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Review

Septo-hippocampal dynamics and the encoding of space and time

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Encoding an event in memory requires neural activity to represent multiple dimensions of behavioral experience in space and time. Recent experiments have explored the influence of neural dynamics regulated by the medial septum on the functional encoding of space and time by neurons in the hippocampus and associated structures. This review addresses these dynamics, focusing on the role of theta rhythm, the differential effects of septal inactivation and activation on the functional coding of space and time by individual neurons, and the influence on phase coding that appears as phase precession. We also discuss data indicating that theta rhythm plays a role in timing the internal dynamics of memory encoding and retrieval, as well as the behavioral influences of these neuronal manipulations with regard to memory function.

Highlights

The medial septum (MS) influences the generation and organization of spatiotemporal coding and memory in the hippocampus and entorhinal cortex. Recent work has begun to delineate the contribution of specific septal cell types.

In animal models, inactivation of cell populations in the MS impairs performance in spatial working memory tasks.

Electrophysiological studies show the impact of the MS on functional cell types. Entorhinal grid cells show impaired spatial coding during inactivation of all cells or GABAergic cells in the MS. Entorhinal and hippocampal phase precession is impaired by driving from GABAergic cells.

Hippocampal time cells encode time intervals during delays and show loss of time coding and theta sequences during MS inactivation.

Inactivating or driving neurons in the MS does not prevent spatial coding by head direction cells, border cells, or place cells.

These lines of research explore the role of theta in the dynamics of encoding and retrieval, and their potential role in memory function.

The functional role of the medial septum

Considerable evidence indicates that neural substrates of memory function involve the hippocampal formation [1] and associated structures such as the medial septum (MS) [2–4]. Many functional cell types have been described in the hippocampal formation, including place cells [5], grid cells [6], time cells [7], boundary vector cells [8], speed cells [9], and head direction cells [10]. The presence of these cell types raises questions about how network dynamics might contribute to the formation of functional cell types and their potential role in the dynamics of encoding and retrieval of memories. Manipulations that affect memory often alter theta rhythms [4,11], and a functional role of theta rhythm is supported by the rhythmicity of many functional cell types including place cells [12], grid cells [13], time cells [7], boundary vector cells [14,15], and speed cells [16]. This review addresses how septo-hippocampal network dynamics might contribute to the formation of functional cell types, and their potential role in the dynamics of encoding and retrieval of memories, with a special emphasis on the role of theta rhythm modulation by the MS. We use the abbreviation MS to refer to manipulations that include both the medial septum and the adjacent structure, the diagonal band of Broca.

MS and theta rhythm generation

Theta oscillations in the mammalian brain are essential for hippocampus-dependent functions including spatial navigation and memory [17]. In rodents, theta oscillations in the hippocampus are typically in the range of 4–12 Hz and are present throughout exploration as well as during rapid eye movement (REM) sleep [18]. Recent data confirm the role of the MS in regulating theta rhythm in the hippocampus and entorhinal cortex of rodents, supporting earlier studies showing that MS lesions lead to loss of theta [11,19]. Recent studies involve selective manipulation of cellular populations in the MS (Figure 1), which include GABAergic, glutamatergic, and cholinergic neurons [20]. As summarized in Figure 1, MS GABAergic neurons constitute ~28% of MS neurons [20]. Subsets of GABAergic neurons form local projections within the septum to cholinergic and GABAergic neurons, and subsets also target inhibitory interneurons in both the hippocampus and medial entorhinal cortex (MEC) [21–25]. MS GABAergic neurons are a heterogeneous

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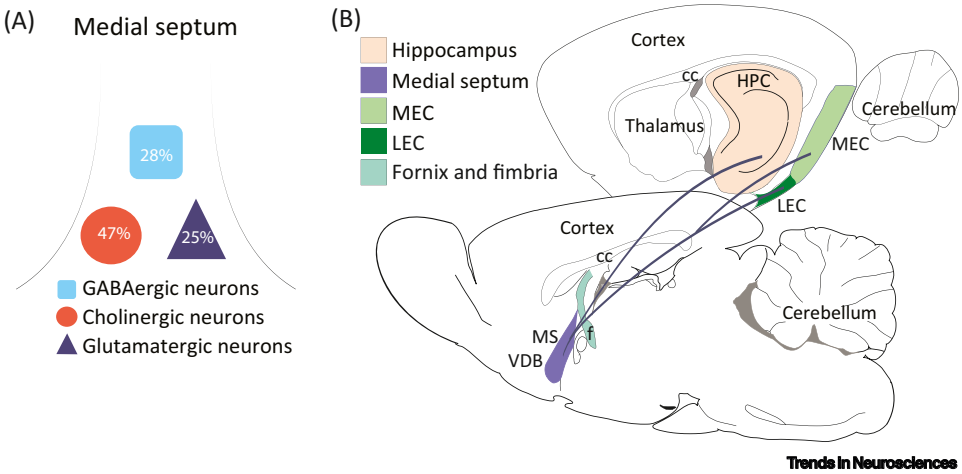

