



Cholinergic modulation of cognitive processing: insights drawn from computational models

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Acetylcholine plays an important role in cognitive function, as shown by pharmacological manipulations that impact working memory, attention, episodic memory, and spatial memory function. Acetylcholine also shows striking modulatory influences on the cellular physiology of hippocampal and cortical neurons. Modeling of neural circuits provides a framework for understanding how the cognitive functions may arise from the influence of acetylcholine on neural and network dynamics. We review the influences of cholinergic manipulations on behavioral performance in working memory, attention, episodic memory, and spatial memory tasks, the physiological effects of acetylcholine on neural and circuit dynamics, and the computational models that provide insight into the functional relationships between the physiology and behavior. Specifically, we discuss the important role of acetylcholine in governing mechanisms of active maintenance in working memory tasks and in regulating network dynamics important for effective processing of stimuli in attention and episodic memory tasks. We also propose that theta rhythm plays a crucial role as an intermediary between the physiological influences of acetylcholine and behavior in episodic and spatial memory tasks. We conclude with a synthesis of the existing modeling work and highlight future directions that are likely to be rewarding given the existing state of the literature for both empiricists and modelers.

Keywords: entorhinal cortex, spatial navigation, oscillatory interference, theta, memory, attention, acetylcholine, computational model

INTRODUCTION

Acetylcholine has a broad range of neuromodulatory influences on the cellular properties of hippocampal and cortical neurons and, as a result, on neural information processing important for behavior. Here we review experimental data on cholinergic modulation of neural networks in the context of different cognitive functions and describe computational models that connect the modulatory effects to each cognitive function. We begin with an overview of the role that computational models play for bridging the gaps in our understanding between physiological and behavioral influences of cholinergic modulation. After this, we review relevant anatomical pathways. We then address the role of acetylcholine in working memory, attention, episodic memory, and spatial memory in turn as understood from experimental data and computational modeling. Finally, we conclude with a synthesis of the unifying threads apparent across domains and discussion of directions of future research that are likely to be rewarding given existing empirical and modeling work.

MODELING ADDRESSES QUESTIONS ABOUT CHOLINERGIC FUNCTION IN THE CORTEX

Acetylcholine plays an essential role in cognitive function. At high doses, drugs such as scopolamine that block the effects of acetylcholine at muscarinic receptors cause a complete breakdown in cognitive function manifesting as delirium (Ostfeld and Aruguete, 1962; Crow and Grove-White, 1973). At lower doses, these drugs impair performance in cognitive tasks assessing

memory function and attentional performance (Beatty et al., 1986). Similar to these robust behavioral effects, physiological data from intracellular recording of single neurons show robust and consistent effects of acetylcholine on the function of individual neurons. These effects include depolarization (Cole and Nicoll, 1984), reductions in spike frequency accommodation (Madison and Nicoll, 1984), enhancement of long-term potentiation (LTP) (Gil et al., 1997) and presynaptic inhibition of glutamatergic (Hasselmo and Bower, 1992; Hasselmo, 1999) and GABAergic synaptic transmission (for review, see Heys et al., 2012 in this issue).

Despite the striking behavioral effects of acetylcholine receptor blockade, and the robust physiological effects of acetylcholine on neurons *in vitro*, the link between these levels of analysis is not clear. In particular, few studies have addressed how the blockade of acetylcholine receptors influences the firing patterns of neurons in awake, behaving animals. In addition, despite the strong behavioral effects of systemic injections of pharmacological agents, the effects of selective lesions of acetylcholine neurons are not always consistent. In the review presented here, we will address the available data on effects of acetylcholine on firing patterns in awake, behaving animals, and also address potential factors influencing the nature of behavioral effects of cholinergic lesions. In particular, we will address network factors influencing behavioral effects including the role of theta rhythm oscillations, top-down feedback control of cholinergic modulation, and the role of novelty in behavioral effects.

Computational modeling of cortical circuits provides a framework for linking the cellular effects of acetylcholine to the spiking activity of neurons in behaving animals and the role of acetylcholine in behavioral function. Therefore, we will frame our discussion in the context of computational models of neural circuits that have direct implications for understanding the link between the cellular influences of acetylcholine and cognitive performance (Hasselmo et al., 1992, 1995, 2002; Hasselmo and Schnell, 1994; Hasselmo, 1999; Menschik and Finkel, 1999; Norman et al., 2006; Burgess et al., 2007; Hasselmo, 2008). These models include analysis of cholinergic effects on circuit dynamics in the hippocampus (Hasselmo and Schnell, 1994; Hasselmo, 1999; Menschik and Finkel, 1999), models of the functional role of theta rhythm oscillations (Hasselmo et al., 2002; Norman et al., 2006) and models of grid cell firing in entorhinal cortex (Burgess et al., 2007; Hasselmo, 2008).

Discussion of these topics requires some review of previous data on the anatomy of cholinergic innervation of cortical structures, the modulatory influences on acetylcholine, and different techniques used to study the role of acetylcholine in behavior.

ANATOMICAL OVERVIEW

Cholinergic projections

Acetylcholine is released from neurons projecting to a broad range of cortical and subcortical sites. These projections can be split into two groups: the magnocellular basal forebrain

cholinergic system and the brainstem cholinergic system (Mesulam et al., 1983a,b; Everitt and Robbins, 1997; Mike et al., 2000). As summarized in **Figure 1**, the basal forebrain cholinergic system includes cells located in the medial septal nucleus (MS), the vertical, and horizontal limbs of the diagonal band of Broca (DB), and the nucleus basalis magnocellularis (nBM; i.e., nucleus basalis of Meynert). These structures send cholinergic (as well as noncholinergic) projections to a broad range of sites in the neocortex as well as limbic cortices such as cingulate cortex, entorhinal cortex and hippocampus, and other structures including the basolateral amygdala and the olfactory bulb (Mesulam et al., 1983a). The entorhinal cortex receives some of the densest cholinergic innervation of cortical structures (Mesulam et al., 1983a). The cholinergic fibers in cortical structures have many axonal varicosities that are not associated with postsynaptic densities (Umbriaco et al., 1994, 1995), suggesting that acetylcholine influences neurons via diffuse extrasynaptic modulation termed volume transmission (Descarries et al., 1997). Therefore, the effects of acetylcholine in computational models are commonly implemented as uniform modulation of cellular parameters of depolarization and synaptic transmission throughout the local circuits of a model (Hasselmo et al., 1992, 1995; Hasselmo and Schnell, 1994).

