

NEURONAL OSCILLATIONS AND MEMORY RETRIEVAL

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Neuronal oscillations are phenomenon that spans multiple levels of brain organization, from a single cell level to distributed neuronal networks (46). Biophysically, they originate from periodic changes in excitability of neurons, which, when occurring in synchrony, give rise to detectable rhythmic fluctuations of extracellularly recorded potential. The proper timing of excitation and inhibition is under control of inhibitory interneurons, which are recognized as a principal component of rhythmicity generators in neuronal networks. The interest in neuronal oscillation was ignited by discovery suggesting synchrony as a solution to long-standing binding problem, where different aspects of a perceived object, processed in different brain areas must be bound to form unitary percept (18). Neural synchrony at various scales has been conjectured to be basis of reciprocal interaction between neuronal populations (46, 16). The study of brain oscillations emerged as a key approach to understand dynamic coordination underlying cognition (4).

One of the fundamental cognitive functions is memory. During learning, traces of experience are imprinted in engram of coactive cells, which is further strengthened or otherwise modified during periods of consolidation and reconsolidation. The adaptive function of memory is based on brain's ability to retrieve relevant pattern of activity that guides behavior in the context of the momentary state of the external world. The mechanisms that ensure fast and precise retrieval of correct memory content are virtually unknown.

Hippocampus, the central hub of episodic memory network, has been target of numerous electrophysiological studies which led to extensive body of knowledge about oscillatory activity in this area and its importance for memory (11). What is the role of oscillations in memory retrieval? Only recently, experimental approaches enabled inspection of neuronal networks' activity during short-lived period of memory recall (22).

Here, we provide a brief outline of retrieval circuitry and describe hippocampal oscillations and underlying mechanisms of their generation. Then, building on previous findings relating hippocampal rhythms to memory processing, we discuss published findings (22, 43) and results from our further analysis of oscillatory activity during spatial memory recall.

NEURAL CIRCUITRY OF MEMORY RETRIEVAL

The declarative memory – memory for facts (semantic memory) and events (episodic memory), is dependent on hippocampus and associated structures of the medial temporal lobe. Bilateral ablation of hippocampus results in inability to form new long-term memories and a graded retrograde amnesia (38). The mnemonic functions of the hippocampal formation have been extensively studied in rodents, where it has been shown that principal cells in the hippocampus proper code for position of the subject in the environment (33). The activity of these so called *place cells* constitutes formation of spatial or cognitive map of the environment (34) and is believed to provide a physiological substrate of spatial memory. This concept has been further supported by numerous experiments using selective tagging and manipulations of cells active during encoding stage and in memory retrieval (28).

Hippocampus includes subregions CA1 and CA3 and the dentate gyrus. The main cortical input is provided by entorhinal cortex that forms together with hippocampus and subiculum a closed loop (EC-DG-CA3-CA1-subiculum-EC). Whereas the input from the lateral entorhinal cortex conveys information about sensory stimuli within the environment (e.g. objects), the activity in the medial entorhinal cortex is tightly related to spatial information processing. The main cell types sending the information into hippocampus are grid cells (providing spatial metric), head-direction cells (directional information), border cells (relation to environmental borders) and speed cells (running speed) (19, 27, 42). Moreover, some cells in the medial entorhinal cortex display a rate coding for spatial context identity (26).

A specific role is attributed to CA3 region for its dense network of recurrent collaterals, which account for the vast majority of the inputs on each pyramidal cell. This autoassociative network architecture enables formation of association between an arbitrary combination of inputs, so that later a partial cue is sufficient for retrieval of the whole stored pattern, corresponding to an *attractor state* of the network (37). The sparse and strong input from DG onto CA3 is proposed to ensure orthogonalization of input ensuring the appropriate pattern separation. The position of dentate gyrus in the retrieval cascade is not fully understood, with possible limitations of its importance in relation to type of memory task and different roles of young adult-born vs developmentally born cells (14, 25, 26, 29).

There are other structures with strong hippocampal interplays that are engaged in memory encoding and recall. The prominent one is the prefrontal cortex, where the cells display modulation by contextual aspects of the experience and their activity drives top-down control of memory retrieval (36).

RHYTHMIC ACTIVITY IN THE HIPPOCAMPUS

The major source of our knowledge about hippocampal rhythmic oscillations originate from direct recordings of local field potentials from hippocampus of rodents prompted by an early notion that rhythmic activity is of essential relevance to hippocampal function

(48). According to the EEG patterns detected in hippocampus, two main modes of network activity can be distinguished. During locomotion, exploratory behavior, attention and REM sleep, LFP patterns are dominated by sinusoid-like waves of frequency between 5 and 12 Hz called theta rhythm. On the other hand, passive immobility and non-REM sleep are accompanied by more irregular activity with transient occurrence of slow sharp waves and ultrafast ripples (150–250 Hz) corresponding to massive synchronous discharge of hippocampal neurons. Theta and non-theta states are considered to reflect an “online” vs “offline” regimen of information processing in the hippocampus (6, 11).

