

Review Paper

Potential roles of cholinergic modulation in the neural coding of location and movement speed



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ABSTRACT

Behavioral data suggest that cholinergic modulation may play a role in certain aspects of spatial memory, and neurophysiological data demonstrate neurons that fire in response to spatial dimensions, including grid cells and place cells that respond on the basis of location and running speed. These neurons show firing responses that depend upon the visual configuration of the environment, due to coding in visually-responsive regions of the neocortex. This review focuses on the physiological effects of acetylcholine that may influence the sensory coding of spatial dimensions relevant to behavior. In particular, the local circuit effects of acetylcholine within the cortex regulate the influence of sensory input relative to internal memory representations via presynaptic inhibition of excitatory and inhibitory synaptic transmission, and the modulation of intrinsic currents in cortical excitatory and inhibitory neurons. In addition, circuit effects of acetylcholine regulate the dynamics of cortical circuits including oscillations at theta and gamma frequencies. These effects of acetylcholine on local circuits and network dynamics could underlie the role of acetylcholine in coding of spatial information for the performance of spatial memory tasks.

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Contents

1. Introduction	52
2. Overview of cholinergic function	53
2.1. Role of acetylcholine in spatial behavior	53
2.2. Cholinergic modulation and functional response properties of neurons	54
2.3. Possible neocortical influences on the firing of grid cells and place cells	54
3. Cholinergic modulation of cortical circuit properties	55
3.1. Cholinergic modulation of presynaptic inhibition and intrinsic properties could influence place cells	55
3.2. Presynaptic inhibition of synaptic transmission and modulation of intrinsic properties could also influence grid cells	56
3.3. Cholinergic modulation of visual areas of the neocortex	57
3.4. Cholinergic modulation during waking and sleep	58
4. Cholinergic modulation of cortical network oscillatory dynamics	58
4.1. Association of acetylcholine levels with theta rhythm	58
4.2. Mechanisms of cholinergic regulation of theta rhythm properties	59
4.3. Cholinergic modulation and theta-gamma coupling	59
4.4. Theta rhythm regulation of network interactions	60
5. Summary	60
Acknowledgements	60
References	60

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1. Introduction

Acetylcholine plays an important role in regulating the function of cortical structures. Empirical evidence indicates a role of acetylcholine in cognitive functions including learning and memory, attention to sensory stimuli, as well as a substantial role in regulating transitions between waking and sleep. This article will focus on the role of acetylcholine in regulating sensory influences on the coding of spatial representations for memory function in rodents. We will provide a brief overview of behavioral evidence, but will primarily focus on neurophysiological studies of the role of acetylcholine in the network dynamics of cortical structures.

Given our focus on coding of location and movement speed, we will focus on cortical structures including the entorhinal cortex and hippocampus as well as regions of the neocortex interacting with these regions. Extensive data indicates a role of the hippocampus in spatial memory function, starting with the discovery of place cells in the hippocampus (O'Keefe, 1976). Hippocampal place cells show selective firing based on the spatial location of a rat, generating spikes primarily when a rat visits single locations in the environment (O'Keefe, 1976; O'Keefe and Burgess, 1996, 2005), and place cell firing rates change with running speed. These neurons appear to be important for spatial memory function, as lesions of the hippocampus impair the learning of a new spatial location (Morris et al., 1982). The hippocampus has strong bidirectional anatomical connections with the entorhinal cortex, and lesions of the entorhinal cortex also impair spatial memory function (Steffenach et al., 2005). As shown in Fig. 1, both the hippocampus and the entorhinal cortex receive extensive innervation from cholinergic neurons in basal forebrain nuclei including the medial septum and vertical limb of the diagonal band, as well as input from GABAergic and glutamatergic neurons in these nuclei (Alonso and Kohler, 1984; Gaykema et al., 1990; Pang et al., 2011; Oh et al., 2014).

Recent data demonstrate the spatial specificity of neurons in the medial entorhinal cortex (MEC) termed grid cells (Fyhn et al., 2004; Hafting et al., 2005, 2008) that fire when a foraging rat visits a regular array of locations in the environment falling on the vertices of tightly packed equilateral triangles. Grid cells also usually show selective firing at specific time intervals during running on a treadmill (Kraus et al., 2015). Many neurons in entorhinal cortex, including grid cells, show changes in firing rate and rhythmic

frequency with running speed (Kropff et al., 2015; Hinman et al., 2016). Manipulations of visual inputs such as rotation or barrier movement will alter the location of firing of place cells and grid cells (Muller and Kubie, 1987; Hafting et al., 2005; Barry et al., 2007), indicating an important role of input from visual cortical regions to entorhinal cortex. Similarly, task demands can alter the location of firing, indicating a role for prefrontal cortex. As shown in Fig. 1, neocortical structures receive cholinergic input from basal forebrain structures such as the horizontal limb of the diagonal band, and the substantia innominata (Mayo et al., 1984; Carey and Rieck, 1987; Laplante et al., 2005; Oh et al., 2014). The following sections will analyze the potential role of cholinergic modulation in regulating the spatial function of cortical coding.

2. Overview of cholinergic function

2.1. Role of acetylcholine in spatial behavior

Microdialysis measurements of acetylcholine levels in rats demonstrated that hippocampal acetylcholine release increases during states of arousal and active exploration (Marrosu et al., 1995; Acquas et al., 1996), as well as during experience with spatial novelty (Aloisi et al., 1997; Giovannini et al., 2001; Bianchi et al., 2003). Acetylcholine levels also increase during learning of a spatial memory task (Stancampiano et al., 1999) and during object exploration (Stanley et al., 2012).

Numerous studies have shown robust impairments of spatial memory behavior after lesions of the medial septum (Winson, 1978; Givens and Olton, 1990), which destroy a range of inputs including cholinergic, GABAergic and glutamatergic input. Behavioral effects have been tested after selective lesions of cholinergic neurons in the medial septum/diagonal band (MSDB) complex using the neurotoxin saporin conjugated with an antibody giving it selectivity for cholinergic neurons in rats and mice. The effect of these selective lesions of cholinergic innervation tend to be weaker than the effect of medial septum lesions (Parent and Baxter, 2004), but do show some behavioral effects. These lesions appear to specifically influence memory for the spatial location of objects, as saporin MSDB lesions impair memory for the spatial context of objects in a where-which task in rats (Easton et al., 2011), but do not impair their episodic memory in a what-where-which task. This surprising dissociation was attributed to