The brainstem cholinergic system, which includes neurons located in the pedunculopontine tegmental nucleus (PPT) and laterodorsal pontine tegmentum (LDT) principally innervate the

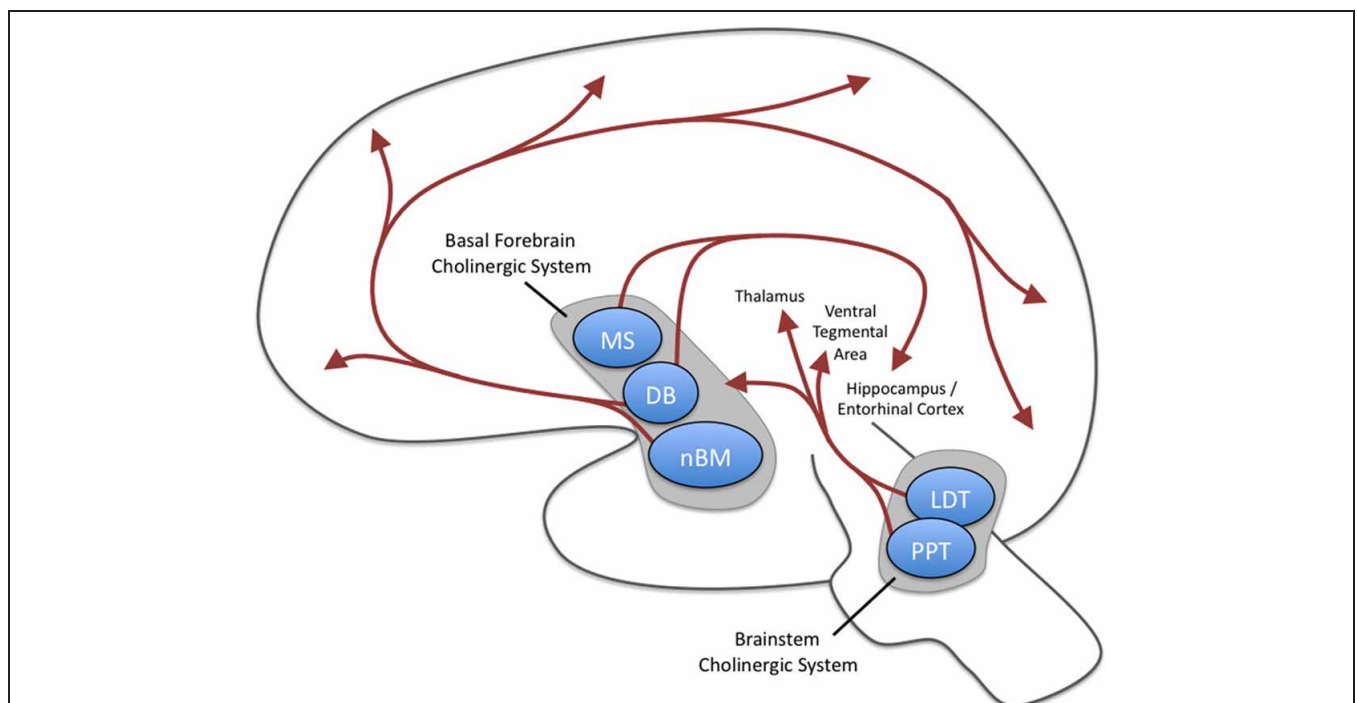


FIGURE 1 | Major cholinergic projections of the central nervous system.

Two groups of projections exist: the magnocellular basal forebrain cholinergic system and the brainstem cholinergic system. The magnocellular basal forebrain cholinergic system includes the medial septal nucleus (MS), the vertical and horizontal limbs of the diagonal band of Broca (DB), and the nucleus basalis magnocellularis (nBM). The horizontal limb of the DB and

nBM has extensive diffuse projections to neocortex as well as projections to basolateral amygdala and olfactory bulb (these latter two are not shown here). The MS and vertical limb of the DB project to hippocampus and entorhinal cortices. The brainstem cholinergic system includes the pedunculopontine tegmental nucleus (PPT) and laterodorsal pontine tegmentum (LDT) and projects predominantly to the thalamus but also to the basal forebrain region.

thalamus and basal ganglia but also innervates the basal forebrain and serves as a minor component of the cholinergic innervation of cortical structures (Mesulam et al., 1983a; Rye et al., 1987). Each of projections are particularly well positioned to have broad impacts on neural processing. For example, stimulation of the cholinergic projections into the ventral tegmental area (VTA) induces dopamine release—an effect that contributes to the addictive properties of smoking cigarettes (Pidoplichko et al., 2004). Mesulam and colleagues proposed the ch1–6 nomenclature to specifically refer to the distinct pathways as shown in **Table 1**.

Projections into basal forebrain

An important unanswered question concerns the mechanisms of regulation of acetylcholine levels within cortical circuits. Although rarely simulated explicitly in computational models of cholinergic function, such regulatory mechanisms play a critical role in shaping the cognitive influences of acetylcholine. Incorporation of these pathways into future modeling work would be fruitful, and, as such, we briefly review these connections here. Regulatory feedback originates from cortical structures and from bottom-up control of cholinergic neurons. In contrast to the broad range of targets of the cholinergic neuron projections, a comparatively restricted set of areas send excitatory or inhibitory feedback to the basal forebrain. Within the neocortex, glutamatergic feedback projections to the basal forebrain originate in the medial and ventral prefrontal and agranular insular cortices (Carnes et al., 1990; Záborsky et al., 1997).

Stimulation of the hippocampus causes reductions in medial septum activity (McLennan and Miller, 1974a,b) that may arise from weak GABAergic projections from the hippocampus to the medial septum (Toth et al., 1993), or from connections via a circuit that includes anterior thalamus. Additional regulatory feedback comes from the GABAergic projections from the nucleus accumbens (Mogenson et al., 1983; Záborsky and Cullinan, 1992) as well as glutamatergic projections from the amygdaloid complex (Grove, 1988). Finally, the ascending reticular activating system, including the the pedunculopontine and laterodorsal nucleus, median raphe, and VTA, as well as the hypothalamus provide a wide range of neuromodulatory influences on cholinergic output of the basal forebrain including noradrenergic, serotonergic, and cholinergic input (Jones and Cuello, 1989). While the specific modulatory influences of each of the reciprocal projections is beyond the scope of this review (for a related review, see Fadel, 2011), it is worth highlighting that the anatomical regions from which these projections originate are frequently attributed with functions relevant to the regulation of the quality of information processing in the brain.

Cholinergic receptor subtypes

There are two general classes of acetylcholine receptors that can be dissociated by their binding affinity for muscarine and nicotine. At present, computational models of cholinergic function do not usually focus on dissociating the contribution of each of these receptor types. However, each has distinct properties that would have differential functional influences on cognition. The development of pharmacological therapies requires an understanding of the relative contributions of each receptor subtype for cognitive function. Thus, with the goal of drawing attention to the differential contributions of these receptor subtypes in future modeling work we have included an introduction to these receptor subtypes here and describe relevant observations regarding the contributions of each for the domains of cognition reviewed.

Receptors that are activated by muscarine (but not nicotine) are referred to as muscarinic cholinergic receptors and are G-protein coupled metabotropic receptors. Within the central nervous system there are five subtypes of muscarinic receptor that are differentiable via amino acid structure and immunohistochemistry: the M1 receptor is located predominantly at the post-synaptic sites (and is functionally related to the M3 and M5 receptors). The M1 receptor mediates post-synaptic effects of the activation of muscarinic receptors, including depolarization and suppression of spike-frequency accommodation (Dasari and Gullledge, 2011). M2 receptors are located at both pre- and post-synaptic sites and are functionally related to the M4 receptor (Mrzljak et al., 1993). The cholinergic modulation of glutamatergic synaptic transmission via activation of muscarinic receptors on glutamatergic terminals appears to involve the M4 subtype of receptor (Shirey et al., 2008; Dasari and Gullledge, 2011).