Theta oscillations represent relatively slow (5–12 Hz), high amplitude oscillations.

Disruption of the medial septum, which contains cholinergic and GABAergic neurons projecting to hippocampal formation, abolishes theta in the hippocampal network (30, 48). The classical model of theta generation thus postulates the central role of medial septum as a theta pacemaker. Activation of GABAergic neurons projecting to hippocampus inhibits perisomatic interneurons, thereby reducing frequency of IPSPs on pyramidal cells (44). This rhythmic disinhibition coupled with tonic inhibition exerted by cholinergic activation of interneurons may underlie theta at somatic level. Another important component of theta corresponds to EPSPs elicited by entorhinal projections at distal dendrites of pyramidal cells. In consequence, theta rhythmicity is accompanied by hyperpolarization of the somata coupled to depolarization of the dendrites (24).

However, the mechanism that underlies theta entrainment in hippocampus is likely much more complex than depicted in abovementioned model, involving several types of interneurons with corresponding microcircuitry motifs. In particular, the intrinsic properties of hippocampal network to oscillate with theta frequency seem to play the crucial role. The *in vitro* studies and computational models unveiled emergence of theta in hippocampal network driven by non-rhythmic input or in a completely isolated hippocampus (e.g. 2, 17).

Gamma oscillations are fast oscillations within 25–100 Hz range and, in the hippocampus, they are typically observed during theta states, superimposed on higher-amplitude theta waves. The hippocampal gamma oscillations have been further divided into slow gamma (25–50 Hz) and fast gamma (60–100 Hz) spectrum, with slow and fast gamma amplitude being differently modulated by phase of theta (12, 39), displaying different relation to speed of locomotion (1, 52) and presumably supporting different hippocampal operations (10). The classical models of gamma generation include the ‘I-I model’, where either tonic or stochastic drive to interconnected network of interneurons produces gamma oscillation. In the ‘E-I model’, gamma rhythm emerges from reciprocal interaction between pools of excitatory and inhibitory neurons (8). The experimental data support the notion that fast gamma oscillations in CA1 are entrained by excitatory input from medial entorhinal cortex targeting stratum lacunosum-moleculare while input from CA3 gives rise to slow gamma (39, 49). Further, slow gamma in CA3 is driven by input from dentate gyrus (20).

Gamma oscillations are also present in virtually all of the brain areas, suggesting their universal function in neural processing. Based on experimental evidence and theoretical considerations, it has been proposed that gamma binds activity of cells in time, so that the output of neurons coactive within a gamma cycle can be effectively integrated in the

downstream population (5, 8). Should this communication be effective, both “sender” and “receiver” populations have to be synchronized within the same frequency band (16).

HIPPOCAMPAL OSCILLATIONS IN MEMORY RETRIEVAL

There are several studies describing involvement of hippocampal oscillations in memory-guided behavior. Disruption of theta leads to impaired performance in hippocampus-dependent delayed T-maze task. It is proposed, that this is a consequence of an essential role of theta in intrinsically driven dynamics of hippocampal activity. During a single theta cycle, the hippocampal place cells are active in a sequential manner, reflecting a corresponding sequence of locations on the animal’s trajectory (41). This phenomenon called theta sequences is proposed to reflect intrinsically coordinated activity that emerges with learning (15). Attenuation of theta by septal inactivation led to disruption of coordinated sequential place cells activation with altered performance in the task (47).

There are also studies depicting a possible link between hippocampal gamma rhythm and memory retrieval. During slow gamma states, activity of place cells tend to signal the upcoming locations, while during fast gamma periods place cells’ activity reflects current or past positions (3, 51). During individual slow gamma cycles, longer paths are represented compared to fast gamma cycles and these trajectories sweep ahead of animals’ current location (51). This has been linked to slow-gamma mediated retrieval of stored pattern from autoassociative CA3 network.

Moreover, an increase in hippocampal gamma has been described on central arm of delayed T-maze task, when animal has to make memory-guided decision which arm to enter (32, 39, 49).

These studies deal with hippocampal activity and behavior guided by recent activity. This type of sequential memory retrieval is an essential aspect of episodic and working memory. It can be viewed as a travelling ‘bump of activity’ along asymmetric connections between cell assemblies, representing subsequent positions along trajectory or subsequent episodes during mental travel.

