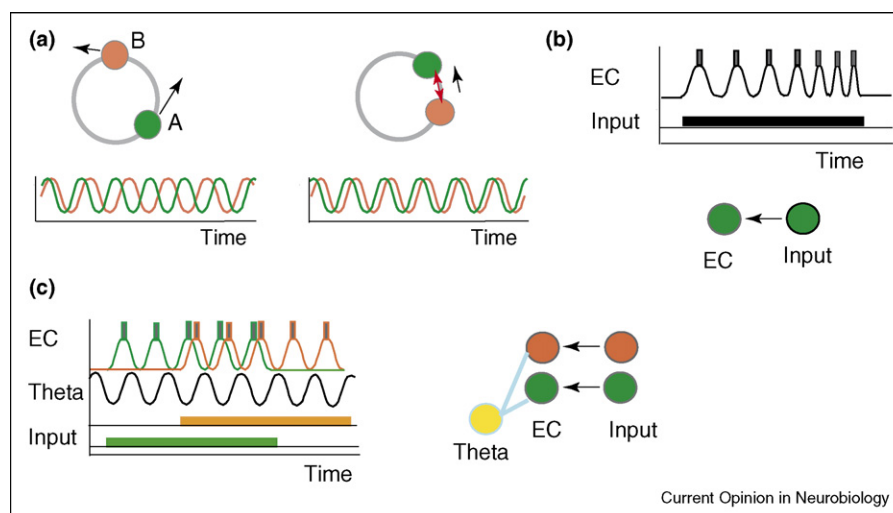
In the presence of positive input from the association cortices, each cell in the superficial layer of the entorhinal cortex is activated as a spontaneous oscillation that varies

slowly, giving a slow increase in a natural frequency of the spontaneous oscillation (Figure 3b). The change in natural frequency is here assumed to be a theoretical prerequisite for phase advancement after coupling with LFP theta oscillation. Owing to the electrical coupling between each cell oscillation and LFP theta oscillation (Figure 3c), a phase shift gradually emerges according to the increase in natural frequency from a slower value to a faster value than theta frequency. The oscillation phase of cell firing relative to LFP theta oscillation rapidly converges to a value at each instance even in the presence of any perturbation. The relative firing timing among different cells is robustly kept through their indirect coupling with LFP theta oscillation. The robustness of phase locking ensures stability of phase precession at each instance, both at the single-cell level and in a population of cells that have alternative activation.

The biological entity that is responsible for the assumed oscillation with frequency increase has not been identified. In the entorhinal cortex, there is not only LFP theta oscillation [27] but also cells that have intrinsic oscillations [28,29]. For example, cells in entorhinal cortex layer II have intrinsic oscillations at 5–15 Hz. These neurons or their local circuits are of interest as candidates for the origin of theta-phase precession.

Several other theoretical models have been proposed for theta-phase precession at the single-cell or local network levels in CA3 or CA1. For theoretical interest, it is worth

Figure 3



Neural dynamics associated with the mechanism of theta-phase precession. **(a)** General principle of phase locking in coupled nonlinear oscillations (schematized as rotation of particles A and B on a circle.) Fast oscillations (A; long arrow) and slow oscillations (B; short arrow) run independently in the absence of coupling (left) but they result in the same frequency oscillation in the presence of coupling (right). Their phase difference continuously changes on the left but remains constant on the right, where A advances to B. The state with constant phase difference is called 'phase locking.' **(b)** When the entorhinal cortex (EC) unit receives input at the preferred position, it is assumed to have spontaneous oscillation. The natural frequency is assumed to increase gradually. **(c)** The entorhinal cortex unit also receives input from the local field potential (theta), which causes phase locking (a). The gradual change assumed in (b) gives gradual phase shift. The phase difference between two entorhinal cortex units is kept constant depending on the early-late relationship of the input onset.