Inotropic, cholinergic receptors that are activated by nicotine but not muscarine are designated as nicotinic receptors (nAChRs). In the brain, they exist as either heteropentamers of alpha and beta subunits or as homopentamers of alpha7 subunits. The diverse range of receptor properties, as well as their temporal and spatial specificity of expression, has a huge range of

Table 1 | Anatomical overview of cholinergic projections with corresponding Ch1–6 nomenclature.

System	Cholinergic cell group	Containing nuclei	Target
Basal forebrain	Ch1	Medial septum	Hippocampus
Basal forebrain	Ch2	Vertical limb of the diagonal band of Broca	Hippocampus
Basal forebrain	Ch3	Lateral part of horizontal limb of the diagonal band of Broca	Olfactory bulb
Basal forebrain	Ch4	Nucleus basalis magnocellularis (i.e., nucleus basalis of Meynert), Globus pallidus, neurons lateral to the vertical limb, and neurons in the medial part of the horizontal limb of the diagonal band of Broca	Neocortex, Basolateral amygdala
Brainstem	Ch5	Pedunculopontinus, cuneiform, parabrachial area	Thalamus, Basal ganglia
Brainstem	Ch6	Lateral tegmental nucleus	Thalamus, Basal ganglia

effects on the function of the brain. nAChRs have been found to be essential for development (Bear and Singer, 1986; Imamura and Kasamatsu, 1991; Hensch, 2004), regulation of cell survival and death (Treinin and Chalfie, 1995; Labarca et al., 2001; Hruska and Nishi, 2007; Hruska et al., 2009; Barbagallo et al., 2010), plasticity (Lagostena et al., 2008; Tu et al., 2009; West et al., 2010), and excitability (Albuquerque et al., 2009; Tu et al., 2009; Penton et al., 2011; Ondrejcek et al., 2012).

As an example, within the hippocampus, nAChRs are expressed primarily in the interneurons where they likely play a role in gating communication (Albuquerque et al., 2009). Alpha4beta2 (type I) receptors are sensitive to low concentrations of Ach (0.1–1 μ M) (Miwa et al., 2011), and have been described on the soma and dendrites of CA1 interneurons of mice (Alkondon et al., 1997; McQuiston and Madison, 1999; Mike et al., 2000; Sudweeks and Yakel, 2000), likely coinciding with chronic activation by basal levels of Ach (Albuquerque et al., 2009). Alpha4beta2 (type II) receptors are less sensitive than alpha4beta2 (type I) receptors (Miwa et al., 2011), and have been identified on the axonal segments of CA1 interneurons, where their activation by low concentrations of ACh can induce release of GABA without triggering an action potential (Alkondon et al., 1999). Alpha3beta3 beta2 receptors can be found on the axons of pyramidal associated interneurons (Albuquerque et al., 2009). Alpha7 nAChRs display much faster dynamics, a high calcium permeability, and activated by the ACh precursor choline (Albuquerque et al., 2009). Alpha7 receptors are found on the somata (Mike et al., 2000) and dendrites (Xu et al., 2006) of hippocampal neurons where they can regulate calcium responses, as well as on the axon terminal where they enhance transmitter release (Gray et al., 1996).

ACETYLCHOLINE AND COGNITIVE FUNCTION

Acetylcholine plays an important role in a range of cognitive domains: across empirical methods, working memory, attention, episodic memory encoding, and spatial memory processing are repeatedly found to depend upon acetylcholine for normal function. For each of these domains, a great deal of empirical evidence exists documenting this dependency. Similarly, a great deal is known regarding the physiological influences of acetylcholine on cellular or network dynamics. Our goal in the following section is to review how computational models have linked these seemingly disparate bodies of knowledge. Toward this end, we will discuss each cognitive domain in turn. For each domain, we first review evidence that acetylcholine is required for that type of cognition. We then review the physiological influences of acetylcholine that are likely to subserve that cognitive function, as suggested by the existing computational models. Finally, we describe the modeling work that links the physiology to the cognitive function with a specific focus on the implications and predictions that were born out of the relevant simulations.

WORKING MEMORY

Working memory provides a temporary store for information used during decision-making (Baddeley, 2000; Baddeley and Wilson, 2002; Hasselmo and Stern, 2006). Many animal studies have indicated that working memory networks are selectively

active for familiar and novel stimuli. Familiar stimuli activate the prefrontal cortex (PFC) and parietal cortex of animals performing tasks involving delayed match to sample (DMS) (Fuster, 1973), cued-choice behavior (Fujisawa et al., 2008), object recognition (Asaad et al., 1998), and object localization (Monosov et al., 2010). The parahippocampal cortex and hippocampus, on the other hand, preferentially act as a working memory buffer during novel stimulus presentation. Unit recordings from rats (Young et al., 1997) and primates (Suzuki et al., 1997) and functional magnetic resonance imaging (fMRI) in humans (Schon et al., 2004, 2008) all show elevated activity in parahippocampal regions correlated with active maintenance in working memory tasks, with studies showing relatively higher activity for novel stimuli (Stern et al., 2001).

Of note, lesions of the inferior prefrontal convexity impair performance on DMS tasks with small sets of stimuli where the small size of the set makes each stimulus more familiar (Passingham, 1975; Bachevalier and Mishkin, 1986). Contrasting perirhinal and prefrontal lesions in rats, Otto and Eichenbaum (1992) showed that perirhinal lesions impaired performance on both an 8- and 16-set odor stimuli in a delayed non-match to sample study in rats. In contrast, prefrontal lesions affected the 8-set odor stimuli response, but did not impair performance for the larger stimulus set. These studies suggest that although the PFC is active for novel stimuli (or large stimuli sets), lesions of the PFC significantly disrupt working memory for familiar stimuli (or small stimuli sets) in contrast to lesions of parahippocampal cortices that impair memory for trial-unique stimuli (Gaffan and Murray, 1992; Zola-Morgan and Squire, 1993) and not familiar stimuli (Corkin, 1984; Otto and Eichenbaum, 1992; Eacott et al., 1994).

Cholinergic effects on working memory tasks

In both PFC and parahippocampus, depletion of cholinergic inputs disrupts performance of working memory systems. Crosson et al. (2011) has shown a significant disruption in primate spatial working memory following cholinergic-depletion of the PFC induced by basal forebrain lesions. Further, local infusions of scopolamine into the perirhinal cortex in rats was shown to slow the acquisition of working memory dependent (i.e., trace) fear conditioning task (Bang and Brown, 2009). Such impairments have been found to vary in a dose-dependent fashion with infusions of the M1-antagonist Pirenzepine (Esclassan et al., 2009; see also Ohno et al., 1994). Similar results have also been observed in humans following systemic injections of scopolamine in DMS tasks (Robbins et al., 1997; Koller et al., 2003) and visuospatial tasks (Thomas et al., 2008). The latter study showed impairments with scopolamine injections that were rescued by administration of donepezil, a cholinesterase inhibitor that could also improve performance from baseline in naïve patients (Thomas et al., 2008), corroborating similar rescue studies in rodents (Friedman, 2004; Padlubnaya et al., 2005). fMRI studies in humans also show reduced correlations between delay period activity and subsequent memory after scopolamine administration (Schon et al., 2005). In a study comparing the effect of systemic injections of scopolamine and the nicotinic receptor antagonist mecamylamine in humans, patients were impaired on an *n*-back memory test with scopolamine

alone, and were synergistically impaired with scopolamine and mecamlyamine (Green et al., 2005). Muscarinic blockade, however, does not impair performance on short-term memory tasks such as digit span (Broks et al., 1988) suggesting the familiar stimuli used in these paradigms may have already sufficiently strengthened synaptic connections, thereby reducing the need for cholinergic input to modulate mechanisms of active maintenance. This suggests that the cholinergic modulation of working memory might be more important for novel than for familiar stimuli.