Figure 1. Diagram of medial septum (MS) neural populations and their projections to the hippocampus and entorhinal cortices. The MS contains three primary neuronal subtypes, as illustrated schematically together with their respective percentages in mice: GABAergic neurons (blue), cholinergic neurons (red), and glutamatergic neurons (purple). Sagittal diagram of major connections of mouse MS to hippocampus and entorhinal cortex. The MS and VDB project to both the hippocampus and entorhinal cortex. Abbreviations: cc, corpus callosum; f, fornix and fimbria; HPC, hippocampus; LEC, lateral entorhinal cortex; MEC, medial entorhinal cortex; VDB, vertical limb of diagonal band of Broca.

population, and different subtypes have been described based on molecular profiling, activity patterns, and anatomical projections to different regions [24–29]. These include rhythmically active neurons that are predicted to be the primary pacemaker of ongoing theta oscillations in the hippocampus [30]. MS GABAergic neurons include subtypes such as parvalbumin (PV)- and calbindin (CB)-expressing neurons [23,26,31]. Recent advances in genetic targeting allow more specific targeting of separate populations within the MS. Specifically, the introduction of optogenetic manipulation combined with Cre–lox recombination using viral transfection strategies allows regional, temporal, and cell-type specificity in manipulations [32]. When targeting MS PV neurons, optogenetic activation of this population drives theta oscillations in both the hippocampus and MEC [33–37]. Optogenetic inhibition of septal GABAergic neurons reduces theta power by ~60% during REM sleep [38], and causes up to 69% reduction in peak theta amplitude during open field exploration [39]. These optogenetic data clearly indicate a strong role of MS GABAergic neurons in pacing theta rhythm.

MS GABAergic neurons regulate temporal and spatial coding

MS GABA cells and the hippocampus

Selective manipulation of MS neurons and theta rhythms allows analysis of their influence on functional cell types and temporal coding in the hippocampus (Table 1). Temporal coding appears in the form of theta phase-specific firing, which occurs in both hippocampal pyramidal cells and in different classes of interneurons [40–42]. This temporal coding via theta phase specificity is often associated with phase precession (Figure 2) in which spikes occur at earlier phases within the theta cycle as an animal traverses a firing field [12,43]. Phase precession is associated with a difference between the network theta rhythm frequency in the local field potential and a higher spiking frequency of individual neurons, as measured by autocorrelograms (Figure 2) in the hippocampus [43] and the entorhinal cortex [44,45]. This precession of spiking across theta phases may augment spatiotemporal coding because the combination of spiking and theta phase provides more information about the location of the animal than does spiking alone. When several cells fire within a theta cycle, they spike in sequence, such that the order of locations visited is

Table 1. Effects of MS manipulations on hippocampal physiology and memory

MS experiment type	Theta oscillations, precession, and sequences	Functional cell types	Memory
Stimulation	**GABA** Theta frequency stimulation drives theta oscillations [33,34,37] Scrambled stimulation disrupts theta oscillations [69] **Glutamate** Theta frequency stimulation drives theta oscillations [74] **Acetylcholine** Spares theta oscillations [84]	**GABA** Spares place cells [34]	**GABA** Frequency- and/or task-dependent Impairs DNMP with scrambled or supra-theta stimulation [35,69] Spares DNMP with theta frequency stimulation [35] **Acetylcholine** Delay period stimulation impairs delayed spatial alternation [85]
Inhibition	**Acetylcholine** Scopolamine impairs precession but spares sequences [95] **Non-selective** Reduces theta oscillations [48,49] Spares theta precession [48] Impairs theta sequences [49]	**Acetylcholine** Scopolamine impairs place cells [91,92] Lesion spares place cells [93] **Non-selective** Spares place cells [54] Impairs time cells [49,70]	**GABA** Delay period inhibition spares DNMP [70] Lesion impairs spatial working memory [66,67] **Glutamate** Impairs social [80] and spatial memory [76] **Non-selective** Delay period inhibition impairs spatial and cued working memory [68]

represented in precise temporal order within each cycle [43,46]. These temporally organized sequences of spiking within theta cycles are known as theta sequences. It is theorized that temporal coding and representation of successive locations by theta sequences are essential for memory formation [43,47]. Whole MS inactivation and theta reduction disrupts place cell phase precession in some but not all neurons [48], and abolishes theta sequences [49]. More selective optogenetic driving of PV cells to push hippocampal oscillation above the endogenous theta rhythm range (10–12 Hz) does not alter place cell spatial specificity but does disrupt phase precession in many neurons [34]. Autocorrelograms (Figure 2) of hippocampal spiking during PV cell driving of theta show a shift to higher intrinsic rhythmic frequencies relative to the driving frequency, but only in a subset of neurons [34]. This higher intrinsic frequency relative to the network could arise from cellular conductances such as hyperpolarization-activated cyclic nucleotide-gated (HCN) channels that could either respond to more synchronized inhibition with higher resonance frequency relative to driving frequency [50] or respond with transient shifts to different phases [51], similarly to the effect of inductance in electrical circuits.