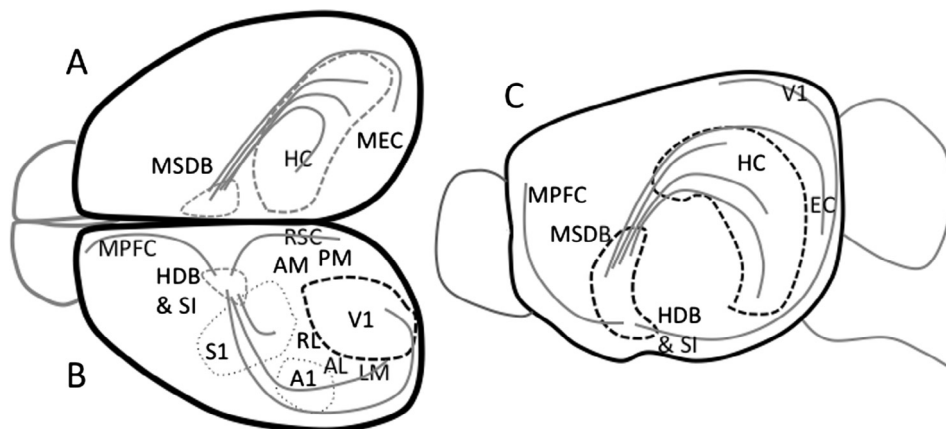


Fig. 1. Cholinergic modulation of rodent cortical structures described in this review. (A) Schematic dorsal view of mouse brain showing cholinergic neurons in the medial septum and vertical limb of the diagonal band (MSDB) that innervate the hippocampus (HC) and the medial entorhinal cortex (MEC). (B) Cholinergic neurons in the substantia innominata and horizontal limb of the diagonal band (SI & HDB) activate cholinergic receptors in neocortical regions including the medial prefrontal cortex (MPFC) and primary visual cortex (V1), primary somatosensory cortex (S1), primary auditory cortex (A1) and retrosplenial cortex (RSC) as well as higher order visual areas. Higher order visual areas in the rodent include areas LM, AL, RL, AM and PM (Wang et al., 2011). (C) Sagittal view of the mouse brain schematically showing cholinergic innervation arising from the MSDB to innervate hippocampus and entorhinal cortex and from SI to innervate neocortical regions including V1 and MPFC. Schematic diagrams based on Oh et al. (2014).

an impairment in the rapid updating of place cells when object locations differ across spatial contexts, consistent with cholinergic MSDB lesions causing impairments in the formation of new place cell representations in different contexts (Ikonen et al., 2002). In mice, saporin MSDB lesions cause impairments in the recognition of the spatial location of objects (Cai et al., 2012), but do not impair novel object recognition. Saporin MSDB lesions have also been shown to cause impairments of performance in the Morris water maze (Berger-Sweeney et al., 2001; Moreau et al., 2008) though the effect on Morris water maze performance has not appeared in all tests (Parent and Baxter, 2004). Cholinergic MSDB lesions have also been shown to cause impairments of matching-to-place in the water maze that do not depend upon the delay between sample and test (Baxter et al., 1995) and they impair delayed matching to place in the T-maze (Johnson et al., 2002), but effects on delayed non-match to place require combining cholinergic lesions with lesions of GABAergic input (Pang and Nocera, 1999; Pang et al., 2001). Overall, these behavioral studies indicate a potential role of cholinergic innervation in forming representations of spatial location relevant to memory-guided behavior. These behavioral effects of cholinergic lesions are consistent with the effects of cholinergic manipulations on physiological recordings described in the next section.

2.2. Cholinergic modulation and functional response properties of neurons

The functional role of cholinergic modulation could be elucidated by the effect of cholinergic manipulations on the functional firing properties of neurons in cortical structures including place cells in the hippocampus and grid cells in entorhinal cortex. The firing of hippocampal place cells changes during infusions of the drug scopolamine that blocks muscarinic acetylcholine receptors at the site of recording (Brazhnik et al., 2004). Infusions of the drug scopolamine into the ventricles caused an increase in the firing of place cells outside of the usual place cell firing field of the neuron, while reducing the peak firing rate of the place cells (Brazhnik et al., 2003). Similar effects were seen with local dialysis of scopolamine or other selective muscarinic antagonists into the tissue near the recording site (Brazhnik et al., 2004).

Recordings of place cells have also been performed after lesions of the fornix, which contains cholinergic fibers as well as other fibers arising from the medial septum. Recordings after fornix lesions show a reduction in the spatial specificity and reliability of firing of place cells, and show that place cells are more sensitive to maze rotation (Shapiro et al., 1989). The potential role of cholinergic modulation in this effect is supported by the fact that these effects are reduced by hippocampal grafts of fetal cholinergic basal forebrain tissue (Shapiro et al., 1989). Hippocampal cells also show selective firing at specific time intervals during running on a running wheel (Pastalkova et al., 2008) or treadmill (Kraus et al., 2013) and the specificity of this time cell firing is lost with inactivation of the medial septum (Wang et al., 2015).

Data also suggests a potential role of cholinergic modulation in regulating the function of grid cells. A potential role of cholinergic modulation has been demonstrated for grid cells. Inactivation of the medial septum with infusions of muscimol causes a loss of the spatial periodicity of grid cells (Brandon et al., 2011; Koenig et al., 2011), without causing a loss of the head direction selectivity of neurons in medial entorhinal cortex (Brandon et al., 2011). This effect could be due to loss of cholinergic, GABAergic or glutamatergic innervation, but a role for cholinergic modulation is supported by evidence that systemic injections of scopolamine also cause a reduction in the spatial periodicity of grid cells (Newman et al., 2014).

Computational models and indirect experimental evidence suggest that the loss of spatial specificity of firing could be associated with a role of cholinergic neurons in coding the running speed of an animal. The power and frequency of theta oscillations have been shown to increase with running speed in rodents (Jeevjee et al., 2008a; Hinman et al., 2011). Systemic administration of the muscarinic antagonist scopolamine flattens the typically positive correlation between running speed and entorhinal theta frequency in rats (Newman et al., 2013), which may affect the integration of locomotor information into memory processes. In addition, calcium imaging of the activity of cholinergic neurons in the medial septum has demonstrated a linear relationship between activity of cholinergic neurons and running speed (Davidson et al., 2014). Many neurons in the medial entorhinal cortex including grid cells, head direction cells and interneurons show systematic increases in firing rate with running speed (Wills et al., 2012; Kropff et al., 2015; Hinman et al., 2016), while some MEC neurons show reductions in firing rate or changes in theta rhythmicity with running speed (Hinman et al., 2016). Inactivation of the medial septum results in the reduction of the latter two properties, while enhancing the positive coding of running speed by firing rate.

Thus, existing evidence suggests a role of acetylcholine in the spatial coding by place cells and grid cells. This might be partly due to a role of acetylcholine in the visual influences on place cells and grid cells described in the following section.

2.3. Possible neocortical influences on the firing of grid cells and place cells

Visual cues have been shown to influence spatial coding by grid cells and place cells. In particular, the rotation of visual cues on the walls of a spatial environment can cause a similar magnitude rotation of the firing location of place cells (Muller and Kubie, 1987) and grid cells (Hafting et al., 2005). In addition, the location of the firing fields of place cells and grid cells can be influenced by shifting the location of barriers in a rectangular environment to compress or expand along one dimension (O'Keefe and Burgess, 1996). The same manipulation causes compression or expansion of the spacing between grid cell firing fields (Barry et al., 2007).