Persistent spiking in the entorhinal cortex

Intracellular recording from *in vitro* slice preparations of rat medial entorhinal cortex (EC) suggest a mechanism for the working memory of novel stimuli that is modulated by acetylcholine. Single neurons in medial EC typically spike in an unsustained fashion after a single depolarizing current. However, bath application of cholinergic agonists like carbachol in the presence of a depolarizing current injection produces persistent spiking that continues after the termination of the depolarizing stimulus (Klink and Alonso, 1997; Egorov et al., 2002; Yoshida et al., 2008). One possible cellular mechanism for this sustained activity suggests that cortical glutamatergic synaptic input, released after stimulus presentation during an attention-driven task, triggers calcium-induced spiking in medial EC neurons while also providing feedback on cholinergic axons. Acetylcholine activation of muscarinic receptors activates a calcium-sensitive non-specific cation current (I_{CAN}) on medial EC neurons allowing further depolarization from calcium-influx resulting in self-sustained persistent spiking (see Hasselmo and Stern, 2006 or Hasselmo and Sarter, 2011 for review).

Acetylcholine may support active maintenance through sustained activation

Several computational models have shown how these intrinsic mechanisms for persistent spiking activity could provide a mechanism for maintenance of working memory for novel inputs during performance of DMS tasks and encoding of long-term memories. Fransén et al. (2002) simulated biophysical networks of the EC with a predominant muscarinic-activated non-specific calcium current, I_{NCM} (now known as I_{CAN}). The presence of I_{NCM} allowed simulated pyramidal cells to sustain spiking activity after transient depolarization even after removing a persistent sodium current (NaP), potassium (K_M) current, or a combination of NaP , K_M , afterhyperpolarization potassium current (K_{AHP}), and internal calcium. The removal of currents involved in action potential generation and the I_{NCM} degraded any sustained spiking during the delayed working memory behavior correlates tested.

These intrinsic cellular properties strongly suggest cholinergic gating of persistent spiking onset actively switch neurons into maintenance modes that can represent new information. *In vivo* studies have shown elevations in entorhinal and hippocampal activity from rodents (Young et al., 1997), monkeys (Suzuki et al., 1997), and humans (Stern et al., 2001; Schon et al., 2004, 2005) which could represent persistent spiking selectively gated by acetylcholine to specific stimuli. Such selective

gating is necessary to maintain information even in the presence of distractor stimuli (Suzuki et al., 1997). Subjects administered scopolamine are impaired in tasks with distractor stimuli such as the n-back task (Green et al., 2005) further suggesting that cholinergic modulation gates the role of persistent activity.

More work is needed, however, to fully understand the gating mechanism gleaned from *in vitro* and computational modeling of persistent spiking. A predilection for novel environments (Acquas et al., 1996; Thiel et al., 1998) and objects (Degroot et al., 2005; Stanley et al., 2012) to increase rat hippocampal acetylcholine levels also argues toward cholinergic gating of preferential signal throughput carrying new information. Lack of cholinergic modulation via deafferentation of the rat EC spares working memory for familiar odor stimuli, but impairs working memory of novel stimuli, in a delayed non-match to sample task (McGaughy et al., 2005). Similar lesions also reduce rat exploration of novel objects (Winters and Bussey, 2005) and impair formation of novel association for location and context (Easton et al., 2010). Further study is also necessary to see neurotransmitter dynamics over extended learning periods. In a recent study, Gupta et al. (2012) looked for a cue-elicited increase in medial EC unit spiking activity of overtrained rats during the delay period of an appetitive, delayed spatial response task. Medial EC neuron firing rate surprisingly dropped during the delay period. If this drop in firing rate had been cholinergic modulated, at what point in the animal's learning did acetylcholine's role change? Shedding light on how and when persistent neuronal activity is regulated via acetylcholine will unlock key pharmacological insights into diseased states impairing working memory.

ATTENTION

The ability to *effectively process* stimuli depends upon the healthy function of the cholinergic system (for reviews, see Sarter et al., 2005; Hasselmo and Sarter, 2011; Klinkenberg et al., 2011). Here, we conceptualize effective processing as the ability of neural tissue to adequately update its pattern of activation in response to external stimuli or events to meet task demands and to resolve ambiguity. Under this conceptualization, we assume that attention is the active process under which the brain ensures a given signal is effectively processed. There is a clear correspondence between cholinergic function and attention, as shown through behavior that is readily linked to physiological observations through modeling. In this section, two such models are described following a brief review of relevant behavioral and physiological data.

Cholinergic modulation supports attentional processing

Studies of people who smoke have led to the understanding that the selective cholinergic agonist nicotine facilitates attentional processing (for a review, see Mansvelder et al., 2006). Supporting evidence includes demonstrations that smokers deprived of nicotine are impaired on attention demanding tasks and that nicotine administration can return their performance to baseline levels. In non-smokers, nicotine has been shown to boost visual attention performance (Ernst et al., 2001).

Experiments monitoring acetylcholine release through microdialysis in freely moving rats have observed relative increases in acetylcholine associated with attention-like behavior (Moore

et al., 1992; Inglis et al., 1994; Sarter et al., 1996; Himmelheber et al., 2000). Much of what has been learned regarding the relationship between acetylcholine release and attention has been derived from the sustained attention task (the SAT) developed by Sarter and colleagues. In this task, rats are required to continuously attend to a house light—pressing a lever whenever the light is turned on and withholding lever presses when the light is extinguished. Importantly, the stimuli appear at irregular intervals requiring that the animal sustain its attention to avoid missing stimuli. In this task, Arnold et al. (2002) found a peak efflux of nearly 140% of baseline levels as animals performed the SAT but found an efflux of about 50% as animals performed the matched control tasks that did not tax attention but were matched for factors such as novelty and movement (see also Himmelheber et al., 1997). Interestingly, acetylcholine efflux demonstrated a higher correspondence to attentional demand than it did to task performance in this task (Kozak et al., 2006) and in other attention demanding tasks (e.g., the five-choice serial reaction time task, Passetti et al., 2000; Dalley et al., 2001). With this observation in mind, Sarter and colleagues have argued that the dynamics of acetylcholine release reflects attentional effort (for relevant reviews, see Sarter et al., 2005, 2006).

Methodological advances, making it possible to detect changes in choline levels with sub-second temporal resolution using amperometry (Parikh et al., 2004), have brought further insight into the anatomical specificity of cholinergic release. Parikh et al. (2007) found that large changes in acetylcholine levels occurs at very fast (~ 1 – 2 s) timescales during cue detection in rats and smaller changes in baseline acetylcholine levels occur over slower timescales (\sim minutes) between trials. Further, they found significantly elevated phasic acetylcholine release in medial PFC, but not in motor cortex when animals detected a cue in the SAT, despite both receiving cholinergic projections. Errors in cue detection did not elicit a concomitant increase in synaptic acetylcholine, and subsequent cholinergic deafferentation of the medial PFC led to significant impairments in cue detection. In contrast, operant cue stimuli, assessing habituated responses, do not appear to be subserved by acetylcholine (Himmelheber et al., 1997).