MS GABA cells and the entorhinal cortex

In contrast to the hippocampus, the MS appears to be essential for spatial coding by grid cells in the MEC (Table 2). During pharmacological septal inactivation with muscimol infusions, the hexagonal firing pattern of grid cells is lost [52,53], whereas border cells, head direction cells, and other spatially modulated cells in the MEC maintain their spatial firing [52,53], and hippocampal place cells also maintain their place preference [53,54]. Entorhinal neurons show both theta phase locking [55–58] and phase precession to spatial location [13,59,60]. Individual spiking rhythmicity shows a systematic frequency increase with running speed [16,44,61] that is reduced in total darkness [61], suggesting an influence of sensory coding. The MS may play an important role in sensory integration because MS GABAergic neurons that project to the entorhinal cortex display rhythmic firing during locomotion events [25,62]. In contrast to its lack of effects on hippocampal precession, optogenetic driving of septal PV cells does disrupt entorhinal cortex grid cell phase precession [36]. In addition, optogenetic driving of MS CB terminals in the MEC enhances phase precession in the MEC [63]. Surprisingly, optogenetic pacing of PV cells does not disrupt grid cell spatial firing, even

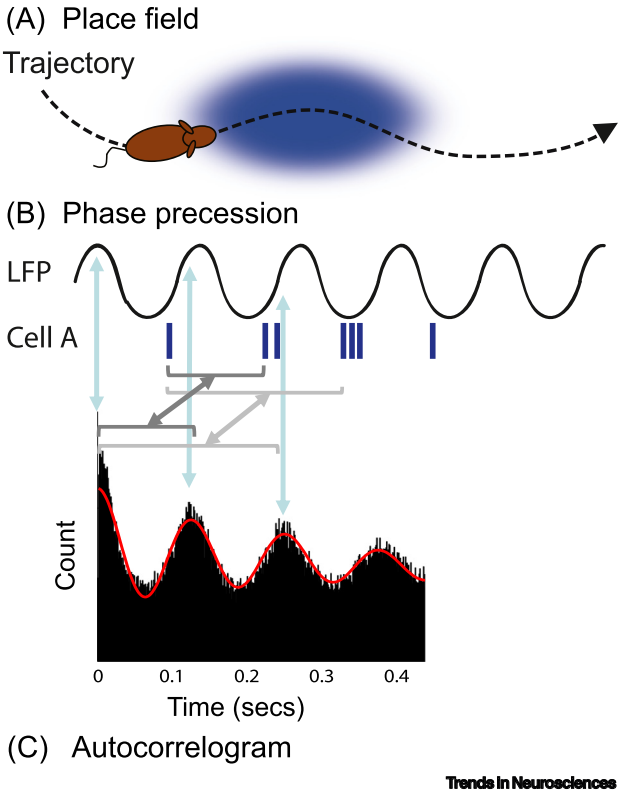

Figure 2. Schematic illustration of theta phase precession and theta rhythmicity. (A) An animal runs on a trajectory through the firing field of a single place cell. (B) Local field potential (LFP) shows theta rhythm oscillations at ~8 Hz. Cell A illustrates how precession involves spiking that starts out at late phases of theta, but shifts to earlier phases of theta. (C) An autocorrelogram sums up time intervals between individual spikes (gray brackets shown for two example intervals). If the mean spike intervals are shorter than the period of the LFP oscillation, autocorrelogram peaks appear at shorter periods (higher frequency) than LFP theta rhythm.

when driving oscillations well above theta range (30 Hz) [35,36]. However, selective inactivation of MS GABAergic neurons has been shown to impair grid cell spatial coding [64]. These data indicate that septal rhythmicity has circuit-selective effects on different regions and functional cell types, with greater sensitivity of time cells and grid cells.