As noted above, manipulations of cholinergic modulation influence the firing properties of place cells and grid cells. Cholinergic modulation could also be relevant to the effect of novelty on the firing properties of grid cells and place cells. Recordings from rats exploring a novel environment show a larger spacing between the firing fields exhibited by each individual grid cell compared to the baseline spacing observed in a familiar environment (Barry et al., 2012a). This expansion of spacing could underlie the shifts in the firing location of place cells (termed remapping) that occurs in novel environments. This expansion of spacing has been proposed to arise from the increase of acetylcholine levels in novel environments (Barry et al., 2012a). Models of grid cell firing provide a framework for understanding how acetylcholine levels could influence the firing properties of grid cells via influences on circuit mechanisms, including the presynaptic inhibition of synaptic transmission, or the intrinsic currents regulating the spike timing of entorhinal neurons. These cholinergic influences will be reviewed in Section 3 below.

The visual influences on grid cells could involve different aspects of the coding of visual stimuli including optic flow (Raudies et al., 2012) or the angle of visual stimuli in an environment (Milford et al., 2010; Milford and Schulz, 2014; Raudies and Hasselmo, 2015; Raudies et al., 2016). Cholinergic modulation of these computations in visual areas of the neocortex could contribute to the coding of spatial location by grid cells. Some properties of grid cell responses may arise from the configuration of visual input to the medial entorhinal cortex. The compression or

expansion of the spacing between grid cell firing fields described above (Barry et al., 2007) can be specific to individual grid cell modules with different initial spacing (Stensola et al., 2012) that predominate at different dorsal to ventral positions within MEC. The visual cortical areas on the dorsal surface of the rodent brain show retinotopic mapping (Wang and Burkhalter, 2007; Garrett et al., 2014), and a similar retinotopic mapping may map the dorsal portions of the retina to the dorsal portions of the medial entorhinal cortex. The dorsal retina would respond to features in the ventral visual field near the animal, which are less likely to be affected by barrier location. The ventral portions of MEC might respond to the dorsal visual field that includes features on distant barriers that would make them more sensitive to the location of barriers.

Consistent with this, recent data from rodents show that responses of different visual regions (see Fig. 1) are restricted to specific portions of the visual field (Garrett et al., 2014). The rostralateral area (RL) in the rodent visual cortex responds to the ventral visual field (ground plane), whereas the lateromedial area (LM) responds to the dorsal visual field (where distal barriers would appear). Anatomical data show that the rostralateral (RL) and anterolateral (AL) areas but not LM project to the dorsal MEC (Wang et al., 2011). Rodent visual regions also show different functional responses to visual properties. For example, the anteromedial area (AM) responds to high temporal frequency (moving stimuli) with low spatial frequency, whereas the posteromedial area (PM) responds more to low temporal frequency (more static stimuli) with higher spatial frequency and other areas show differential responses (Andermann et al., 2011; Marshel et al., 2011; Wang et al., 2011, 2012; Glickfeld et al., 2014). These data suggest a division of processing similar to the “what” and “where” pathways of primate neocortex (Ungerleider and Mishkin, 1982). Primate visual cortex has regions that respond to specific features of the direction and speed of optic flow (Rodman and Albright, 1987; Duffy and Wurtz, 1997) and a few rodent neurons show responses to the pattern flow caused by two components of motion (Juavinett and Callaway, 2015) similar to that in monkeys (Smith et al., 2005). The separation of “where” and “what” pathways has been proposed for entorhinal cortex to distinguish spatial responses in medial entorhinal from lack of spatial coding in lateral entorhinal cortex (Hargreaves et al., 2005; Knierim et al., 2006; Eichenbaum and Lipton, 2008) which responds to objects (Deshmukh and Knierim, 2011, 2013).

Cholinergic modulation of neuronal responses in the visual cortex could contribute to potential influences of systemic cholinergic modulation on spatial firing of neurons in entorhinal cortex and hippocampus. It has been shown in rodents that cholinergic neurons are selective in their projections and functional modulation of sensory cortices, with a clear topographic projection of horizontal diagonal band neurons to the visual cortex (Laplante et al., 2005; Kim et al., 2016). Ionophoretic applications of acetylcholine increase the firing response of neurons to sensory input or thalamic stimulation without enhancing tuning selectivity in the visual cortex of rodents (Sato et al., 1987) or marmosets (Zinke et al., 2006). The same manipulation of cat visual cortex neurons, however, caused increases in the orientation and directional selectivity to visual stimuli (Sillito and Kemp, 1983; Murphy and Sillito, 1991). This also reduced the extent of spatial integration, evident by a shift of a neuron’s preferred length toward shorter bars and a concomitant decrease in its spatial summation area (Roberts et al., 2005). Activation of cholinergic receptors also causes long-term enhancement of the magnitude of visual evoked potentials (Kang and Vaucher, 2009; Kang et al., 2015) and the behavioral sensitivity to specific visual orientations (Kang et al., 2014). Manipulations of cholinergic input also influence attentional modulation in visual cortex. Acetylcholine enhances the response to an attended stimulus, whereas cholinergic blockade reduces the

enhancement of neural response due to attention (Herrero et al., 2008).

Cholinergic modulation also plays a role in attentional mechanisms mediated by the prefrontal cortex. Selective saporin lesions of cholinergic innervation of the prefrontal cortex have been shown to impair sustained attention for the detection of brief visual cues (McGaughy et al., 1996; McGaughy and Sarter, 1998). During this task, cue detection is associated with changes in acetylcholine levels on preceding trials (Parikh et al., 2007). Optogenetic induction of transient increases in acetylcholine levels in the cortex of mice are associated with enhanced cue detection and with increased false positives in this task (Gritton et al., 2016). The role in sensory coding is supported by electrophysiological studies showing enhanced reliability of sensory-evoked activity in the neocortex during optogenetic activation of the basal forebrain in rats (Goard and Dan, 2009).

These *in vivo* studies indicate a potential role of acetylcholine in regulating the functional properties of different cortical regions. The next section will describe circuit level neurophysiological effects of acetylcholine that could contribute to a functional role of acetylcholine in encoding of the spatial dimensions of behavior in rodents.

3. Cholinergic modulation of cortical circuit properties

Acetylcholine release in cortical structures including the neocortex, entorhinal cortex and hippocampus modulates both principal neurons as well as interneurons on a cellular and synaptic level. These physiological effects could alter the spatial coding of neurons such as place cells and grid cells due to effects within the hippocampus and entorhinal cortex, but also due to effects within the visual areas of neocortex.