Cholinergic depletion studies further underscore the importance of acetylcholine for attentional processing. Injections of 192 IgG-Saporin into a cholinergic nucleus causes selective cell death of the cholinergic cells (Wiley et al., 1991). Using this approach, McGaughy et al. (1996) found that selective cholinergic deafferentation of cortex, by infusing 192 IgG-saporin into the nucleus basalis/substantia innominata of the basal forebrain, of rats previously trained on the SAT elicited selective deficits in stimulus detection. Further, they were unable to restore preoperative performance after extensive additional training but found that the final performance across animals correlated with the residual integrity of the cholinergic pathways. Consistent with the observed relationship between cholinergic efflux and attentional demand (e.g., Arnold et al., 2002), the behavioral consequence of corticopetal cholinergic projections lesions varies as a function of the attentional demands of the task employed. For example, Turchi and Sarter (1997) found that such lesions of the corticopetal cholinergic projections were particularly detrimental to performance on a more difficult crossmodal divided attention

variant of the SAT (i.e., response cues could be presented as either visual or auditory stimuli) relative to performance on a unimodal form of the SAT. It is likely that the attention benefiting properties of acetylcholine occur in the PFC: targeted lesions of cholinergic projections to the PFC in rats increased sensitivity to distractor cues and led to increased impulsive responses during SATs (Dalley et al., 2004; Newman and McGaughy, 2008).

Mutant mice, in which $\alpha 7$ nicotinic receptors have been removed, show effect that suggest that the $\alpha 7$ receptors, at least, play an important role in attentional processing. $\alpha 7$ receptor knockout mice take longer to reach asymptotic performance on attention demanding tasks and exhibit greater numbers of errors than do wild-type mice (Young et al., 2004).

Acetylcholine supports processing of extrinsic signals

Given the clear importance for acetylcholine in attentional processing, what are the relevant physiological processes? Fortunately, physiological studies of cholinergic function, particularly in cortical tissue, tell a relatively coherent story: acetylcholine potentiates afferent projections while suppressing intrinsic projections, thereby allowing for greater processing of extrinsic stimuli (for a review, see Hasselmo, 1999; Hasselmo and Sarter, 2011). Early unit recording studies in anesthetized animals showed enhanced spiking responses of cortical neurons during acetylcholine application (Krnjevic and Phillis, 1963). Similarly, the amplitude of evoked potentials in somatosensory cortex following somatic stimulation was amplified following basal forebrain stimulation (Tremblay et al., 1990). More recent studies in awake, behaving animals allow analysis of the modification of functional properties. The local application of acetylcholine enhances the response of primary visual cortex neurons to visual input (Sato et al., 1987; Disney et al., 2007) and enhances the direction selectivity of individual neurons (Murphy and Sillito, 1991).

Concomitant with enhanced afferent input, high acetylcholine levels also suppress recurrent connections at glutamatergic feedback synapses as observed in piriform cortex and region CA3 of the hippocampus (Hasselmo and Bower, 1992, 1993; Hasselmo et al., 1995; Linster et al., 1999; Kremin and Hasselmo, 2007). For example, Linster et al. (1999) found that stimulation of the cholinergic projection to piriform (olfactory) cortex in rodents increases the amplitude of the evoked response resulting from stimulation of the lateral olfactory tract and decreased the amplitude of the evoked response resulting from stimulation of the posterior piriform cortex. Similarly, slice preparations have shown that acetylcholine causes selective presynaptic inhibition of glutamatergic synaptic transmission at feedback synapses, but not at afferent synapses from the lateral olfactory tract (Hasselmo and Bower, 1992).

In visual cortex, acetylcholine sharpens visual receptive field tuning through a reduction in spatial integration (Roberts et al., 2005; Roberts and Thiele, 2008; Silver et al., 2008). Specifically, Roberts et al. (2005) showed that local iontophoresis of acetylcholine into the visual cortex reduces the preferred length of visual stimuli for cortical neurons. This is consistent with the idea that cholinergic modulation reduces the response of neurons to input from more distant points on the retinotopic

map in primary visual cortex, potentially due to presynaptic inhibition of intracortical excitatory synapses that reduces the excitatory spread of activity (Disney et al., 2006; Disney and Aoki, 2008). Consistent with this, administration of acetylcholinesterase blockers to human subjects reduces the retinotopic spread of fMRI activity in response to visual stimuli (Silver et al., 2008).

Consistent with the behavioral data that draw attention to nicotinic receptors playing a particularly important role in attentional processing, physiological studies show that amplification of afferent signals likely depends on nicotinic receptors. High cholinergic levels cause direct nicotinic enhancement of thalamo-cortical afferent synapses (Gil et al., 1997; Disney et al., 2007) and potentiate synapses in the dentate gyrus and region CA1 of the hippocampus (Gray et al., 1996; Giocomo and Hasselmo, 2005). Conversely, suppression of the intrinsic synapses likely depends on muscarinic receptors. Muscarinic receptor blockade has effects on neuronal responses that resemble reductions of attentional response to afferent input in behavior. In the primary visual cortex, blockade of muscarinic but not nicotinic receptors impairs the attentional modulation of V1 neurons (Herrero et al., 2008; Deco and Thiele, 2009).

Acetylcholine tunes network dynamics for more effective processing

Computational models bolster the understanding that the physiological influences of acetylcholine support selective processing of extrinsic stimuli, thereby leading to greater signal to noise quality of perceptual processing. Simulations have shown that the ability to dynamically switch between processing extrinsic versus intrinsic signals improves the quality of encoding of stimuli (e.g., Hasselmo et al., 1992; Linster and Hasselmo, 1997). For example, Hasselmo et al. (1992) simulated the findings of Hasselmo and Bower (1992), showing that application of cholinergic agonist suppresses transmission at intrinsic synapses, using a neural network model of piriform cortex. The model consisted of a single layer of rate coded point neurons receiving feed forward connections, representing afferent projections carrying sensory information, and recurrent feedback connections, representing intrinsic projections carrying information about the activation state of the neural network. The strength of the connection between the model neurons and the recurrent connections were tuned via Hebbian synaptic modification during stimulus presentation. Without cholinergic modulation, the input from the recurrent feedback connections interfered with accurate encoding of stimuli if the activity patterns were similar to previous inputs. However, cholinergic presynaptic inhibition of these recurrent feedback connections during the presentation of new stimuli, simulating the role of acetylcholine in cortical processing, minimized this interference.

The suggestion that acetylcholine serves to improve the signal-to-noise of neural information processing raises the question of why the system would not be tuned for optimal information processing at all time. There are two reasons why the ability to gate external information processing may be advantageous. The first is that there are times when the ability to generally tune out the external world is beneficial (e.g., while consolidating memories, as

discussed in the next section). The second reason is that the ability to selectively gate information processing may allow for flexible modification of behavior to the same environmental stimuli by regulating which brain areas are used in processing (see Gold, 2003 for review of related evidence).