Table 2. Effects of MS manipulations on entorhinal cortex physiology

MS experiment type	Theta oscillations, precession, and sequences	Functional cell types
Stimulation	**GABA** Theta frequency stimulation drives theta oscillations [35,36] Stimulation of PV+ neurons disrupts grid cell precession [36] Stimulation of CB+ neurons enhances precession [63] **Acetylcholine** Modest effect on theta frequency [86]	**GABA** Spares grid cell spatial firing [36,63] **Acetylcholine** Spares grid cell spatial firing and theta frequency speed coding [86]
Inhibition	**GABA** Reduces theta oscillations [38,39] **Acetylcholine** Spares theta oscillations [39] **Glutamate** Spares theta oscillations [39]	**GABA** Impairs grid cell spatial firing [64] **Acetylcholine** Spares speed coding [39] **Non-selective** Impairs grid cell spatial firing [52,53] Spares head direction and border cells [53]

MS GABA cells and memory

The aforementioned physiological effects may underlie the behavioral role of the MS and theta oscillations in spatial memory [65]. Selective lesions of all GABAergic MS neurons impair spatial working memory [66,67]. Inactivation of MS PV neurons by designer receptors exclusively activated by designer drugs (DREADDs) increased reference memory errors in an eight-arm maze [63]. Optogenetic inhibition of the whole MS disrupts delayed non-match to position (DNMP) and cue-guided working memory [68]. Optogenetic driving of MS PV neurons with scrambled (i.e., random) stimulation eliminates endogenous theta rhythms and impairs memory when presented during the delay period or retrieval period of a DNMP spatial working memory task [69]. Surprisingly, even driving MS PV neurons at a specific theta frequency (8 Hz) impairs memory performance during retrieval in DNMP or object location recognition [69]. In another study, driving MS PV neurons with supra-theta (10–20 Hz) frequency stimulation of MS PV neurons impaired performance when presented during the encoding, but not retrieval, portions of a delayed spatial alternation task, whereas driving oscillations within theta range (8 Hz) did not affect task performance [35]. Interestingly, short photoinhibition (~10 s) of MS GABAergic neurons during the delay period had no effect on delayed spatial alternation behavior, despite significant reductions in hippocampal theta power and remapping of delay-period time cells [70], suggesting that prolonged theta disruptions are necessary to affect memory performance. These studies not only indicate that the theta rhythmicity of MS GABA cells plays an important role in memory but also that optogenetic stimulation of different patterns and durations has specific influences on memory. The emerging picture from these studies is that, when theta rhythms and spatial coding in the entorhinal cortex are intact, spatial memory is conserved; however, when theta rhythms and MEC spatial coding are disrupted, memory deficits can be observed. Table 2 provides an overview of related findings.

MS glutamatergic contributions to theta rhythms and memory

What about the involvement of other cell types in the MS? Septal glutamatergic neurons comprise ~25% of the MS neuronal population [20] and are characterized by a heterogeneous firing pattern [71] and projection targets across several brain regions [72]. MS glutamatergic neurons provide excitatory inputs to cholinergic, GABAergic, and other glutamatergic neurons within the MS (Figure 1), and most connections are to fast-spiking putative GABAergic neurons [73,74]. MS glutamatergic neurons also provide long-range excitation to both interneurons and pyramidal cells in CA1 and CA3 [72,74], as well as to pyramidal cells in the MEC [22,75].

MS glutamate cells and theta dynamics

Rhythmic optogenetic activation of septal glutamatergic neurons can drive hippocampal theta rhythms [74]. Septal glutamatergic neurons likely entrain rhythms through local septal connections to GABAergic and cholinergic neurons. However, septal glutamatergic neurons may not be essential for theta rhythms because optogenetic silencing of MS glutamatergic neurons had no significant effect on theta power or frequency in the entorhinal cortex [39]. Although the behavioral effects of glutamatergic neurons may not be mediated by changes in theta, a role in navigation is suggested by the fact that optogenetic activation of these neurons drives locomotion events in the head-fixed animal [72]. In addition, several subpopulations of glutamatergic neurons have been identified during a spatial navigation memory task, and one subpopulation is predominantly active during locomotion [76]. These results are consistent with fiber photometry experiments in the MEC showing that septal glutamatergic terminal activity correlates with speed [75], as well as with behavioral data demonstrating that embryonic reduction of septal glutamatergic neurons results in deficits in locomotion in adult mice [77]. Together, these data indicate that septal glutamatergic neurons may contribute to MEC speed coding [16,72,75]. Thus, septal glutamatergic neurons may provide crucial information for grid cell periodicity, as many models of grid cell generation require input about speed [78,79].