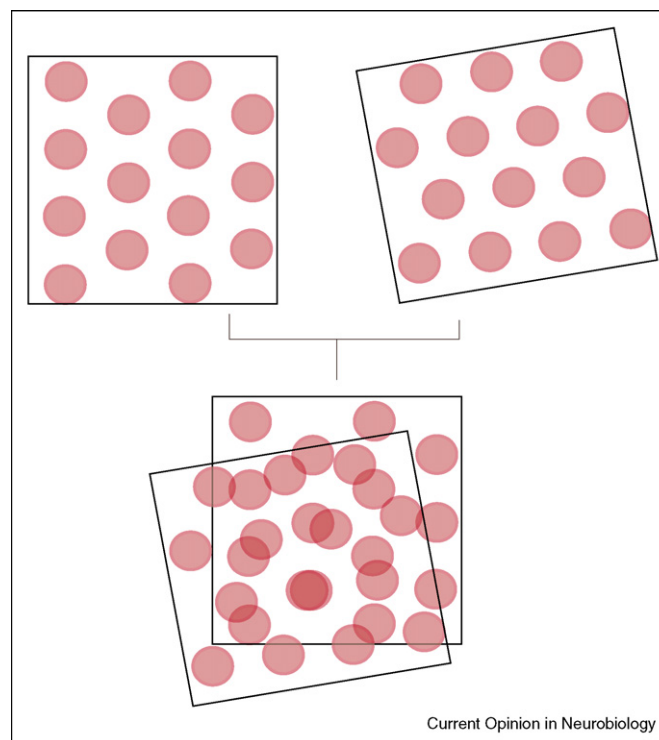
considering these models as candidates for the entorhinal neuron dynamics. Because these models are partially related to one another, it is convenient to categorize them into two groups: one that assumes propagation activities in a network that has geometrical connections [30–32] and one that assumes intrinsic dynamics of a single cell or a few cells [5,33–36]. Models in the former group assume that theta-phase precession appears as wave propagation over neurons that have asymmetric connections. That is, this kind of phase precession could appear after memory formation. This cannot apply to the entorhinal cortex in the condition of novel experience [37].

Our model is one that that assumes intrinsic dynamics of a single cell or a few cells. Although the details of individual models are beyond the scope of this review, we will discuss two points in this section. First, the slow and fast oscillations assumed by O’Keefe and Recce [5] are included in our model as a result of coupling between the entorhinal cell and LFP theta oscillation. If slow and fast oscillations are directly coupled, they lose their frequency difference (Figure 3a). In the presence of natural frequency change and LFP theta coupling, a fast oscillation of firing emerged as associated with a slow oscillation of LFP theta (Figure 3c). In the resultant set of slow and fast oscillations, their relative timing is not

arbitrary but converges to an instantaneous value because of phase locking. Thus, the present model gives a comprehensive view including a property of slow and fast oscillations. Second, in the assumption of gradual threshold decrease obtained after learning [36], this decrease is apparently similar to the slow variable in our model. However, we here emphasize the definite contribution of the nonlinearity in the neural system. As seen also in [33], the firing is determined not by the time when an internal activity crosses the threshold value but by the autonomous oscillation dynamics of each neuron.

Our model of the entorhinal neuron firing is based on the assumption that these cells demonstrate position-specific activation, similar to that of place cells. However, recent studies have reported the existence of ‘grid cells’, which are activated whenever the position of an animal coincides with any vertex of a regular grid of equilateral triangles that spans the surface of the environment [9,38]. How grid fields lead to formation of place fields remains an open question. We so far simply propose that superposition of grid cells that have the same space scale and but different orientation can create a single grid field in an environment, giving a single place field (Figure 4). Thus, a population of grid cells consistently gives a single entorhinal unit in our model. It should be noted that

Figure 4



A simple illustration of place preference of entorhinal cortex units. Grid cells fire periodically. If two grid cells have the same space scale and different orientations in their grid (top), then the summation of the two grid fields in general gives one major field with a strong firing rate (bottom). This provides the place field that is available at the hippocampus.

gradual increase in natural frequency can be regulated as a function of space through the mechanism of grid field formation in a given space scale in the entorhinal cortex. That is, phase precession as a function of position [5] seems to be a natural consequence of the grid cell property.

