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Review

Transition of Septo-Hippocampal Network Modes between Theta and Non-Theta States

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Abstract: Hippocampus plays a crucial role in spatial and episodic memory. The acquisition of new memories is impossible without participation of the hippocampus. There are two main functional states or “modes” of the hippocampal activity, theta and non-theta state. They have different behavioral correlates and clearly different spectral content of the LFPs and neuronal spiking. Hippocampal theta state is present under active exploratory behavior, locomotion, cognitive situations requiring attention and REM sleep. Slow-wave sleep and quiet wakefulness (immobility, eating, grooming) represent the non-theta hippocampal state. The nodal point for the regulation of hippocampal activity is the MS. The activation or suppression of different types of MS cells appears to be responsible for controlling hippocampal theta and non-theta states. Functional coupling between MS neurons and hippocampal interneurons varies in a state-dependent manner.

Keywords: Teevra cells; Komal cells; medial septum; freely behaving animals; ripples; delta; theta

1. Introduction

Hippocampus plays a crucial role in spatial and episodic memory. The acquisition of new memories is impossible without participation of the hippocampus (Vinogradova, 2001; Corkin, 2002; Buzsáki and Moser, 2013). Information procession in hippocampal neuronal networks requires dynamic coordination of activity across large groups of neurons. Such coordination can be indirectly observed as rhythmical oscillations of local field potentials (LFPs).

There are two main functional states or “modes” of the hippocampal activity, theta and non-theta state (Buzsáki, 2002; Schultheiss et al., 2020). They have different behavioral correlates and clearly different spectral content of the LFPs and neuronal spiking. Hippocampal theta state is present under active exploratory behavior, locomotion, cognitive situations requiring attention and REM sleep. Slow-wave sleep and quiet wakefulness (immobility, eating, grooming) represent the non-theta hippocampal state (Vanderwolf, 1969; Buzsáki, 2002; Young and McNaughton, 2009; Colgin, 2013).

In theta state, hippocampal LFPs exhibit strong regular theta (4-12 Hz) and gamma oscillations (Bragin et al., 1995; Csicsvari et al., 2003; Tort et al., 2009; Belluscio et al., 2012). In non-theta state, hippocampal activity is dominated by a slower and irregular oscillation in the delta (0.5-4 Hz) frequency range, interrupted by highly synchronous neuronal activity, sharp wave-ripple complexes (SWR) (Buzsáki, 2015). SWR may be accompanied by an increase in gamma power and coherence (Sullivan et al., 2011; Carr et al., 2012). Depending on the amplitude of the LFPs, the non-theta state is divided by some authors into large and small irregular activity, LIA and SIA, respectively (Jarosiewicz et al., 2002). Theta and non-theta hippocampal states are traditionally characterized as two opposite and mutually exclusive states, “online” and “offline” modes of information processing (Buzsáki, 2002).

Hippocampal activity is modulated by direct projections from the medial septum (MS). Lesion or inactivation of the MS abolishes hippocampal theta, and theta-bursts of MS neurons are believed to drive it (Vinogradova et al., 1980; Smythe et al., 1991; Wang et al., 2015). During hippocampal SWR, some MS neurons are activated (Borhegyi et al., 2004; Viney et al., 2013) while others are inhibited (Dragoi et al., 1999; Borhegyi et al., 2004). Thus, different brain states could be facilitated by different forms of septo-hippocampal connections (Vertes and Kocsis, 1997). While the role of the MS in theta generation has been extensively studied and has a solid foundation, the functional interactions between the MS and hippocampus during different behavioral states are largely unknown. Reflecting the change of ongoing behavior, a transition between theta and non-theta hippocampal states is a complex event. Different studies have shown that the activity of MS and hippocampal cells and their mutual influence change during the transition between functional states (Bland et al., 1999). For example, part of the MS theta-related (positively associated with the hippocampal theta) cells increases firing rate approximately 500 ms before the onset of theta state. Similar “theta-on” cells in the hippocampus change their activity consistently with the appearance of theta rhythm. On the other hand, during the transition from theta to non-theta state, none of the theta-related cell groups change their activity in advance, before the transition (Bland et al., 1999). However, the specific mechanisms of transition between theta and non-theta hippocampal states remain to be elucidated. In this review, we summarize available experimental data concerning the transition between hippocampal theta and non-theta states and propose possible mechanisms underlying this state transition.