MS glutamate cells and memory

Although inactivation of MS glutamatergic neurons does not reduce theta oscillations, recent evidence shows that these neurons may play a role in memory. First, direct MS projections to the dorsal CA2 region of the hippocampus are predominantly glutamatergic [80], and DREADD-mediated inhibition or optogenetic induction of LTD in these MS–CA2 projections impaired social recognition memory in mice. Second, a subpopulation of MS glutamatergic neurons display learning-related changes in activity during a five-arm spatial learning task, and inhibiting this activity results in significant impairments in task performance [76]. These studies provide behavioral evidence of MS glutamatergic contributions to learning and memory, but more research will be necessary to determine whether these effects are related to changes in network oscillations.

MS cholinergic contributions to theta rhythm and memory

MS cholinergic cells and theta rhythms

Cholinergic neurons make up the largest portion of septal neurons (~47% in mice), but they show slow-firing patterns [20,81] and their role in theta rhythm is unclear. Extracellular recordings from MS reveal that firing of septal cholinergic neurons correlates with high theta power during running and REM sleep, whereas these neurons are quiescent during non-theta periods such as slow-wave sleep (SWS) [82]. Earlier experiments also suggested that the septal cholinergic system may regulate hippocampal theta power [83]. However, direct manipulations of septal cholinergic neurons show little effect on hippocampal theta rhythms [37,84]. Optogenetic activation of cholinergic neurons may allow theta rhythms to dominate by suppressing non-theta activity, including the occurrence of sharp-wave ripples [84,85]. Prolonged activation of septal cholinergic activity using DREADDs produced a small but significant effect on theta peak frequency in the MEC, but had no effect on peak theta power [86]. Likewise, optogenetic inhibition of septal cholinergic neurons shows no significant reduction in MEC theta oscillations [39]. Further, conditional deletion of the *Nkx2-1* gene in the septum during development, which results in extensive depletion of cholinergic neurons, increases peak theta frequency and alters the theta frequency-running speed relationship, but has no effect on theta power [87]. Given the modest effects of cholinergic manipulations on theta rhythm, cholinergic neurons do not appear to be the primary 'pacemaker' for hippocampal rhythms; they may instead have a more modulatory role. For example, MS cholinergic neurons may work in tandem with GABAergic neurons to drive theta entrainment of hippocampal spike bursts because selective optogenetic stimulation of either cell type does not entrain spike bursts, whereas non-selective MS stimulation does [88].

Cholinergic modulation of spatial and temporal coding

Studies involving modulation of the cholinergic system do not suggest a crucial role for MS cholinergic neurons in the generation of spatial firing. Global blockade of muscarinic receptors via systemic injections of scopolamine results in a significant reduction in grid cell spatial tuning [89], but more specific targeting of the cholinergic system via modulation of septal cholinergic neurons by DREADD activation revealed no change in grid cell spatial firing [86]. Similarly, although systemic blockade of muscarinic acetylcholine (ACh) receptors disrupted the relationship between running speed and intrinsic theta frequency [90], more selective local inhibition or excitation of MS cholinergic neurons did not [39,86]. In the hippocampus, the spatial coding of place cells appears to be impaired by systemic injections of scopolamine [91] or local infusions of scopolamine [92], but direct lesions of MS cholinergic neurons have no such effect [93]. Some studies suggest that ACh may be more involved in stabilizing or updating hippocampal spatial codes than in their initial generation [93,94] via effects such as shifting the theta phase of place cell firing [94]. These effects highlight the need for careful consideration of methodology when interpreting the effects of cholinergic manipulations because pharmacological disruption of cholinergic signaling does not always produce the same effects as direct manipulation of MS cholinergic neurons.

Cholinergic modulation may contribute to phase precession in the hippocampus because systemic administration of the cholinergic antagonist scopolamine disrupts place cell phase precession by reducing place cell firing rates to levels that more closely match the frequency of theta rhythm recorded from the same electrodes in region CA1 [95]. This manipulation leaves theta sequences intact [95], suggesting that phase precession and theta sequences are generated by distinct mechanisms. More selective experiments will be necessary to determine the specific contribution of MS cholinergic neurons, including rapid measurement of changes in ACh levels during behavior (Box 1).

Computational models of septohippocampal function

The previous sections have described experimental data on the role of the MS in generating theta phase precession, in the generation of different functional cell types, and in memory functions. This raises the question of how septohippocampal network dynamics underlie memory functions. Computational models can be instrumental in helping to answer this question. Modeling studies have addressed how the MS generates theta rhythm dynamics in the hippocampus [96–98], as well as the mechanism of theta phase precession in hippocampal place cells [12,99] and entorhinal grid cells [79]. The loss of grid cell precession during rhythmic optogenetic pacing of GABAergic neurons [36] supports the idea that entorhinal precession arises from an interaction of network oscillations with cellular oscillatory conductances [79], but does not support this as a mechanism to drive grid cell firing. By contrast, the data showing spared hippocampal precession upon MS inactivation [48] and rhythmic activation [34] suggest that hippocampal precession does not require septal regulation, and instead could involve interaction of oscillatory conductances within single neurons. The loss of theta sequences with septal inactivation supports a role of the MS in setting the relative phases of neurons that are important for sequential ordering. In linking these mechanisms to memory function, many models of hippocampal function focus on the broad class of associative memory models [100,101] which can store sequences of spiking patterns, as used in models for theta phase precession [102,103]. The next section interprets the functional role of the MS in terms of the separation of encoding and retrieval that is required by associative memory models.