Acetylcholine acts at two major categories of receptors, the nicotinic receptors (nAChR) and the muscarinic (mAChR) receptors. Both of these receptor categories have further subtypes. These receptors can be found both pre- and postsynaptically on both interneurons and principal cells (Levey et al., 1995; Picciotto et al., 2012) as well as astrocytes (Van Der Zee et al., 1993; Sharma and Vijayaraghavan, 2002). These receptors affect the intrinsic currents of excitatory principal cells in the cortex, altering the timing of spiking (Madison and Nicoll, 1984; Heys et al., 2010). In addition, these receptors modulate excitatory and inhibitory synaptic transmission selectively at different pathways (Hasselmo, 1999, 2006). Finally, a significant portion of the network effects of acetylcholine likely result from the modulation of specific subtypes of inhibitory interneurons, which are in a powerful position to control rhythmic activity, synaptic inputs to and spiking output from pyramidal neurons (McQuiston and Madison, 1999a; McQuiston, 2014). The effects of acetylcholine on cortical circuits are reviewed in more detail in this section and are summarized in Table 1.

3.1. Cholinergic modulation of presynaptic inhibition and intrinsic properties could influence place cells

The effects of cholinergic manipulations on place cells described above could be related to specific circuit level effects of acetylcholine. Within the hippocampus, acetylcholine acts differentially on different synaptic pathways that are segregated to different anatomical layers (Hasselmo, 1999, 2006). Acetylcholine differentially regulates the two major synaptic input pathways in region CA3 and region CA1 of the hippocampus, causing presynaptic inhibition of glutamatergic synaptic transmission from longitudinal association fibers (Hasselmo et al., 1995), and the Schaffer collaterals in stratum radiatum of region CA1 (Hasselmo and Schnell,

Table 1
Cholinergic modulation of cortical physiology.

-
1. Modulation of synaptic transmission
 - a. Nicotinic enhancement of thalamocortical glutamatergic transmission
 - b. Muscarinic presynaptic inhibition of feedback glutamatergic transmission
 - c. Muscarinic presynaptic inhibition of GABAergic synaptic transmission
 - d. Muscarinic enhancement of long-term potentiation
 2. Modulation of intrinsic properties of neurons
 - a. Muscarinic depolarization due to reduced leak potassium current
 - b. Muscarinic suppression of spike frequency adaptation due to reduction of calcium-sensitive potassium current
 - c. Muscarinic activation of persistent spiking due to calcium-sensitive non-specific cation current (CAN)
 - d. Nicotinic depolarization of inhibitory interneurons, including VIP and SOM interneurons
-

1994a,b). This presynaptic inhibition primarily depends upon M4 muscarinic receptors (Dasari and Gullledge, 2011). In contrast, acetylcholine does not as strongly influence glutamatergic synaptic transmission at the entorhinal cortex inputs in str. lacunosum moleculare in region CA3 (Kremen and Hasselmo, 2007) and str. lacunosum moleculare of region CA1 (Hasselmo and Schnell, 1994a,b).

The selective presynaptic inhibition of excitatory recurrent connections in CA3 and connections to CA1 could act to reduce the internal spread of excitation and allow more selective firing in response to sensory input. When muscarinic presynaptic inhibition of excitatory recurrent connections is reduced, this will increase the amount of excitatory spread and could thereby cause the increase in out-of-field firing observed with ventricular or local infusions of scopolamine during recordings from hippocampal place cells (Brazhnik et al., 2003, 2004), as well as the reduction in place cell reliability observed with lesions of the fornix that remove MSDB input (Shapiro et al., 1989). The stronger effect of excitatory recurrent connections after lesions of cholinergic innervation could also explain why place cells tend to fire in the same manner across different environments in rats with saporin lesions of cholinergic neurons in the MSDB (Ikonen et al., 2002).

Early associative memory models of cortical function used different dynamics during encoding and retrieval (Anderson, 1972; Kohonen, 1972, 1984; Hopfield, 1982; Amit, 1988). In these models the spread of activity through excitatory recurrent synapses was suppressed during encoding to allow accurate Hebbian modification of connections between cells within the circuit. Modeling shows how muscarinic presynaptic inhibition of recurrent synapses would prevent retrieval of previously stored overlapping patterns during encoding of new patterns, thereby preventing a build-up of interference between overlapping patterns (Hasselmo et al., 1992; Hasselmo, 2006).

Cholinergic modulation also influences the intrinsic currents of hippocampal pyramidal cells, causing a direct depolarization through the block of a leak potassium current (Cole and Nicoll, 1984), and causing a decrease in spike frequency accommodation by blocking calcium-dependent potassium currents that normally cause slowing of spike firing rate (Madison and Nicoll, 1984) due to activation of postsynaptic M1 receptors (Dasari and Gullledge, 2011). Cholinergic modulation also activates the CAN current underlying persistent spiking (Jochems and Yoshida, 2013; Knauer et al., 2013). Thus, the net effect of acetylcholine is to enhance the spiking response of excitatory neurons to afferent synaptic input. Blockade of these cholinergic effects will reduce the excitability of cortical principal cells, and thereby the blockade of cholinergic receptors could contribute to the decrease in the peak firing rate of place cells observed during infusions of scopolamine (Brazhnik et al., 2003, 2004). The loss of this intrinsic increase in excitability could make neurons less responsive to visual environmental cues at the same time that they respond more to the unsuppressed recurrent connections that drive activity based on previous environments. This may contribute to the recon-

vergence of place cell firing to patterns found in previously visited familiar environments in rats with lesions of cholinergic neurons in the MSDB (Ikonen et al., 2002).

Acetylcholine also influences the intrinsic properties of interneurons in the hippocampal formation. Activation of nicotinic receptors causes depolarization of many interneurons (McQuiston and Madison, 1999c). Early studies using electrical stimulation showed fast alpha7 mediated EPSPs (Frazier et al., 1998), but optogenetic activation of ACh fibers appears to primarily elicit slower EPSPs (hundreds of milliseconds) dependent on alpha4beta2 receptors (Bell et al., 2015a). Muscarinic receptors cause a range of effects in hippocampal interneurons, including hyperpolarization, depolarization, or biphasic hyperpolarization followed by depolarization (McQuiston and Madison, 1999a). Muscarinic receptors appear to consistently depolarize VIP interneurons (Bell et al., 2015b), cause an afterdepolarization potential in O-LM cells that can result in persistent spiking (McQuiston and Madison, 1999b; Lawrence et al., 2006a), and also appear to tune the response of other stratum oriens interneurons to fire in response to theta frequency inputs (Lawrence et al., 2006b). Acetylcholine also causes presynaptic inhibition of inhibitory synaptic transmission within the hippocampus coupled with direct depolarization of interneurons (Pitler and Alger, 1992; Behrens and ten Bruggencate, 1993). Research in neocortex shows muscarinic presynaptic inhibition of inhibitory synaptic transmission arising from fast-spiking cells (Kruglikov and Rudy, 2008). Modeling of the cholinergic effects causing interneuron depolarization coupled with presynaptic inhibition of inhibitory synaptic transmission shows how this modulation can enhance the signal-to-noise ratio of neuronal firing in cortical structures (Patil and Hasselmo, 1999). Thus, the effects on synaptic transmission and the spiking properties of pyramidal cells and interneurons could also contribute to the lowering of signal-to-noise ratio seen as a reduction of in-field to out-of-field firing in place cells during infusions of scopolamine (Brazhnik et al., 2003, 2004). Similarly, circuit level effects of acetylcholine could influence the firing of entorhinal grid cells as described next.