Another view of the role of acetylcholine in attentional processing, described by Yu and Dayan (2005), suggests that acetylcholine selectively gates top-down versus bottom-up processing. This view is in contrast to the previously described model that acetylcholine boosts the signal-to-noise quality of neural processing in that it explicitly assumes that background processing is not only retrieval, but instead can serve as a top-down source of contextual disambiguation. Under this conceptualization, perceptual uncertainty can be offset by selectively gating in top-down biases in neural processing through cholinergic regulation. Such a mechanism allows for effective perceptual inference under ambiguous conditions (Yu and Dayan, 2002). Such a view is well supported by the empirical literature (see Yu and Dayan, 2005, for a relevant review) and merits additional direct investigation both in animal models and through additional simulations.

EPISODIC MEMORY

The pivotal role that acetylcholine plays for cue processing directly predicts the importance of acetylcholine for encoding new memories. The fidelity of a memory is fundamentally limited by how effectively the relevant information was processed at encoding. Indeed, it has been shown that administering scopolamine to subjects prior to encoding a list of words produces drastic reductions in accuracy of subsequent free recall of the words, but that administering after encoding does not impair subsequent free recall (Ghoneim and Mewaldt, 1975; Petersen, 1977). Yet, a surprising number of studies using animal models have reported spared memory function following disruption of the basal forebrain cholinergic system (e.g., Voytko et al., 1994). Sarter and colleagues (2003) point out, however, that the animal subjects of these experiments are typically over trained and are highly familiar with the stimuli and task demands. As such, they suggest that little attentional effort is required to perform these tasks. Consistent with this argument, memory deficits were observed, for example, when novel stimuli were used in a recognition memory task following local infusions of scopolamine into perirhinal cortex in monkeys (Tang et al., 1997) and in recognition studies of novel objects or delayed non-match to sample with novel odors in rats (McGaughy et al., 2005; Winters and Bussey, 2005). Taken together, these data suggest that acetylcholine is specifically beneficial in circumstances when the neural attractors do not yet exist for representing the task stimuli in a manner adequate for good behavioral performance.

Behavioral studies highlight the likely role that nicotinic cholinergic receptors play in supporting the formation of episodic memories. Studies in healthy humans have found improved performance on memory tasks following the administration of nicotine or selective nicotinic agonists (Howe and Price, 2001; Kitagawa et al., 2003). In rodents, nicotine has been shown to boost memory performance in a passive avoidance task (Faiman et al., 1991). Mutant mice, missing the gene for the beta2 subunit of nicotinic receptors were not found to benefit from nicotine on

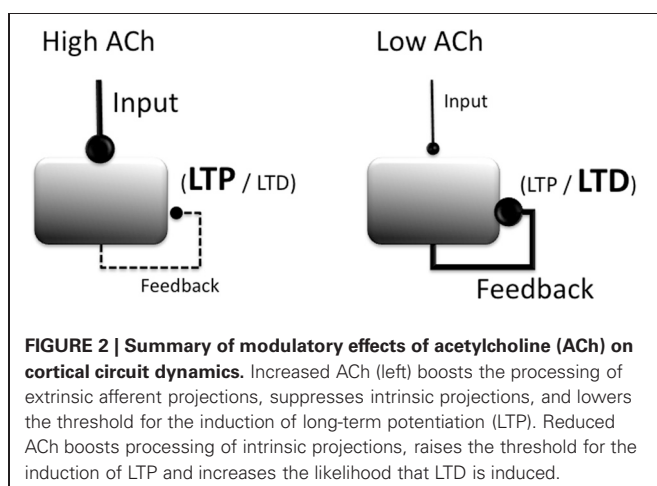
the same task (Picciotto et al., 1995). Across studies performed in animals, both the $\alpha 4\beta 2$ and the $\alpha 7$ nicotinic receptors have been found to support performance on memory tests (Bohme et al., 2004; Chan et al., 2007; Pichat et al., 2007).

Acetylcholine likely supports the creation of novel attractors in cortical circuits in two ways. The first, as described in the previous section, is to increase the extent that afferent signals influence cortical activity while simultaneously decreasing the extent that intrinsic signals influence activity. The second way, which will be described in greater detail in this section, is to enhance physiological phenomena that support the encoding of memories. Hasselmo (1999, 2006) reviews a number of such phenomena; here, we discuss two that are particularly relevant for existing computational models: (1) lowering the threshold for the induction of LTP, and (2) boosting the amplitude of theta oscillations. Each are described below.

Acetylcholine enhances LTP

Neurophysiological studies demonstrate that acetylcholine modulates synaptic plasticity. For example, in rats, LTP induced by tetanic stimulation of synapses on CA1 basal dendrites was shown to be greatest when the stimulation was delivered during walking relative to during awake-immobility, slow wave sleep or rapid eye movement sleep (Leung et al., 2003). This effect was blocked by either scopolamine or by IgG-saporin lesions of the medial septal cholinergic projections into the hippocampus, suggesting that the effect was due to the increased release of acetylcholine that occurs during walking (Marrosu et al., 1995; see also Ovsepiyan et al., 2004).

In vitro studies similarly show that cholinergic agonists, including selective agonists for both muscarinic and nicotinic receptors, lower the threshold for LTP induction in region CA1 of the hippocampus (Blitzer et al., 1990; Huerta and Lisman, 1993, 1995; Adams et al., 2004), in the EC (Yun et al., 2000; Cheong et al., 2001), and in piriform cortex (Patil et al., 1998). For example, a single burst of high frequency stimulation, although typically ineffective at inducing synaptic plasticity, is sufficient to induce LTP in hippocampal CA1 neurons following bath application of carbachol (Huerta and Lisman, 1993). These effects of cholinergic modulation are illustrated in **Figure 2**.



Nicotinic receptors are well positioned to alter the dynamics of plasticity induction. Application of nicotine to hippocampal slices facilitates the induction of LTP (e.g., Fujii et al., 1999). Independent pharmacological manipulation of the $\alpha 4\beta 2$ and $\alpha 7$ receptors have revealed that both are capable of inducing LTP but that the $\alpha 7$ receptors, in particular, induce a more stable form of LTP (Krocker et al., 2011). Notably, however, nicotinic receptors can also inhibit the induction of LTP by exciting local inhibitory interneurons (e.g., Ji et al., 2001) thereby inducing a temporal and spatial sensitivity to the influences of cholinergic modulation.

Theta rhythms are important for learning

The amplitude and occurrence of hippocampal theta oscillations are intimately tied to acetylcholine further motivating the idea that acetylcholine plays an important role for memory encoding. Theta, a prominent oscillatory rhythm that is clearly observed in local field potentials of the hippocampus of rats (e.g., Vanderwolf, 1969; Buzsaki et al., 1983; Buzsaki, 2002) and humans (Kahana et al., 1999) appears when stimuli are presented during memory tests in humans (Raghavachari et al., 2001). The amplitude of theta is predictive of improved memory encoding. In humans, for example, Sederberg et al. (2003) found that the amplitude of intracranially recorded theta oscillations during encoding in a free recall task was significantly greater for subsequently recalled words than for forgotten words. Similarly, rabbits reach a criterion performance level in an eye-blink conditioning protocol in fewer trials when trial presentation was restricted to epochs of elevated hippocampal theta power than when trial presentation was restricted to epochs of low theta power (Griffin et al., 2004; see also Asaka et al., 2000, 2002).