Associative memory models require separate timing of encoding and retrieval

As we describe in the sections below, recent experimental data support computational models that propose a role for theta rhythm in the separation of dynamics for encoding and retrieval in different phases of theta rhythm oscillations [104] (Figure 3). The proposed separation of encoding and retrieval was based on the essential mathematical requirements of Hebbian associative memory used in standard models of the hippocampus [104,105]. Associative memory function

Box 1. Fluorescent sensors improve acetylcholine (ACh) measurement

Although ACh is implicated in many cognitive processes and neurological diseases, the dynamics of ACh transmission at fine spatial and temporal resolution remain less understood owing to the technical limitations of ACh measurement. However, recent advances in optical measurement have led to the development of genetically encoded fluorescent sensors, $GRAB_{ACh}$ (GPCR activation-based ACh sensor) and iAChSnFR, that allow ACh measurement at finer spatial and temporal resolution [153–155]. Using optical recording techniques such as head-mounted miniscopes, *in vivo* two-photon imaging, and fiber photometry, these sensors can be adopted to drive advances in our understanding of ACh transmission. Early studies using these sensors show that ACh release in hippocampus and cortex increases with locomotion onset [156], and correlates with running speed [85,154], as also suggested by fiber photometry recordings of Ca^{2+} in cholinergic MS neurons [157]. $GRAB_{ACh}$ measurements have also shown that ACh release is correlated with theta power and anti-correlated with the number of sharp-wave ripples in the hippocampus [85]. Studies of hippocampal memory function show that ACh release drops in the hippocampus during the delay period of a spatial alternation task [85], but increases during reward consumption in an operant conditioning task [155]. These studies represent some of the first applications of this new technique and provide a starting point for numerous future studies.

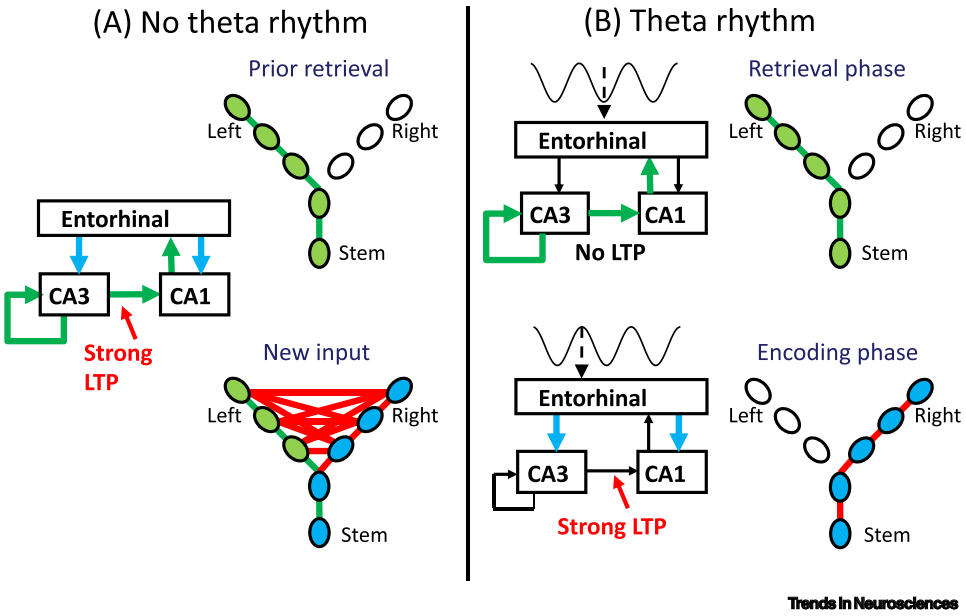

Figure 3. Potential role of theta phases in separating encoding and retrieval during delayed spatial alternation or delayed non-match to position tasks. (A) With no theta rhythm, the retrieval of a prior left-turn response mediated by internal connections (green) can be used to guide a new right-turn response. However, if the input of the right-turn response (blue) can occur at the same time as retrieval and synaptic modification, this results in synaptic modification (red), strengthening undesired associations between the prior retrieval (green) and the new input (blue), and impairing future responses. (B) Because theta rhythm separates encoding and retrieval, the retrieval of the prior response (green) occurs on one phase of theta when there is no synaptic modification. The encoding of entorhinal input (blue) then occurs when synaptic modification is strong (red), resulting in storage of only the new trajectory of the right-turn response without interference. This allows effective future retrieval to guide behavior. Abbreviation: LTP, long-term potentiation.