3.2. Presynaptic inhibition of synaptic transmission and modulation of intrinsic properties could also influence grid cells

Selective muscarinic presynaptic inhibition of glutamatergic synaptic transmission has also been shown in the medial entorhinal cortex (Hamam et al., 2007). This selective presynaptic inhibition could contribute to the change in spacing between grid cell firing fields seen in novel environments (Barry et al., 2012b). In attractor network models of grid cells (Burak and Fiete, 2009), the strength of excitatory recurrent connectivity relative to the strength of inhibitory feedback to entorhinal principal neurons influences the spacing between grid cell firing fields (Beed et al., 2013). Blockade of cholinergic presynaptic inhibition of both excitatory and inhibitory synapses in medial entorhinal cortex can

alter this balance. This could contribute to the change in spacing between grid cell firing fields observed in novel environments.

Another model of grid cell firing fields uses oscillatory interference between velocity-controlled oscillators that change their frequency with the direction of running (Burgess et al., 2007). The spacing between grid cell firing fields in these models is sensitive to the timing of spiking by the modeled neurons. Cholinergic modulation in these models can influence the spacing of grid cell firing fields by altering the intrinsic resonance frequency of neurons through inhibition of the hyperpolarization activated cation current (h current), as shown in slice preparations of entorhinal cortex (Heys et al., 2010; Heys and Hasselmo, 2012). This change in resonance frequency would manifest as a change in the speed of rebound spiking. A change in the speed of rebound spiking has been shown to directly influence the spacing between grid cell firing fields in these types of models (Hasselmo, 2014; Hasselmo and Shay, 2014; Shay et al., 2016).

Muscarinic receptor activation also causes strong depolarization and reduction of spike frequency accommodation in both pyramidal cells and stellate cells (Klink and Alonso, 1997b). Muscarinic receptors also activate a calcium-sensitive non-specific cation current (CAN current) that causes afterdepolarization responses in pyramidal cells, resulting in persistent spiking after depolarization in the presence of acetylcholine (Klink and Alonso, 1997a; Fransén et al., 2002, 2006; Yoshida and Hasselmo, 2009; Jochems et al., 2013). This after depolarization has also been modeled in three different ways as contributing to the firing properties of grid cells. The first model employs a slow velocity dependent modulation of CAN (Hasselmo and Brandon, 2012). The second model tunes CAN-dependent frequency by velocity as in the oscillatory interference model (Hasselmo, 2008). The third model utilizes CAN-dependent rebound spiking in an attractor dynamic model (Navratilova et al., 2012). The persistent spiking model is supported by data on persistence of firing of grid cells after passing through a firing field (De Almeida et al., 2012). Thus, effects of acetylcholine on synaptic transmission or the intrinsic properties of excitatory cells and inhibitory interneurons within the entorhinal cortex could influence the firing properties of grid cells. However, effects of acetylcholine could also be mediated indirectly by effects on the visual input from neocortex as described next.

3.3. Cholinergic modulation of visual areas of the neocortex

Acetylcholine has effects on synaptic transmission and neuronal intrinsic properties in the neocortex that could alter the influence of sensory input on place cells and grid cells. The principle of selective cholinergic suppression of excitatory feedback and enhancement of afferent input also proves to generalize to neocortical structures. In an early study, connections within somatosensory neocortex showed greater presynaptic inhibition than afferent input arising from the white matter (Hasselmo and Cekić, 1996). This was subsequently confirmed in a study using thalamocortical slice preparations of somatosensory cortex, showing muscarinic presynaptic inhibition of excitatory recurrent connections in neocortex and also showing nicotinic enhancement of afferent input (Gil et al., 1997). Selective effects on recurrent relative to thalamocortical input have also been shown in auditory cortex (Hsieh et al., 2000).

Release of acetylcholine in visual cortex has been shown to increase during patterned visual stimulation (Laplante et al., 2005). Nicotinic enhancement of thalamocortical input by acetylcholine is supported by the distribution of nicotinic receptors on thalamocortical terminals and cholinergic enhancement of afferent input in visual cortex (Disney et al., 2007). In the visual cortex, optical imaging was used to show muscarinic cholinergic

suppression of the internal spread of activity along excitatory recurrent connections compared to afferent input (Kimura and Baughman, 1997; Kimura, 2000). This indicated that acetylcholine should reduce the functional spread of activity on excitatory recurrent connections in visual cortex. This is supported by the *in vivo* experimental data by Roberts et al. (2005), mentioned in Section 2.3 showing that iontophoretic application of acetylcholine decreases the extent of spatial integration, assessed by measuring a neuron's length tuning and spatial summation area. These effects appear to contribute to the influence of top-down attention on the dynamics of visual cortex processing (Herrero et al., 2008). This work has been extended to human subjects in a study showing that the acetylcholinesterase blocker donepezil reduces the extent of the spread of activity in visual cortical areas associated with foveal stimulation (Silver et al., 2008). Changes in the relative balance of thalamic input and synaptic feedback could underlie the fact that knockout of specific muscarinic receptors reduces contrast sensitivity and frequency selectivity in V1 as well as altering receptive field size (Groleau et al., 2014, 2015). Cholinergic modulation has also been shown to cause long-term enhancement of visual evoked potential and behavioral sensitivity (Kang and Vaucher, 2009; Kang et al., 2014, 2015) that could be relevant to the coding of visual cues for spatial location.

As noted above, grid cells and place cells are sensitive to the visual cues in an environment, which can cause rotation of firing fields or compression or expansion of the spacing between grid cell firing fields. These effects could be modulated by cholinergic effects in the visual areas of neocortex that could influence the coding of running speed in these structures via effects on different classes of interneurons. Neocortical interneurons have specific defining markers that define three nonoverlapping category markers: parvalbumin (PV), somatostatin (SST), and ionotropic serotonin receptors (5HT3A) (Lee et al., 2010; Rudy et al., 2011). The 5HT3A category contains interneuron subtypes with additional markers including vasoactive intestinal protein (VIP) and neuropeptide Y (NPY). Studies have revealed cortical circuitry that appears to be consistent across different regions, showing that activation of VIP neurons appears to selectively inhibit SST and PV interneurons (Lee et al., 2013; Fu et al., 2014), thereby disinhibiting neocortical pyramidal cells.