2. Peculiarities in the hippocampal activity during different functional states

Hippocampal network activity is spatially and temporally tuned in behavior-dependent manner. The spiking of some pyramidal cells and interneurons is organized within theta-, gamma-, LIA, SWR and other theta- and non-theta-field activity. This organization is supported by well-studied intrahippocampal projections and coordinated by local interneurons, as well as by the other structures such as entorhinal cortex and MS.

During theta oscillations CA3-CA1 pyramidal cells are preferently active at the trough of dorsal hippocampal CA1 theta cycle (Csicsvari et al., 1999; Lasztóczi et al., 2011). Diverse local interneurons participate in this activity by rhythmic inhibition to distinct pyramidal subcellular compartments (Somogyi et al., 2014). In contrast to theta-state, CA1 neuronal activity in non-theta states is irregular and generally diffuse (Buzsáki et al., 1983, 1986; Bragin et al., 1995). However it increases significantly and synchronizes during SWR (Buzsáki et al., 1992).

In 1987 Colom and Bland described, although in urethane anesthetized rats, the presence in the hippocampus of non-complex-spike cells which were inactive during theta-state and discharged preferently during LIA. They called these cells “theta-off” as opposed to “theta-on”, classical “theta” cells (Colom and Bland, 1987; Ford et al., 1989a). In CA1 and CA3, in addition to theta-related, theta-unrelated cells, discharging with simple or complex spikes or "silent", were recorded, and functional heterogeneity among pyramidal neurons of the dorsal hippocampus was demonstrated in relation to the generation of current LFPs (Bland et al., 2005).

Different types of hippocampal interneuron also show distinctive activity in relation to theta- and non-theta states (Klausberger and Somogyi, 2008). Most CA1 interneurons increase their firing rate from non-theta to theta periods (Czurkó et al., 2011; Varga et al., 2012) possibly due to a combination of decreased inhibition from MS GABAergic cells, increased excitatory input from CA3 pyramidal cells and/or other inputs (Fuhrmann et al., 2015). During SWR, a particular mode of neural network activity during the non-theta state, hippocampal interneurons demonstrate functional heterogeneity. Axo-axonic cells are suppressed (Viney et al., 2013), and parvalbumin-containing (PV^+) basket cells are activated and increase their firing rates. Mean firing rate of OLM cells also increase during SWR although they had a generally lower firing probability during ripples (Varga et al., 2012).

Transitions between different hippocampal functional states seem to occur relatively fast, within a few seconds (Schultheiss et al., 2020). Analyzing hippocampal rhythmical activity in freely behaving rats, it has been recently shown that synchrony in one frequency band is suddenly replaced by synchrony in another. Pronounced delta or theta rhythm usually occurs when synchrony in the other band is weak. However, it is worth noting that such transitions are not always “clean”: in some cases, delta and theta correlate positively over short time intervals (Schultheiss et al., 2020).

When the animal changes behavior from theta- to non-theta state, hippocampal network excitability is also changed. Activity of local interneurons, septal and entorhinal inputs have a different temporal structure than during theta oscillations. During transitions from non-theta to theta state in freely moving and sleeping rats, regardless of the animal behavior, firing rates of hippocampal theta cells (presumably interneurons) were significantly reduced. In contrast, the activity of complex-spike cells (presumed pyramidal cells) during the transition period was increased (Stewart, 1993).

The main role in the hippocampal neuronal activity changing is played by the MS inputs. In the next section, we will discuss possible mechanisms by which MS may control hippocampal theta and non-theta states. We would only like to note here that in all fields of the hippocampus interneurons inhibit each other (Rees et al., 2016). This creates an antagonistic relationship between the different types of interneurons. And the MS innervation significantly affects the balance of inhibition between hippocampal interneurons.