requires separate dynamics for (i) encoding, when Hebbian plasticity is applied during reduced synaptic transmission, and (ii) retrieval, when reactivation of retrieved memories is mediated by synaptic transmission with reduced Hebbian modification [100,104–106]. Consistent with this model, external input from the entorhinal cortex drives synaptic currents on one phase of theta, whereas synaptic currents on a different phase are driven by internal retrieval from within the hippocampus [107,108]. Synaptic modification occurs best during the phase of strong external input [108–110]. Without the separation of encoding and retrieval dynamics on separate phases, associative memory function breaks down owing to the interference caused by retrieval of old memories during the encoding of new memories [104]. For example, in the DNMP task, encoding of a previous response would cause the wrong response (Figure 3), consistent with data reviewed above showing that DNMP impairments are caused by lesions of GABA neurons [67], inactivation of MS PV neurons [63], optogenetic inhibition of the whole MS [68], scrambled optogenetic stimulation [69], and supra-theta frequency stimulation [35].

Decoding on different phases of rodent theta

Decoding of spiking data supports the transition between encoding and retrieval on different phases of theta in rodents. Decoding reveals current agent location on the descending phase of theta, and the hypothetical future location on the ascending phase [111]. Similarly to earlier data on phasic behavior, theta shows intermittent phase-locking with the step cycle [62], and decoding shifts from current location at forelimb plant times to coding of future locations between plant times [112], which could indicate a transition from encoding of the current location on particular phases to retrieval-based prediction of the future location at later phases.

Spiking also occurs on different phases of theta during exposure to familiar versus novel odors [113], and in familiar versus novel environments [94,114], suggesting that the encoding of novel information occurs on particular phases, whereas retrieval drives spiking on different phases. Theta resets to the best phase for encoding in a working memory task [115], and optogenetic manipulations of interneurons on different phases of theta cause selective effects on encoding versus retrieval [116]. Recent work shows a striking difference in the phase of spiking in response to an environmental barrier that is currently present versus spiking associated with the retrieval of a memory of where a removed barrier was previously located [14]. Gamma oscillations associated with different inputs occur on different phases of theta in rats [117]. In the CA1 region of hippocampus, the slow gamma oscillations that are considered to represent retrieval from CA3 show less power on early trials relative to later trials [118]. Similarly to the separation of dynamics on different phases of theta, at a lower frequency there is evidence for separation of retrieval of different directional trajectories on alternating cycles of theta [58,111]. Collectively, these data suggest that network oscillations play a role in the transition between encoding of new representations at one phase and a graded increase in retrieval, or comparison with previously stored representations, on a different phase. It should be noted, however, that these data could also indicate transitions between the phase coding of different relative timepoints during retrieval-based prediction that do not always require new encoding.

Phases of human theta rhythm

Data from humans also support separate phases of encoding and retrieval. Studies show increases in theta rhythm activity during active encoding in humans [119–121]. Somewhat similarly to rodent sniffing and stepping behavior, the reaction times of human button-press responses in a memory task are distributed at theta rhythmic intervals [122]. Theta rhythm resets to opposite phases during encoding versus retrieval phases of a memory task in humans [123], and the best pattern decoding of electroencephalography (EEG) activity is obtained on opposite theta phases during encoding and retrieval [124]. Thus, a range of models and data in rodents and humans support separation of encoding and retrieval dynamics within theta cycles.

Encoding of time

Surprisingly, the coding of spatial location and time appear to share mechanisms because the same neuron can code for both location and time. Neurons in the hippocampus show systematic coding of time during regular intervals of running in a running wheel [7] or on a treadmill [125], or even when head-fixed [126]. A shared mechanism is suggested by the fact that a neuron in the hippocampus can fire as both a place cell and a time cell [125], and a neuron in entorhinal cortex can fire as both a grid cell and a time cell [127].

Both forms of coding appear to involve theta. Similarly to place cells and grid cells, the duration of time within a the firing field of a time cell is associated with systematic precession of the phase of spiking [7,128]. In a task that requires discrimination between different temporal intervals, the size of time cell firing fields and the scale of temporal theta phase precession changes with the duration of intervals being timed [129]. In addition, in the same way as grid cells show multiple spatial scales [44,130], time cell firing fields show multiple scales from seconds to minutes [131,132].