Changes in acetylcholine levels during locomotion may influence visual responses of mouse primary visual cortex (V1). Locomotion was found to increase the gain of excitatory neurons in V1 (Niell and Stryker, 2010). This increase in gain appears to be initiated by inhibitory interneurons that express VIP, as calcium imaging in behaving mice shows that these VIP neurons respond to locomotion (Fu et al., 2014). These VIP neurons inhibit interneurons that express somatostatin, thereby disinhibiting the excitatory pyramidal neurons to allow greater spiking activity. Importantly, this response to locomotion depends on powerful cholinergic activation via nicotinic AChRs (Fu et al., 2014). Rabies-virus-based retrograde tracing identified the source of acetylcholine in cholinergic neurons of the diagonal band of Broca, which give rise to direct projections to the upper layer VIP neurons in V1. As noted above, VIP interneurons belong to the 5HT3A category (Lee et al., 2010), which have been shown to be directly and strongly depolarized by nicotinic receptors (Porter et al., 1999; Christophe et al., 2002).

Thus, the modulation of VIP neurons in primary visual cortex by the activity of cholinergic neurons in the basal forebrain seems to be important for regulating the enhancement of neuronal responses based on locomotion in mice. The activation of this VIP-SST disinhibitory pathway was both necessary and sufficient for inducing the synaptic plasticity potentiating the visual responses (Fu et al., 2015), providing a further link of acetylcholine to synaptic plasticity. Notably, VIP neurons in other primary

sensory cortices, namely the primary somatosensory barrel cortex and – although weaker – the primary auditory cortex, also respond to locomotion (Fu et al., 2014). Consistent with the speed modulation of neuronal responses in visual cortex, calcium imaging of the activity of cholinergic neurons in the MSDB has demonstrated a linear relationship between activity of cholinergic neurons and running speed (Davidson et al., 2014), supporting the notion that running speed modulates activity of cholinergic neurons in the diagonal band of Broca.

A similar mechanism appears to underlie effects of reinforcement signals (reward and punishment) on auditory cortex responses, in which activation of VIP neurons inhibits SST and PV cells (Pi et al., 2013), consistent with earlier studies showing disinhibition mediated by layer I interneurons (Letzkus et al., 2011). A similar mechanism also appears to mediate increases and decreases in spiking activity during whisker movements due to M1 cortical inputs to VIP interneurons (Lee et al., 2013). Stimulation of the basal forebrain has been shown to activate VIP interneurons but not PV interneurons via nicotinic cholinergic receptors (Alitto and Dan, 2012). Acetylcholine directly depolarizes VIP neurons (Lee et al., 2010; Fu et al., 2014) and depolarizes SST but not PV cells in neocortex (Kawaguchi, 1997). Testing of connectivity patterns between interneuron sub-types using pair-wise recordings in slices of visual cortex revealed that VIP interneurons strongly inhibit SST cells, and SST cells inhibit almost all other interneurons including PV cells (Pfeffer et al., 2013), thereby setting up complex dynamics of inhibition or disinhibition that influence pyramidal cells. Activation of muscarinic acetylcholine receptors also causes presynaptic inhibition of inhibitory synaptic transmission arising from fast-spiking neurons in somatosensory cortex (Kruglikov and Rudy, 2008). These muscarinic effects reduce feedforward inhibition of thalamocortical input (Kruglikov and Rudy, 2008) at the same time that nicotinic receptors enhance synaptic transmission at thalamocortical synapses (Gil et al., 1997). These effects have been proposed to contribute to the enhancement of sustained attention by acetylcholine in the neocortex (Hasselmo and McGaughy, 2004). These studies provide examples of a local functional circuit that appears to be replicated within neocortex.

3.4. Cholinergic modulation during waking and sleep

The role of acetylcholine in modulation of different cortical structures including hippocampus, entorhinal cortex, and neocortex suggest a potential role for cholinergic neurons in orchestration of processing within these structures. The cholinergic effects could be exerted independently within each structure as anatomical data indicates that individual cholinergic neurons project to relatively delimited regions of the cortex (Price and Stern, 1983). However, microdialysis evidence indicates strongly coordinated changes in acetylcholine levels in neocortex and hippocampus during different phases of sleep versus waking (Marrosu et al., 1995). Acetylcholine levels are high during active waking, show decreases during quiet waking, and decrease to less than 1/3 of waking levels during slow wave sleep (Marrosu et al., 1995). Most of this paper shows the role of high acetylcholine levels in enhancing the encoding of sensory input. However, the coordinated decrease in acetylcholine levels during quiet waking and slow wave sleep has been proposed to release the presynaptic inhibition from hippocampus back to neocortex, allowing activity based on recently formed associations in the hippocampus to spread back to the neocortex and drive consolidation of memories in the neocortex (Hasselmo, 1999). This is consistent with theories of consolidation that were simulated in models of hippocampal-cortical interactions (Alvarez and Squire, 1994; McClelland et al., 1995; Hasselmo et al., 1996).

This proposal is consistent with the muscarinic cholinergic presynaptic inhibition of glutamatergic transmission shown at a number of stages of cortical feedback connections, including the excitatory recurrent connections in region CA3 (Hasselmo et al., 1995; Vogt and Regehr, 2001; Kremin and Hasselmo, 2007), the connections from region CA3 to region CA1 (Hounsgaard, 1978; Valentino and Dingledine, 1981; Hasselmo and Schnell, 1994b; de Sevilla et al., 2002), and the feedback connections within neocortical structures (Hasselmo and Cekic, 1996; Gil et al., 1997).

This model of the role of acetylcholine in consolidation (Hasselmo, 1999) led to some functional predictions that have been tested. If a reduction in cholinergic presynaptic inhibition enhances consolidation during slow wave sleep, then an increase in acetylcholine levels during slow wave sleep should impair consolidation. This was tested in a study in which subjects were administered the acetylcholinesterase inhibitor physostigmine during slow wave sleep. These subjects then showed reductions in subsequent tests of declarative memory consolidation performed after the subjects were awakened (Gais and Born, 2004). On the other hand, the model predicts that reductions in acetylcholine modulation during waking should enhance consolidation. This was shown in a study in which scopolamine was administered to block muscarinic cholinergic receptors after encoding of information, and subjects showed an enhancement of consolidation on a later memory test (Rasch et al., 2006) similar to the enhancement of consolidation seen with quiet rest after encoding (Dewar et al., 2009, 2014). The change in acetylcholine levels during quiet rest appears to enhance the consolidation of spatial memories (Craig et al., 2015, 2016). Thus, modeling and experimental data shows a link between cellular mechanisms of muscarinic presynaptic inhibition and behavioral studies in animals and humans.

4. Cholinergic modulation of cortical network oscillatory dynamics

The cholinergic modulation of different components of cortical circuits appears to influence the network oscillatory dynamics observed in different cortical structures. This includes influences on oscillations in the theta frequency range (often described as 3–12 Hz in rodents) as well as in the gamma frequency range (described as 40–100 Hz in rodents). This section will review data on cholinergic modulation of network oscillatory dynamics.