3. Role of the medial septum in the control of hippocampal theta and non-theta states

A key structure in the control of hippocampal rhythmical modes is the medial septum (Vinogradova, 1995; Vertes and Kocsis, 1997; Buzsáki, 2002; Colgin, 2013). Lesion or pharmacological inactivation of the MS abolishes theta rhythm and leads to a pronounced non-theta activity in the hippocampus (Green and Arduini, 1954; Petsche and Stumpf, 1962; Mitchell et al., 1982; Mizumori et al., 1990; Vinogradova et al., 1993; Wang et al., 2015). Electrical, pharmacological, or optogenetic stimulation of the MS, on the contrary, induces a stable theta rhythm in the hippocampus (Brazhnik et al., 1985; Vandecasteele et al., 2014; Astasheva et al., 2015).

The MS is composed of glutamatergic, cholinergic, and GABAergic neurons (Brashear et al., 1986; Kiss et al., 1997; Sotty et al., 2003). The population of GABAergic neurons is heterogeneous and consists of calretinin- and PV$^+$ cells. All neuronal populations, except calretinin-containing GABAergic cells, project to the hippocampus (Mesulam et al., 1983; Freund, 1989; Manseau et al., 2005). For more detail about MS neurons and their interactions, see works by (Mysin et al., 2015; Tsanov, 2015; Müller and Remy, 2018).

Glutamatergic hippocampal MS projections innervate both pyramidal cells and interneurons (Manseau et al., 2005; Fuhrmann et al., 2015). There are conflicting data on their physiological role. On the one hand, glutamatergic MS neurons directly excite interneurons that control input to CA1 both from Schaffer collaterals and perforant pathway (Fuhrmann et al., 2015). On the other hand, optogenetic stimulation of MS glutamatergic projections in the fimbria-fornix had no effect on the hippocampal theta rhythm (Robinson et al., 2016). On the contrary, stimulation of glutamatergic cell bodies inside the MS induces a theta rhythm in the hippocampus, which frequency was tightly modulated by stimulation (Fuhrmann et al., 2015; Robinson et al., 2016). Thus, intraseptal glutamatergic connections seem to be much more important for the regulation of hippocampal rhythmical modes. Direct MS glutamatergic projections to the hippocampus probably play only a modulating role and may take part in the place cell formation (Fuhrmann et al., 2015).

The role of MS cholinergic neurons in the regulation of hippocampal rhythmic activity seems to be similar. Stimulation of cell bodies of MS cholinergic neurons generates sustained theta rhythm in the hippocampus (Vandecasteele et al., 2014; Dannenberg et al., 2015). Stimulation of their axon terminals in the hippocampus, on the contrary, has only a modulating effect: increase activity of interneurons and decrease firing rate of pyramidal cells (Dannenberg et al., 2015). Though some authors believe that MS cholinergic neurons may directly affect the hippocampal activity, maintaining high level of acetylcholine in the hippocampus (Ma et al., 2020). Using long-term recording of MS cholinergic neurons and optogenetics it was shown in freely behaving mice that these neurons were highly active during theta-dominating states (active exploration and rapid eye movement sleep). During non-theta states (slow-wave sleep) MS cholinergic neurons were almost silent, and their optogenetic activation suppressed ripple oscillations in CA1 (Ma et al., 2020).

PV^+ GABAergic MS neurons seem to make the main contribution to the regulation of hippocampal functional states. It is GABAergic MS neuronal activity that correlates most strongly with hippocampal theta rhythm (Borhegyi et al., 2004; Varga et al., 2008; Hangya et al., 2009). Direct experiments with optogenetic activation of PV^+ GABAergic MS neurons support this notion. Stimulation of both GABAergic MS cell bodies and hippocampal terminals induces theta rhythm and impedes the non-theta activity. The oscillation frequency in the hippocampal LFPs linearly depends on the frequency of stimulation (Dannenberg et al., 2015; Zutshi et al., 2018).