In contrast, there is sparsity of studies examining different type of memory retrieval, such as recall of memory for a familiar spatial context, which is conceptualized as a transition between two continuous attractors.

A paradigm introduced by Jezek et al. (22) where the rats are exposed to sudden change of the environment identity, provides a unique opportunity to access the issue. In the study, rats were exposed to two different environments to develop respective spatial representations. In a testing phase, retrieval of spatial memory was induced by sudden switch of context-defining light cues, while animal was foraging in the arena. The activity of place cells in CA3 was simultaneously recorded, in order to monitor real-time dynamics of memory retrieval. The initial reactivation of proper spatial map typically occurred 200–300 milliseconds after the cue switch, and was followed by a brief unstable period manifested by repeated transitions between representations of both current and previous

contexts. This flickering between memory states was orchestrated by theta rhythm, in that within a single theta cycle exclusive expression of one of the network states was typically present, with transitions being as rapid as subsequent theta cycles. Theta oscillations thus organize hippocampal activity into discrete packets with rhythmic inhibition of network enabling fast reactivation of appropriate memory trace whenever the environment conditions change, or enabling an auto-correction in the case of ambiguous stimuli.

What is the network engaged with during the couple of seconds of instability? Along the light cues switch, visual information providing the only discriminative stimuli about the environment identity suddenly changes. However, the second pathway engaged in navigation, reflecting the inner motion cues and transforming them into information about linear and angular speed still, supports the original environment's representation. Such situation represents thus a conflict between the two basic information pathways used for human and animal navigation – allothetic (allocentric) and idiothetic (egocentric) decoding, respectively. While both are usually supporting each other, in this situation, their conflict emerges as the allocentric coding identifies the position based on environment's appearance, whereas the egocentric decoder keeps continuously tracking position within the original context representation. Both these pathways stream into hippocampal formation via entorhinal cortex (EC). However, the nature of this conflicting input is entirely unclear. Current view points to medial portion of entorhinal cortex (MEC) as to mainly a navigation unit, whereas its lateral part (LEC) is understood to process information about objects and other local properties of the environment. However, the body of evidence based knowledge about role of LEC in spatial navigation and memory is incomparably poorer than that of MEC. While the idiothetic processing is well supported to be processed in MEC, it is of discussion which pathway processes the visual stream that serves the allocentric navigation in the teleportation paradigm. Experiments with LEC lesioning did not lead to a loss of allocentric navigation in water maze (45), however the character of the environment defining cues is rather local than distal and one can assume the LEC could be involved in their processing. Under such a situation, the conflict on hippocampal inputs would mean that MEC feeds the hippocampus with path integration based signal within the previous environment context, whereas LEC would stream the information forcing to reactivate the 'new' environment representation.

Each of the inputs entrains a corresponding hippocampal neural ensemble. However, dynamics of activity in the CA3 network is under strong influence of recurrent collateral system, which represents the majority of synapses on individual pyramidal neurons. The reverberating excitation along the recurrent collaterals keeps the network in the corresponding attractor state with considerable inertia against a change that might e.g. reflect a change in the external world. Thus, even in the presence of changed input, a sufficient inhibition may be necessary for new activity pattern to override the original attractor. The inhibition is provided by theta oscillations. During theta oscillations, population of pyramidal neurons undergoes alternating periods of inhibition and disinhibition, exerted by an orchestrated activity of inhibitory interneurons. Within each theta cycle, period of increased excitability provides thus pyramidal cells opportunity to process the information and an appropriate memory pattern can be retrieved. At the end of the cycle, the ongoing

activity is silenced and competition between incoming inputs is triggered again (43). While at the beginning of theta cycle the conflicting inputs can retrieve neuronal patterns reflecting both the new and old spatial contexts, gradual emergence of attractor dynamics tends to push the activity into one of the attractors (22, 43), that will be disrupted by subsequent inhibition and the whole cycle repeats.

These considerations are backed up by a computational model (43), where in the absence of inhibition very strong input was necessary for map transitions to occur and sufficient theta modulation was essential for rapid retrieval of new spatial representation. Analysis of LFP traces from teleportation experiment revealed an increase in theta rhythmicity following the switch of the spatial contexts (50). We suggest that observed augmentation of theta oscillations promotes retrieval of memory for the new spatial context by enhanced inhibition of hippocampal network, so that the external input can effectively induce transitions between the attractors.