The link between theta and learning is extended by an interesting set of findings demonstrating a dependence between theta phase and the induction of LTP. In short, LTP is preferentially induced during the peak of theta in the local field potential whereas LTD is preferentially induced during the trough of theta in the local field potential. This was first discovered by Huerta and Lisman (1995) when they found that a single tetanic stimulation burst was sufficient to induce LTP in a hippocampal slice when the stimulation was delivered selectively at the peak of theta oscillations generated following the bath application of carbachol. Further, they found that co-application of a muscarinic antagonist blocks this induction of LTP. This phase specific induction of plasticity has since been replicated *in vivo* in anaesthetized animals (Hölscher et al., 1997) and in awake behaving animals (Hyman et al., 2003).

Acetylcholine modulates theta

Theta rhythm is modulated by cholinergic and GABAergic inputs from the medial septum via the fornix (Stewart and Fox, 1990; Vertes and Kocsis, 1997; Buzsaki, 2002), and increases in acetylcholine are associated with theta oscillations (Monmaur et al., 1997; Zhang et al., 2010). However, hippocampal theta may depend on two separate frequency components, namely a cholinergic-independent, movement-related theta rhythm at 8–9 Hz (type 1) and a lower frequency 6–7 Hz cholinergic-dependent component (type 2) (Kramis et al., 1975; Jeewajee

et al., 2008). *In vivo* studies of rats have shown that infusions of cholinergic agonists into the medial septum increase hippocampal theta power whereas infusions of cholinergic antagonists reduce hippocampal theta power (for a detailed review, see Vinogradova, 1995). Cholinergic inputs from the basal forebrain are important for this oscillatory activity; in rats, lesioning the septal nuclei substantially reduces hippocampal theta (Green and Arduini, 1954) and selective lesions of the septal cholinergic neurons greatly decreases the magnitude of theta (Lee et al., 1994).

Models show how theta may support learning

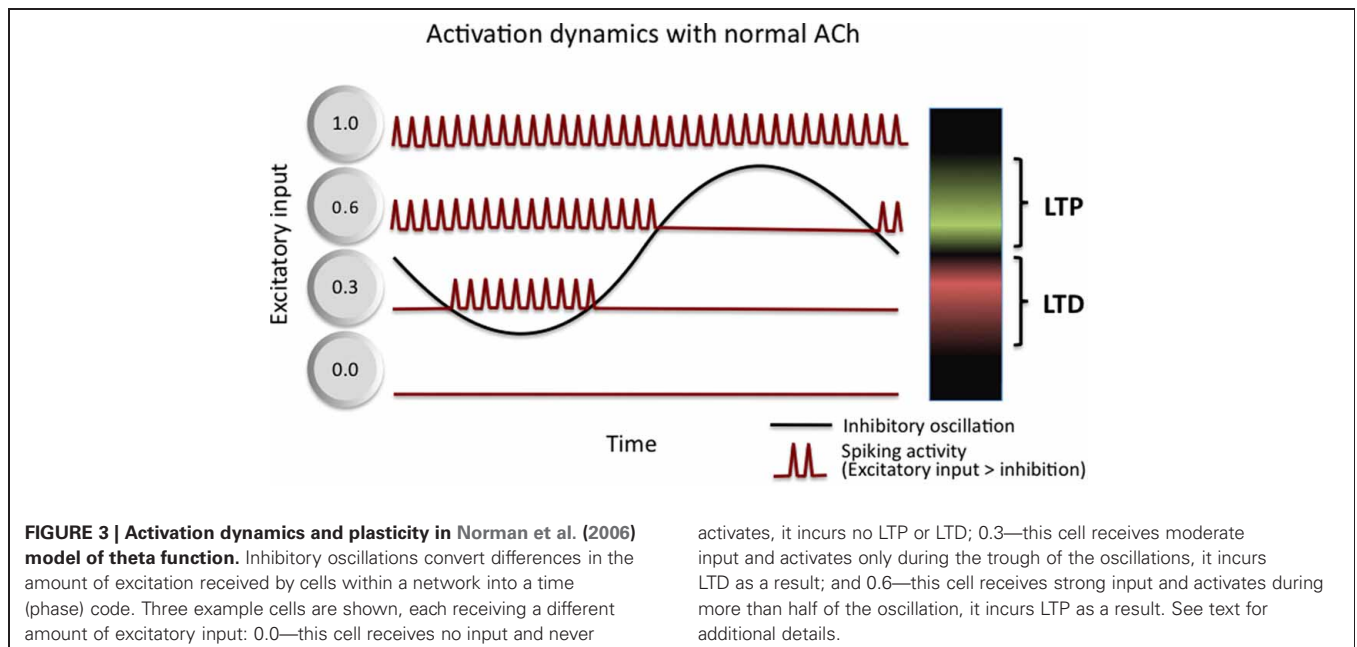
Computational models show that the ability of acetylcholine to simultaneously modulate the plasticity induction threshold and the relative strength of intrinsic and extrinsic projections has important functional effects. For example, Linster and Hasselmo (1997) found that such modulation had a substantial impact on the ability of a neural network model of piriform cortex to perform pattern separation among similar odor stimuli. Specifically, by blocking the retrieval of previously stored representations (through suppression of transmission at intrinsic synapses), the state of the network during presentation of novel stimuli was less biased toward states that had been previously potentiated.

A related model, described by Hasselmo (1994), underscores the importance of blocking the retrieval of prior associations during novel encoding. This model demonstrates that a break down in the separation between retrieval and encoding can lead to the excessive strengthening of synapses. Across a range of simulations, it was shown that if left unchecked, such runaway growth of synapses can manifest in symptoms similar to those seen in Alzheimer's disease including neural degeneration, retrograde amnesia, dementia, and eventually anterograde amnesia (see also Hasselmo, 1997).

Along these lines, a model proposed by Hasselmo et al. (2002) suggests that encoding and retrieval were kept distinct

by occurring at opposite phases of the theta rhythm in the hippocampus. In this model, network parameters such as the strength of afferent projections into area CA1 from EC and the threshold for modification of synapses from area CA3 into CA1 are dynamically modulated on each theta cycle. Specifically, at the trough of theta (recorded at the fissure or at the peak of theta recorded at the CA1 cell layer) the strength of EC projections into CA1 are strongest, and the threshold for LTP induction at synapses from CA3 is lowest, allowing for new encoding. Conversely, at the peak of theta (at the fissure, trough at CA1 cell layer) the strength of CA3 projections into CA1 are strongest and depotentiation of the synapses of these projections onto CA1 neurons occurs most easily, providing for retrieval (and forgetting) of previously learned memories. As such, theta may serve to cycle between a network-tuning regime optimized for encoding new memories and a tuning regime to allow for the expression (and extinction) of previous learning.

A complementary model of the role of theta in memory encoding suggests that theta boosts the signal-to-noise quality, not just of neural information processing, but of memory encoding as well (Norman et al., 2005, 2006). As summarized in **Figure 3**, Norman and colleagues show how inhibitory oscillations, such as theta, can parse neuron-by-neuron differences in sub-threshold depolarization into a phase code. Specifically, only highly excited (i.e., most depolarized) cells activate during the highest inhibition phase while less excited cells activate during the lower inhibition phase. By separating the activation of neurons in time based on the amount of excitation they receive, the oscillation then allows for differential treatment of strongly excited neurons and moderately excited neurons. They argue that the moderately excited neurons interfere with the effective processing of the strongly excited neurons, and as such, serve as a source of noise. They then suggest that phase-specific synaptic induction of LTP and LTD (as described, for example, by Huerta and Lisman, 1995)



serves to boost the signal to noise of memories by strengthening neurons that activate during the high inhibition phase (strongly active) and to weaken neurons that activate during the low inhibition phase (moderately active). Through a series of simulations, they demonstrate that such oscillation driven learning accelerates learning, improves pattern separation of correlated input patterns, boosts the memory capacity of neural networks (Norman et al., 2006), and accounts for counterintuitive behavioral performance on episodic memory tests in humans (Norman et al., 2007).