Projecting GABAergic MS neurons have been subdivided into two populations (Borhegyi et al., 2004; Henderson et al., 2004). The neurons of these populations were named Teevra and Komal cells due to peculiarities of their spike train dynamics (Joshi et al., 2017; Viney et al., 2018). Teevra and Komal neurons suppress each other and discharge in antiphase bursts (Borhegyi et al., 2004; Henderson et al., 2004). Teevra and Komal cells have many significant differences. Their cell bodies are located in different parts of the MS, closer to the center or the periphery respectively (Henderson et al., 2004). Teevra cells are the most rhythmic among MS neurons and fire with short burst duration preferentially at the troughs of hippocampal LFPs. Komal cells have a long burst duration preferring the peak of CA1 theta LFPs (Borhegyi et al., 2004) (Joshi et al., 2017). Teevra cells preferentially innervate restricted septo-temporal CA3 segments (Joshi et al., 2017), while Komal cells send projections to subiculum and entorhinal cortex (Viney et al., 2018).

Computational experiments show that the antiphase discharge regime of two populations of mutually inhibitory bursting neurons is very unstable. Small deviations in the mutual inhibitory balance lead to the complete suppression of one population by the other (Mysin et al., 2015). The antiphase regime stability is most likely provided by glutamatergic and cholinergic neurons of the MS. The computational model reproduces this effect (Mysin et al., 2015). Thus, although glutamatergic and cholinergic MS neurons have direct hippocampal projects, their role is not clear. Local MS connections are very important for maintaining the activity of Teevra and Komal cells (Wu et al., 2003; Dannenberg et al., 2015; Robinson et al., 2016).

Despite numerous data on the control of theta rhythm by MS projections, the role of MS in controlling non-theta hippocampal activity has not been sufficiently studied. On the one hand, complete suppression of MS neuronal activity by procaine or muscimol leads to non-theta state in the hippocampus, very similar to quiet wakefulness or non-REM sleep (Smythe et al., 1991; Lawson and Bland, 1993; Vinogradova et al., 1993; Wang et al., 2015). Based on these data, it could be assumed that the non-theta state in the hippocampus arises as a result of the lack of input from the MS. But on the other hand, experiments in restrained rats show that there is no significant difference in the activity of PV^+ GABAergic MS neurons in the theta (running and REM sleep) and non-theta states (non-REM sleep) (Simon et al., 2006). Recent data on the structure of hippocampal innervation by Teevra cells allow us to hypothesize that MS may play a more active role in the hippocampal non-theta state. Teevra cells predominantly innervate CA3 cholecystokinin-containing basket and axo-axonal neurons (Joshi et al., 2017). In non-theta state, Teevra cells maintain their firing rate, but decrease their rhythmicity (Joshi et al., 2017), while Komal cells reduce their firing rate compared to theta state (Joshi et al., 2017; Unal et al., 2018). Based on these data, we assume that in non-theta state, the antiphase discharge mode of Teevra and Komal cells is destroyed, i.e. Teevra cells suppress Komal cells. This,

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in turn, results in a more constant inhibitory signal from Teevra cells to the hippocampus. More stable inhibition of cholecystokinin$^+$ and axo-axonal neurons reduces perisomatic inhibition of pyramidal neurons. Disinhibition of pyramidal cell bodies enables them to discharge with a higher probability, facilitating the generation of complex spikes and ripple oscillations as a process of synchronization of pyramidal neurons in the CA3 due to local excitatory connections (Viney et al., 2013; Buzsáki, 2015).

The possible mechanism of SWR initiation through disinhibition of pyramidal cells has experimental confirmations. Axo-axonal interneurons in freely moving rats do not fire during SWR (Viney et al., 2013). At the same time, according to some data, Teevra cells do not change their firing during SWR (Joshi et al., 2017). But in the earlier study, it was shown that around 40% of presumably Teevra cells were activated during hippocampal SWR (Viney et al., 2013). Probably, local interneuronal connections also make a significant contribution to the suppression of axo-axonal cells. Axo-axonal cells inhibit other interneurons and receive inhibitory responses (Rees et al., 2016). Stable suppression of axo-axonal neurons by Teevra cells may provoke weakening of their ability to compete with other populations of interneurons. The restructuring of the MS neural network functioning and, as a result, a change in the firing pattern of Teevra cells creates conditions for theta or non-theta hippocampal states.