4.1. Association of acetylcholine levels with theta rhythm

As noted above, microdialysis studies show increases in acetylcholine levels associated with active movement or attention to the environment. The same behavioral states associated with high acetylcholine release in hippocampal and cortical regions are highly correlated with theta rhythm oscillations in the hippocampal formation (Green and Arduini, 1954; Juvet, 1969; Vanderwolf, 1969). The fact that focal injection of atropine, a muscarinic acetylcholine receptor antagonist, into the medial septum of rats and rabbits inhibits theta oscillations in the hippocampus (Kramis et al., 1975) indicates the importance of acetylcholine in modulating theta in the septohippocampal network. Activation of cholinergic receptors in the septum with the nonspecific agonist carbachol can induce theta rhythm oscillations (Bland and Colom, 1993). Microdialysis in the dorsal hippocampus showed an increase in acetylcholine levels correlated with the appearance of theta rhythm oscillations (Monmaur et al., 1997). Using an amperometric approach allowing second-by-second time resolution (Burmeister et al., 2008) for detection of extracellular acetylcholine levels, Zhang et al. (2010) showed that acetylcholine release

occurred over many seconds after the appearance of spontaneous or induced theta oscillations in urethane-anesthetized rats *in vivo*.

Hippocampal theta activity is comprised of two components, which were initially separated pharmacologically. Type II theta is of lower frequency (e.g. 3–6 Hz) and can occur in isolation during alert immobility as well as under urethane anesthesia (Kramis et al., 1975). The pharmacological hallmark of this type is its sensitivity to atropine. In contrast, type I theta is of faster frequency (e.g. 8–12 Hz), prominent during movement, and is resistant to atropine application. However, it is sensitive to ether or urethane anesthesia (Kramis et al., 1975), as well as to application of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine (Soltesz and Deschenes, 1993).

Because of the association of theta oscillations with attention and the planning and execution of movement, theta oscillations have been termed the “on-line” state of the brain (Buzsáki, 2002). In humans, encoding of information is accompanied by increases of theta oscillatory activity in the medial temporal lobe during virtual navigation and working memory tasks (Raghavachari et al., 2001; Ekstrom et al., 2005), as well as during successful memory encoding in a free recall memory task in human epilepsy patients (Lega et al., 2012). In animals, theta has been shown to correlate with the speed of learning of eye-blink conditioning (Berry and Thompson, 1978) and conditioning is more rapid when stimuli are presented during periods of high theta rhythm amplitude (Seager et al., 2002; Griffin et al., 2004). In spatial memory tasks, the magnitude of impairments caused by manipulations of the medial septum correlates with the amount of loss of theta rhythm power (Winson, 1978; Givens and Olton, 1990). The mechanism and functional role of theta rhythm could be associated with changes in cholinergic modulation as described in the next section.

4.2. Mechanisms of cholinergic regulation of theta rhythm properties

Acetylcholine influences theta rhythm dynamics at different locations in the septohippocampal network, including both within the MSDB and within the hippocampus itself. Within the MSDB, cholinergic neurons influence theta rhythm in concert with GABAergic and glutamatergic MSDB neurons. Axon collaterals of cholinergic neurons locally project to and depolarize PV positive GABAergic MSDB neurons via activation of muscarinic AChRs (Wu et al., 2003; Dannenberg et al., 2015). Thus, optogenetic activation of cholinergic MSDB neurons can recruit PV GABAergic MSDB neurons, which show theta rhythmic firing patterns (Varga et al., 2008). The theta-rhythmic activity of GABAergic MSDB neurons can lead to oscillatory local field potential activity in the hippocampal formation via rhythmic inhibition of local inhibitory interneurons in the hippocampus (Freund and Antal, 1988; Serafin et al., 1996; Tóth et al., 1997; Hangya et al., 2009; Wulff et al., 2009). This mechanism involves a prominent role of PV neurons in the MSDB as shown by a more recent study (Amilhon et al., 2015). Consistent with this, optogenetic stimulation of PV GABAergic MSDB neurons at a specific frequency within a range tested from 3–40 Hz precisely controls the frequency of hippocampal oscillations in urethane-anesthetized mice (Dannenberg et al., 2015). Strikingly, driving hippocampal oscillatory activity in this study was most efficient around 10 Hz, similar to the optimal stimulation frequency of 8 Hz when stimulating hippocampal PV interneurons directly in a whole hippocampus preparation (Amilhon et al., 2015).

Activation of cholinergic MSDB neurons promotes the induction of hippocampal theta oscillations of the slower frequency type II theta (Dannenberg et al., 2015). Notably, slower oscillations below the theta range (i.e. between 1 and 3 Hz) are suppressed during cholinergic activation (Vandecasteele et al., 2014; Dannenberg

et al., 2015) similar to results obtained in visual cortex during stimulation of basal forebrain cholinergic neurons (Pinto et al., 2013). The suppression of slow oscillations is accompanied by the suppression of sharp-wave ripple complexes in the hippocampus (Vandecasteele et al., 2014). Thereby activation of cholinergic MSDB neurons supports the temporal organization of neuronal spiking and synaptic inputs. Recently, Robinson et al. (2016) showed that the optogenetic activation of glutamatergic MSDB neurons increases the rhythmicity of spontaneously generated hippocampal theta oscillations through a mechanism dependent on local septal connections. Since glutamatergic neurons can excite both cholinergic and GABAergic MSDB neurons (Xu et al., 2015), these data corroborate the hypothesis of a medial septal relay with a central role for GABAergic MSDB neurons for rhythmic control over cortex and hippocampus. This hypothesis is consistent with the finding that PV neurons in the MSDB not only pace and amplify (Varga et al., 2008; Huh et al., 2010), but also lead (Hangya et al., 2009) hippocampal theta oscillations. In contrast to the proposed role of cholinergic MSDB neurons in promoting a network state for learning and memory, the glutamatergic MSDB neurons appear to have a special role for the initiation of movement and locomotion-related theta oscillations (Fuhrmann et al., 2015). In summary, acetylcholine is associated with regulating aspects of theta rhythm activity in the hippocampal circuits. The modulatory influences could also include the interaction of theta and gamma oscillations as described next.

4.3. Cholinergic modulation and theta-gamma coupling

Studies have shown a phase relationship between the magnitude of gamma frequency oscillations and the phase of theta rhythm oscillations, often referred to as phase-amplitude coupling. Coupling between gamma rhythm amplitude and theta rhythm phase occurs during exploratory activity as well as REM sleep (Bragin et al., 1995; Belluscio et al., 2012). In studies of human subjects, theta-gamma phase amplitude coupling was larger during periods of working memory maintenance, and when gamma power was concentrated during a narrower range of the theta phase, decisions in memory tasks arrived earlier (Axmacher et al., 2010). Such phase-amplitude theta-gamma coupling was also shown to correlate with performance accuracy in a conditional discrimination task, where rats learned to associate contexts with the location of a subsequent food reward (Tort et al., 2009). Understanding the role of acetylcholine in these behavioral tasks could require understanding the role of acetylcholine in regulating these network oscillatory dynamics.