An additional role of theta in recall of spatial context memory might be in coordination of accompanying hippocampo-prefrontal interactions. In prefrontal cortex, cells exhibit phase-locking to hippocampal theta (40) and theta coherence between the regions is observed during their mutual communication (23). In a recent study (35), retrieval of contextual memory was accompanied by theta coherence between hippocampus and prefrontal cortex, where hippocampal theta led prefrontal cortex upon entry of the animal into the environment. Reverse interaction was observed when context-dependent memory was to be retrieved.

The increase in gamma rhythmicity may reflect enhanced information flow within the hippocampal formation. Applying the view linking gamma oscillation with the emergence of functional cell assemblies to memory recall, local gamma synchronizes active neurons in the upstream area, such as the entorhinal cortex, so their effective output is sufficient to drive their downstream target (e.g. CA3 neurons), triggering memory retrieval. The communication through coherence hypothesis (16) postulates importance of synchrony between two oscillating populations for effective communication between them to take place.

It has been shown that slow gamma synchrony appears predominantly between CA1–CA3 subregions, while fast gamma synchrony appears between CA1 and MEC (12, 39, 49). It has been proposed that gamma oscillations in different frequency bands selectively route communication flow between different subregions of hippocampal formation (12). In our pilot observation, we observed a transient increase in fast gamma frequency range linked to memory retrieval. While previous studies tended to relate fast gamma oscillations to communication between the medial entorhinal cortex and CA1 subregion of the hippocampus, it could be possible that fast gamma is involved in EC-CA3 information flow as well (see suppl. data in (12)). Retrieval of contextual memories can be induced by activity of MEC cells (26), but we have to consider a possibility that the first reactivation of new map is driven by input from LEC conveying information about context-defining cues, as discussed earlier. This ambiguity makes any attempts to relate observed changes in gamma frequency band to information flow between specific regions difficult. One study (21) reported increase in slow gamma (20–40 Hz) coherence between CA1 and LEC

accompanying retrieval of odor-place association memory. However, it is not clear how gamma oscillations are related to LEC-CA3 cross-talk, especially considering that gamma coherence described in (21) was specific to direct LEC-CA1 communication.

CONCLUSIONS AND PERSPECTIVES

Here we discussed role of hippocampal oscillations in memory processing, with an emphasis on memory retrieval. While there is considerable amount of studies claiming the importance of oscillatory activity in episodic and working memory, relatively little is known which mechanisms are employed in situations such as retrieval of memory for spatial contexts. Memories for different spatial contexts are stored as different attractors in the autoassociative CA3 network. When a subject is introduced into a familiar spatial environment, sensory information such as presence of specific visual cues induces a transition between respective attractor states. This is complicated by dominant influence of recurrent collaterals, stabilizing network in the original activity state. Here, the inhibition of population activity provided by theta oscillations plays a key role, in that it effectively interrupts attractor dynamics and enables the external inputs to entrain a corresponding neural ensemble. While brain oscillations have been traditionally studied predominantly in the context of neuronal synchrony and interregional communication, results from teleportation experiment points our attention to another prominent role of periodic inhibition – a rhythmic network reset, enabling the external information to sufficiently influence the current activity state and thus flexibly react to changing external input. This function is especially important for autoassociative attractor networks, such as CA3 of hippocampus. The frequency of theta, ~ 8 Hz in rodents, determines relevant memory pattern can be retrieved with latency of few hundreds of milliseconds. Sometimes, as in the case of conflicting input, expression of mutually different patterns can alternate between subsequent theta cycles.

Gamma oscillations accompanying hippocampal theta, are also important in memory processing. Increased gamma synchrony at local and interregional scale would enhance neural computation underlying retrieval. It is proposed that gamma synchrony at specific frequency bands facilitates communication between sub-regions in hippocampal formation, albeit most of the studies were centered on CA1 rather than on CA3 area. Moreover, some authors are cautious to interpret observed gamma coupling as a mechanism of communication through coherence (39, 7), as it might be byproduct of e.g. a feedforward entrainment of downstream network by gamma oscillating upstream population.

An additional interesting issue is the role of gamma oscillations in organizing the attractor dynamics (13). While flickering period after context switch in the teleportation study displayed a strong tendency to express one but not the other representation within a single theta cycle, some theta cycles displayed coactivation of both patterns. It is of question whether gamma oscillations can pace transitions between neural representations of different spatial contexts, mimicking the role of theta at a temporal microscale.