Interactions between the MS and the hippocampus are reciprocal and depend on the network state. Thus, hippocampal projections to the MS are also likely to be involved in the regulation of the neuronal network states. Hippocampo-septal communication is mediated by somatostatin-positive CA1-CA3 neurons (Tóth et al., 1993; Jinno and Kosaka, 2002). These projecting neurons receive input from pyramidal neurons and granule cells and are involved in rhythmic processes in the hippocampus (Blasco-Ibáñez and Freund, 1995; Gulyás et al., 2003; Takács et al., 2008). High-frequency and low-frequency stimulations of hippocampo-septal neurons have different effects. Using optogenetic approach, Mattis and colleagues stimulated hippocampo-septal afferents in an acute slice preparation (Mattis et al., 2014). Stimulations at both theta and ripple frequencies elicit the fast GABAergic postsynaptic response. However, in response to prolonged high-frequency (ripple) stimulation, a slow hyperpolarization of cholinergic and GABAergic MS neurons was observed (Mattis et al., 2014). In behaving rats, it was shown that 60% of MS cells were significantly suppressed during SPW (Dragoi et al., 1999). Thus, periodically occurring ripple events may support the functioning of the MS neural network in non-theta mode.

The role of MS input rhythmicity on the formation of hippocampal theta and non-theta states was confirmed in model studies (Tokuda et al., 2019). Transitions between theta and non-theta states were studied using a dynamical model of the local hippocampal circuit. In the model, as well as in the real hippocampus, neurons demonstrated highly synchronous periodic oscillations in the presence of rhythmic input from the MS. Aperiodic MS activity leads to diffusion-induced chaotic dynamics, just like disappearance of the rhythmicity of MS neurons leads to LIA in place of theta in the real hippocampus (Tokuda et al., 2019).

4. Role of the median raphe nucleus in the control of hippocampal non-theta states

A considerable body of evidence indicates that other brain structures are also involved in the generation and transition between hippocampal functional states. The median raphe nucleus (MRn), a known desynchronizing agent of hippocampal activity, probably controls the hippocampal non-theta state through the influence on the MS or even directly (Vertes, 1981; Peck and Vanderwolf, 1991; Kitchigina et al., 1999; Vinogradova et al., 1999). It was shown in awake rabbits that low-amplitude MRn stimulation disrupted MS bursting and abolished theta activity in the hippocampus, while suppression of MRn activity by local injections of lidocaine had the opposite effect (Kitchigina et al., 1999; Vinogradova et al., 1999). It is thought that control of hippocampal non-theta states may be mediated by serotonergic MRn neurons, which disrupt theta activity of MS and/or hippocampal neurons (Vertes et al., 2010). Single injections of a serotonin reuptake inhibitor into the lateral brain ventricles caused a significant and prolonged decrease in the hippocampal theta rhythm (Kudina et al., 2004).

Different functional modes of the hippocampus may be also facilitated by other neuronal pathways and neurotransmitter systems in the MRn-MS-hippocampus circuit. Non-serotonergic (possibly glutamatergic) projections of the MRn to the MS may contribute to generation of theta state in anesthetized rats in the absence of MS cholinergic tone (Crooks et al., 2012). Earlier, an elevated level of glutamate in the MRn was found to coincide with irregular desynchronized hippocampal activity (non-theta state) (Varga et al., 1998). The authors suggest that theta-related changes in the MRn glutamate level may reveal downstream forebrain influences and represent a feedback regulation of hippocampal activity (Varga et al., 1998).

It is interesting to note that Jackson and colleagues demonstrated that high-amplitude MRn stimulation provoked small-amplitude irregular activity (SIA) in the hippocampus and not the other "typical" non-theta activities like LIA, SWR or slow oscillation (Jackson et al., 2008). Thus, the desynchronizing action of MRn causes a marked general reduction in the amplitude of the hippocampal LFPs and a deep blockade of theta. MRn stimulation failed to affect theta-unrelated hippocampal cells but suppressed the activity of the majority of both theta-on and theta-off cells (Jackson et al., 2008). On the contrary, theta-off cells were observed to discharge continuously during LIA (Colom and Bland, 1987; Ford et al., 1989b). Although response to MRn stimulation was dependent on brain state, cell type, and theta phase, authors supposed that MRn stimulation could elicit a hippocampal non-theta state dissimilar to LIA (Jackson et al., 2008).