Manipulations of the MS affect the coding of both time cells and grid cells. MS inactivation blocks the appearance of time cell firing fields in the hippocampus [49,70], and grid cell firing fields in entorhinal cortex [52,53]. This suggests that time cells and grid cells may share similar mechanisms for the formation of these firing fields in hippocampus and entorhinal cortex that both require septal regulation of theta rhythm.

Encoding of context-dependence

The role of hippocampal spatial representations for memory in a delayed alternation or DNMP task is supported by context-dependent firing based on the past or future trajectory in neurons in the hippocampus [133,134] and entorhinal cortex [135]. These responses could reflect the formation of distinct memory representations based on prior or future context. Recent one-photon imaging of neural population activity during learning of these tasks shows that individual context-dependent neurons appear at different timepoints [136,137] and subsequently maintain their selectivity and correlate with task performance [136]. The formation of conjunctive responses could result from similar intracellular plateau potential dynamics, as observed for induction of place cell firing with intracellular current injection [138,139] or optogenetic depolarization [140]. An important element for the understanding of septo-hippocampal dynamics concerns the mechanism for encoding and retrieval of these context-dependent responses, which could be sensitive to phase-specific theta rhythmic regulation from the MS.

Encoding of egocentric to allocentric transformations

Place cells can be modeled as arising from allocentric coding relative to environmental boundaries by boundary vector cells [8,14,141–144]. However, allocentric codes must arise from sensory input with egocentric coordinates (i.e., relative to the agent viewing the world). Recent work has shown egocentric spatial coding of barriers in cortical inputs and outputs of entorhinal cortex, such as retrosplenial cortex, postrhinal cortex, and dorsomedial striatum [15,145–147], as predicted by models [144]. The presence of egocentric coding in cortical inputs to entorhinal cortex, which exhibits allocentric boundary responses [142,143], indicates that the transformation from egocentric to allocentric coding could occur in entorhinal cortex [148]. Neurons in retrospenial cortex show firing in relation to theta phase [15,149,150]. Although the MS may influence many cell types, the MS input does not seem to be essential for the transformation from egocentric input to the response of allocentric boundary cells because this still appears despite MS inactivation [53]. Instead, the transformation appears to be influenced by knockout of a membrane current, known as *h* current, which also affects the coding of velocity in entorhinal cortex [151] and affects intrinsic oscillatory conductances that could contribute to phase precession [152]. As noted above, allocentric boundary cells show theta phase specificity of current boundaries versus the memory of boundaries [14]. This suggests that phase-specific trace responses could be sensitive to MS inactivation, indicating that the MS may regulate the encoding and retrieval of boundary representations [14] that are essential for matching current egocentric representations with stored allocentric representations of barriers.

Concluding remarks

Numerous studies have implicated the septo-hippocampal system in memory function, but recent data raise an intriguing set of questions. The sensitivity of both grid cells and time cells to MS inactivation suggests an important role of theta rhythmicity in coding the transformations that generate these functional cell types. However, the fact that stimulation of MS can alter entorhinal phase precession without altering grid cell firing indicates an important role of other network inputs for generating functional neuronal responses. Further, the fact that hippocampal neurons can show phase precession during septal inactivation or exogenously paced theta oscillations indicates an important interaction of cellular conductances in driving neuronal dynamics during theta. The behavioral impairments caused by MS manipulations indicate a potential role of the MS in the ordering of phases across different neurons that is necessary for theta sequence coding for memory-guided behavior. The available data raise many specific questions that are itemized in the Outstanding questions section.

Outstanding questions

Inactivation of the MS impairs the spatial firing of entorhinal grid cells and hippocampal time cells, but spares hippocampal place cells, entorhinal boundary cells, and head direction cells. This raises several questions. (i) Does MS inactivation block time cell firing fields in entorhinal cortex? (ii) Does it block trace fields of previous boundaries in the subiculum? (iii) Does it block the rescaling of grid fields in response to shifting of boundary walls (which is blocked by knockout of the *h* current)?

Inactivating or driving neurons of the MS impairs performance in delayed non-match to sample tasks and delayed spatial alternation tasks. Does this occur because MS inactivation affects the formation of context-dependent neuronal activity in these tasks?

What is the role of cholinergic MS neurons in the generation of theta phase precession and theta sequences? Studies show that systemic blockade of ACh receptors disrupts phase precession while leaving theta sequences intact, but whether this effect is driven by MS cholinergic neurons remains unknown.

Some studies have manipulated MS terminals in the hippocampus and entorhinal cortex, but medial septum–diagonal band of Broca cell body manipulations are more common. This raises the question of the relative contributions of local septal projections versus long-range projections of each of the MS neuronal subtypes to the generation of spatial/temporal coding and theta rhythmicity?

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Declaration of interests

The authors declare no conflicts of interest.

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