Interestingly, gamma oscillations in the CA1 area of the rat hippocampus were separable into distinct fast (65–140 Hz) and slow (25–50 Hz) frequency components that were coherent with fast or slow gamma oscillations in the medial entorhinal cortex or CA3, respectively (Colgin et al., 2009). Slow gamma oscillations predominantly occurred at the descending phase, whereas the fast gamma oscillations were coupled to the peak of theta measured at the CA1 pyramidal cell layer. These data are consistent with the theory elaborated below that one phase of theta could involve a stronger influence of medial entorhinal cortex on the firing of cells in region CA1, whereas at another phase region CA3 could have a stronger influence on firing of cells in region CA1 (Hasselmo et al., 2002). Consistently, high gamma power recorded in the superficial layers of the medial entorhinal cortex of freely moving rats was most reduced at the peak of theta compared to the trough following blockade of muscarinic acetylcholine receptors (AChRs) by systemic scopolamine injection (Newman et al., 2013). Taken together, these data show that theta rhythmic activity associated with high cholinergic tone can act as a global synchronizing

mechanism between hippocampal regions, but also across different brain regions as described in the next section.

4.4. Theta rhythm regulation of network interactions

Theta rhythmic activity is thought to provide a temporal framework for the timing of spikes inside or across regions (Skaggs and McNaughton, 1996; Lisman and Jensen, 2013). In humans, Rutishauser et al. (2010) found that the coupling of single unit activity to the underlying theta predicts successful memory formation. In monkeys, between-area phase synchronization and spike theta-phase locking of single units were observed in area V4 of the visual cortex and the prefrontal cortex during a visual working memory task (Liebe et al., 2012). As in the study by Rutishauser et al. (2010), the strength of this intercortical locking was predictive of memory performance. In rodents, theta rhythmic activity was shown to coordinate hippocampal-prefrontal cortex interactions in spatial working memory tasks (Hyman et al., 2005; Jones and Wilson, 2005; Benchenane et al., 2010).

The induction of synaptic plasticity is favored by coordinated action-potential timing across populations of neurons (Markram et al., 1997). Thus, it is not surprising that the temporal framework set by theta oscillations can modify synaptic weights. The same high-frequency stimulus can induce both long-term potentiation (LTP) or long-term depression (LTD), depending on the phase of the theta oscillation at which it is given (Huerta and Lisman, 1995; Hyman et al., 2003). This becomes particularly important in the context of encoding novel information into a network of already stored memories ready for retrieval. Differences in network dynamics at different phases of theta rhythm have been proposed to overcome the problem of interference, when context-relevant information from previously stored memories is recalled at the same time that novel information is being encoded. As a solution for the interference problem, the peak and trough of theta oscillations have been hypothesized to provide separate phases of encoding and retrieval (SPEAR model), (Hasselmo et al., 2002; Hasselmo and Stern, 2014). In this model, the encoding phase involves strong entorhinal input to CA3 and CA1 with weak retrieval activity in CA3. At the same time, LTP is induced on synapses arising from region CA3. In contrast, the model retrieval phase involves weaker entorhinal input but strong retrieval activity in CA3. In this phase, the absence of LTP prevents retrieval from interfering with encoding.

Acetylcholine release in the hippocampus leads to decreased spiking overall, but more theta-phase coupled spiking activity of CA3 principal cells (Dannenberg et al., 2015). The principal neurons in area CA3 of the hippocampus have long been hypothesized to form an auto-associative network important for the retrieval of previously stored memory traces by attractor-network dynamics. Therefore, the decreased spiking activity of CA3 principal neurons during cholinergic activation supports the encoding of novel information by suppressing retrieval processes. In line with the prediction of the SPEAR model, CA3 pyramidal neurons increased spike phase coupling to the local theta rhythm in anesthetized mice (Dannenberg et al., 2015). In freely behaving rats, intrinsic CA3–CA3 synaptic inputs are attenuated on CA3 theta peaks, favoring extrinsic CA3 inputs, whereas extrinsic perforant path–CA3 synaptic inputs are attenuated on CA3 theta troughs, favoring intrinsic CA3 inputs (Villarréal et al., 2007). The change in relative strength of synaptic input is supported by studies showing phasic changes in strength of evoked synaptic transmission on different pathways at different phases of the theta rhythm oscillation in region CA1 as well (Wyble et al., 2000; Villarréal et al., 2007). Interestingly, the differential theta modulation of CA3 afferent inputs only occurs during the initial exploration of a novel environment, but habituates with familiarity. Furthermore, it is blocked by systemic

atropine application at a dose which blocks type II theta rhythm. This increased precision of spike timing upon cholinergic activation might promote plasticity in either the autoassociative CA3 network or in CA3–CA1 projections (Pavlidis et al., 1988; Hölscher et al., 1997; Orr et al., 2001; Hyman et al., 2003).

In line with a more prominent role of the atropine-sensitive lower frequency type II theta, environmental novelty produces a sharp reduction in the theta frequency of foraging rats, which slowly disappears with increasing familiarity (Jeewajee et al., 2008b). Moreover, higher regularity of theta oscillations is accompanied by a more temporally regular theta-rhythmic population output of hippocampal pyramidal cells and lead to running with a less variable and slower speed during exploration via a hippocampus-lateral septum pathway (Bender et al., 2015). Taken together, these data and models point to a strong role of theta oscillations for integrating sensory experiences into episodic memory.

Consistent with the theorized role of these different phases in encoding and retrieval, the human EEG shows reset to different phases of theta rhythm during encoding and retrieval (Rizzuto et al., 2006), and spiking in rat hippocampus appears on different phases of hippocampal theta during match and nonmatch stimuli (Manns et al., 2007). In further support of these theories, gamma coherence with entorhinal cortex versus CA3 has been shown at different phases of theta (Colgin et al., 2009) and activation of inhibition at different phases of the theta cycle has differential effects on encoding and retrieval (Siegle and Wilson, 2014). Thus, the cortical oscillatory dynamics influenced by cholinergic modulation may play an important role in regulating the coding of spatial information for subsequent memory guided behavior.

5. Summary

This review shows that cholinergic modulation may play a role in spatial memory function, potentially through influences on the response of cells coding spatial location such as grid cells and place cells. Cholinergic modulation may be involved in the expansion of spacing between grid cell firing fields that may help trigger remapping of place cells in a novel environment, as supported by reductions of remapping and more consistent firing after lesions of cholinergic innervation. Blockade of cholinergic modulation reduces the spatial periodicity of grid cells, and alterations of grid cell firing properties may be associated with changes in coding of speed by theta rhythmicity in entorhinal neurons. The influence of sensory cues on grid cell firing may be tuned by the cholinergic modulation of synaptic transmission and disinhibitory circuits within the neocortex. Further experiments will help clarify the important role of acetylcholine in regulating the dynamics of encoding and attention relevant to coding of spatial location in cortical circuits.

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