Further studies are required to understand how oscillations in hippocampal formation organize memory retrieval. Specifically, simultaneous recordings of oscillatory activity at various sites of EC-CA3-CA1-PFC loop could detect frequency specific coherence between individual regions, unveiling routes of information flow that underlie attractor transitions. In addition to gamma synchrony, increased theta-mediated coordination of activity flow across hippocampal formation might also be important (31). While top-down prefronto-hippocampal interactions have been described in contextual fear-conditioning and context-dependent memory task (35, 36), it is not clear how prefrontal cortex influences the process of reactivation of memory for spatial context itself.

Impairment in oscillatory mechanisms has become recognized as an important pathophysiological aspect of neuropsychiatric disorders (9). In addition, hippocampal alterations are associated with disorders such as schizophrenia, affective disorders and Alzheimer's disease. Thus, better understanding of oscillations and their abnormalities in the hippocampus and other brain areas will shed more light onto mechanisms of disorganized neuronal activity associated with brain disease and will pave the way to the new therapeutic approaches.

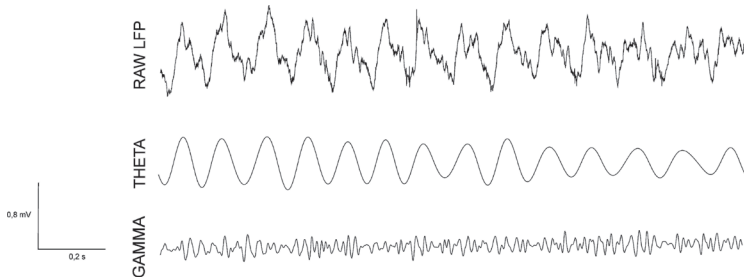


Fig. 1 Local field potential recorded from CA3 subregion of a hippocampus in a rat. Top: Raw LFP trace. Middle: LFP band-pass filtered for theta frequency (5–12 Hz). Bottom: LFP band-pass filtered for gamma frequency (25–100 Hz).

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SUMMARY

Brain oscillations, reflecting rhythmic excitation and inhibition of neuronal populations, play essential role in coordination of neuronal activity. Study of rhythmic activity in hippocampus revealed its importance for memory processing. However, memory retrieval, the final stage of memory cascade, remains an elusive phenomenon. Analysis of hippocampal network activity during spatial memory retrieval pointed to significance of theta oscillations, the EEG pattern in hippocampus (5–12 Hz) that dominates during periods of active (“online”) processing of information. Recurrent excitation in CA3 sub-region of hippocampus keeps the memory network in a stable attractor state. Periodic inhibition during theta oscillations disrupts attractor dynamics and enables memory recall by transition to corresponding network state. The main source of input to hippocampus is entorhinal cortex, whose medial division is dedicated to spatial position representation, while the lateral part is associated with coding for local sensory stimuli. The communication between entorhinal cortex and hippocampus is coordinated by gamma rhythms (25–100 Hz). Which inputs originating in the entorhinal cortex initiate retrieval of memory for spatial context remains unclear. Further studies with simultaneous recording of activity from various hippocampal sub-regions and associated structures could reveal more about dynamics of memory retrieval and their coordination by neuronal oscillations.

Neurální oscilace a aktivace paměti

SOUHRN

Mozkové oscilace, odpovídající rytmickému střídání excitace a inhibice neuronových populací, hrají významnou roli v koordinaci neuronální aktivity. Studium rytmické aktivity v hipokampu poukázalo na esenciální význam oscilací pro paměťové procesy. Finální část paměťové kaskády – proces rozpomínání, však zůstává z velké části neobjasněn. Registrace aktivity hipokampální sítě během reaktivace prostorové paměti u potkanů poukázala na význam theta oscilací, jež představují dominantní hipokampální EEG vzorec (5–12 Hz) během aktivního zpracování informací z vnějšího prostředí. Rekurentní excitace v CA3 podoblasti hipokampu udržuje paměťovou síť v stabilním paměťovém stavu – atraktoru. Periodická inhibice odpovídající theta rytmu, umožňuje oslabení atraktorové dynamiky a ev. změnu příslušného paměťového vzorce. Hlavním zdrojem vstupu do hipokampu je entorinální kůra, jejíž mediální část obsahuje buňky mající vztah k prostorové reprezentaci, zatímco laterální část je asociována s reprezentací lokálních sensorických stimulů. Komunikace mezi entorinální kůrou a hipokampem je koordinována gamma rytmem (25–100 Hz). Které vstupy z entorinální kůry iniciují reaktivace paměti pro prostorový kontext a jaká je role gamma oscilací v tomto procesu, zůstává neobjasněno. Další studie se simultánní registrací aktivity z vícečetných podoblastí hipokampu a asociovaných struktur mohou více podhalit dynamiku procesu rozpomínání a jeho koordinaci neuronálními oscilacemi.

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