5. Functional difference between theta and non-theta states

The relationship between hippocampal theta- and non-theta states has received a relative lack of attention. In contrast to theta-state, the functional significance of non-theta state is not so well-characterized. In general, it is believed that in rodents these two hippocampal modes reflect different network coupling and behavior.

Analyzing cortical-cortical and cortical-hippocampal coherence in freely behaving rats, Young and McNaughton showed that couplings of theta and delta oscillations clearly depended on animal behavior (Young and McNaughton, 2009). The power of the delta rhythm was maximal during grooming and resting (non-theta states), and minimal during locomotion, exploratory behavior and rearing (theta states). In "non-cognitive" behavior, there was also an extensive delta coupling in the frontal cortex, which was not associated with the posterior areas and the hippocampus. On the other hand, the power of theta oscillations and theta coherence between structures increased during non-automatic behavior and were almost unpronounced during immobility or grooming (Young and McNaughton, 2009). The authors believe that different frequencies of rhythmical activity may bind different neuronal assemblies into functional groups in different circumstances. In a recent study in freely behaving rats, this assumption has been confirmed (Schultheiss et al., 2020). Periods of delta-dominated activity were prominent in the hippocampus when animals were stationary or moving slowly (non-theta state). Such delta-dominated modes were orthogonal to theta modes prevailing in running. Delta power and synchrony in the hippocampus were negatively related to the animal speed. Orthogonality of theta and delta modes was also manifested in the interaction of hippocampus with medial prefrontal cortex. While theta coherence between these structures increased during running, delta coherence increased during quiet wakefulness (Schultheiss et al., 2020).

The traditional view that theta and gamma represent "online", and delta reflects "offline" mode of information processing, is opposed by the work of Furtunato and colleagues (Furtunato et al., 2020). Analyzing LFPs in the left and right rat hippocampi during consecutive short-term treadmill runs at the same speed, they observed prominent delta and theta oscillations. Delta power and inter-hemispheric phase coherence in the delta band increased across consecutive treadmill runs. At the same time, theta and gamma power decreased with the trial number. Thus, consecutive treadmill runs enhanced delta power and coherence in the rat hippocampus (Furtunato et al., 2020).

Several studies have noted that learning during non-theta states is less effective than during theta states. In the absence of theta oscillations, the rate of acquisition of eyeblink conditioning in rabbits was significantly slower and the percentage of conditioned responses was lower, compared with animals trained during theta states (Seager et al., 2002; Griffin et al., 2004; Hoffmann and Berry, 2009; Cicchese and Berry, 2016).

The difference in the hippocampal operational modes (theta or non-theta states) is also manifested in pathological conditions such as seizure activity. In a rat model of temporal lobe epilepsy, it was shown that the hippocampal functional state preceding seizures influenced spontaneous seizure activity and determined the success of therapeutic intervention. Optogenetic curtailment was significantly more effective for seizures that emerged from non-theta states (Ewell et al., 2015).

6. Conclusion

The nodal point for the regulation of hippocampal activity is the MS. The activation or suppression of different types of MS cells appears to be responsible for controlling hippocampal theta and non-theta states. Functional coupling between MS neurons and hippocampal interneurons varies in a state-dependent manner.

We assume that loss the balance of mutual inhibition between specific MS cell groups, presumably Teevra and Komal cells, results in a more constant inhibition of some hippocampal interneurons, disinhibition of pyramidal cells, and facilitate the synchronization of pyramidal neurons and generation of SWR during non-theta states.

The orthogonality between theta and non-theta states in the hippocampus probably represents a qualitative difference in network dynamics and not an anticorrelation between two constantly interchanging modes. Probably, one should speak not about the complete independence of different frequency bands, but rather about a "permissive-exclusive" relationship (Schultheiss et al., 2020). The different network modes may serve to implement different aspects of spatial coding, decision-making, or memory processes.

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