Hippocampal memory functions can be extended based on theta-phase coding

Experimental evidence supports our simulations of the entorhinal–hippocampal network and theta-phase precession. In particular, the roles of entorhinal cortex layer II and CA3 seem to be clearly supported by experimental data. According to our computer simulation analyses, by using the network model it was revealed that theta-phase precession is crucial not only for a simple temporal sequence memory but also for integrated memory of spatiotemporal patterns. The spatially self-organized memory generated by means of theta-phase coding has an ability to generate a temporal sequence consistently with behavioral experiences. Here, we summarize the function of theta-phase precession in the CA3 network.

First of all, recurrent connection networks that are generated by theta-phase precession can store the temporal sequence in a wide range of time scales, because the temporal sequence is compressed by theta-phase precession. This endows high selectivity in asymmetric synapse formation for real-time memory formation of our experiences [20,22,23]. The temporal sequence of memory retrieval is able to generate several activity features, including replays in a reverse sequence during sharp waves [39].

When an animal runs around in two-dimensional environments, the sequence memories of instantaneous running are finally integrated in the CA3 to give a geometrical network that represents the spatial environment [21,24,40]. This network functions as a cognitive map during running in familiar conditions. When the animal runs with the memory, the CA3 neurons have both entorhinal-dependent theta-phase precession and recurrent-connection-dependent activation of memory. If the recurrent-connection-dependent activation becomes dominant, CA3 activities part from theta-phase precession. However according to the evidence of pattern completion of place cells in the CA3 [41] and experience-dependent place-field expansion [42], the recurrent connection seems to be functionally significant in the normal condition [24]. Interestingly, in computer simulation after straight-path running, the recurrent connection gives feedforward activation in every theta cycle, to extend the compressed sequence of entorhinal-driven theta-phase precession in the future direction. In the simulation, after full-exploration running the recurrent connections bring expansion in multiple directions or round expansion of the entorhinal-driven activities at

the later phase of each phase precession. The recurrent effect with theta-phase precession enables association of spatial memory and current sequence input every theta cycle. This suggests a neural representation that is consistent with Tulving's description of episodic memory: 'the capacity to re-experience an event in the context in which it originally occurred' [1].

Another key question is whether theta-phase coding works in the human brain. To address this question, we analyzed object–place association memory by considering the environment of scenes and objects and by replacing running behavior with visual saccadic movements in human [43]. Despite the randomness of the saccadic sequence, the CA3 network was self-organized as a unified structure with asymmetric connections to represent object and scenes. The asymmetric connections formed as a consequence of theta-phase coding help to represent the environmental space with various spatial scale cues and then contribute to generate sequential activation of object–place association pairs. This result also indicates the possible importance of theta-phase precession in the human brain, and suggests that the functions of the hippocampus include processing of spatiotemporal information as a fundamental principle for episodic memory operation. In electroencephalogram recordings made from the human scalp during an object–place association memory task, distant synchronization in the theta rhythm was observed to correlate with subsequent memory performance [44].

Conclusion

The hypothesis that the memory function of the entorhinal–hippocampal network works with theta-phase coding was well supported by experimental observations of theta-phase precession. Our theoretical studies indicate that theta-phase coding in the on-line condition is crucial for not only simple temporal-sequence memory but also for integration of spatiotemporal structures in experienced events. This is because of the ability of theta-phase coding to represent relative entities either in time or in space. These results seem to provide a neural entity that underlies the operation of episodic memory in animals and humans.

Acknowledgements

We acknowledge to Dr Roman R Poznanski for helpful reviewing of the manuscript.

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