A prediction of this framework is that LTP versus LTD should be induced as a result of strong versus moderate excitation, respectively. Newman and Norman (2010) were able to verify this prediction by relating the trial-by-trial activation of cortical representations (as assessed with multivariate pattern analysis of scalp EEG data) to trial-by-trial behavioral performance. In the context of cholinergic modulation, this hypothesized relationship would additionally predict that local infusions of scopolamine into the hippocampus would alter the phases of theta at which tetanus stimulation would induce LTP. Specifically, because scopolamine would depress the afferent projections into CA1, each tetanic pulse would provide less excitation thereby shifting the baseline relationship between theta phase and excitation. Thus, there should exist a range of phases at which tetanus stimulation should induce LTD following a scopolamine infusion that would have induced LTP following a saline infusion.

SPATIAL MEMORY

While behavioral studies have provided clear evidence that acetylcholine plays an important role in spatial memory, a number of studies have also challenged this result. A recent comprehensive review of the role of acetylcholine and spatial memory by Deiana et al. (2011) includes discussion of both types of work; thus, we have restricted the scope of our review of these points to a few representative examples. We instead focus our attention on reviewing relevant findings from studies employing single unit recording techniques in awake behaving animals during manipulations of the cholinergic system. No formal computational models of the physiological influences of acetylcholine on spatial processing exist to our knowledge. Thus, instead, we present the oscillatory interference model of grid cell spatial tuning and suggest that acetylcholine may influence the spatial memory system utilizing theta rhythms as an intermediary.

Mixed evidence regarding role of acetylcholine in spatial memory

A wealth of evidence exists demonstrating a functional link between cholinergic function and spatial memory (see Deiana et al., 2011, for a comprehensive review). For example, in humans, administration of muscarinic antagonists prior to performing a virtual analog of the Morris water maze disrupts hippocampal activation as monitored through fMRI (Antonova et al., 2011). In rats, systemic administration of muscarinic antagonists to rats prior to the encoding phase of spatial memory has consistently been found to induce memory deficits in tasks such as the Morris water maze (e.g., Sutherland et al., 1982). Similarly, immunotoxic lesions of the cholinergic septo-hippocampal projection impair performance on the Morris water maze, in delayed

non-match to position tasks on a T-maze, and on a win-shift radial arm maze task (e.g., Leanza et al., 1995; Janis et al., 1998; Johnson et al., 2002). Mice without the beta2 nicotinic receptor subunit exhibit reduced slow exploratory behavior and selective re-expression of the beta2 subunit in the VTA is sufficient to reestablish exploratory behavior (Maskos et al., 2005).

A number of studies have also failed to find deficits in spatial memory tasks following disruption of the cholinergic system (see Deiana et al., 2011 for extensive discussion of this point). In one such line of evidence, Baxter and colleagues have shown that manipulations, such as the selective deafferentation of the cholinergic projections from the basal forebrain for example, elicit minimal, if any, performance impairments on spatial memory tasks (e.g., Baxter and Gallagher, 1996; McMahan et al., 1997; Vuckovich et al., 2004). A separate line of work by Schallert and colleagues has also provided evidence of preserved spatial memory function despite severe disruption of the cholinergic system (Day and Schallert, 1996). Studies utilizing alpha7 nicotinic receptor knockout mice have found little impairment on spatial memory tasks (e.g., Paylor et al., 1998), but this may be the result of compensatory effects in light of a finding showing that reduced surface expression of alpha7 receptors subsequently does impair performance on the Morris water maze (Curzon et al., 2006).

Unit recordings provide window into spatial processing

The hippocampus and medial EC play crucial roles in navigation; lesions of either region lead to deficits on spatial memory tasks (e.g., Morris et al., 1982; Steffenach et al., 2005). The precise roles of such medial temporal lobe structures is a topic of debate and beyond the scope of this review (e.g., see Gray and McNaughton, 1983; McNaughton et al., 1996; Moser et al., 2008; Dickerson and Eichenbaum, 2010), for relevant viewpoints). However, unit recordings in the hippocampus and the medial EC have reliably found that the position of an animal is among the most clearly observable correlates of fluctuations in neuronal activity (e.g., O'Keefe and Dostrovsky, 1971; Ekstrom et al., 2003). Cells in the pyramidal cell layers of hippocampal regions CA1 and CA3, for example, preferentially fire in distinct subregions of testing enclosures, and, as such, have been termed *place cells*. Within the medial EC, Fyhn and colleagues (2004) found that cells fired action potentials, not at a single location like place cells, but rather, at multiple places, marking the vertices of a grid of equilateral triangles, earning them the label *grid cells* (Hafting et al., 2005).

The activity of spatially tuned cells of the hippocampus and EC is believed to provide a window into spatial information processing (e.g., Colgin et al., 2008 and the ensemble activity of spatially tuned populations of hippocampal and entorhinal cells is believed to serve as the substrate of spatial memory (e.g., McNaughton et al., 2006). As such, manipulations that alter the tuning of place cells or grid cells may, equally, provide insight into the mechanisms that subserve spatial memory.

Cholinergic effects on unit recordings

Evidence of the involvement of acetylcholine in deriving the spatial tuning of place cells and grid cell suggests multiple modes of interaction between spatially tuned cells and the cholinergic

system. At a broad level, acetylcholine appears to play a role in the adaptive remapping of spatial tuning following environmental modifications. The location within a testing enclosure where a given cell fires maximally can differ from one enclosure to the next; subtle alterations of the testing enclosure are sufficient for inducing such remapping (Muller and Kubie, 1987), but do not guarantee that remapping occurs. Immuno-toxic lesions of the cholinergic projections into the hippocampus and EC significantly decrease the likelihood that remapping occurs upon entrance to a novel testing environment (Ikonen et al., 2002). Individual differences in the prepotency to remap following such alterations predict the level of spatial memory performance on an independent task (such as the Morris water maze task; e.g., Wilson et al., 2003).

At a more local level, evidence for involvement of acetylcholine in the local network effects responsible for resolving the tuning of place cells in the hippocampus comes from a study by Brazhnik et al. (2004), in which they recorded place cell activity during local infusions of scopolamine into the hippocampus. They found that such infusions lead to significant reductions in the reliability of place cell tuning as assessed both through shifts in place field position and through a decrease in the ratio of in-field versus out-of-field spiking (see also, Brazhnik et al., 2003 for similar results). Unfortunately, the technical challenges inherent to stably recording from single units during local infusions have limited the study of the local influences of pharmacological agents. Evidence from a study employing systemic infusions of scopolamine, however, similarly suggests that entorhinal grid cells also depend critically on the cholinergic system to maintain their spatial tuning (Newman and Hasselmo, 2011). Specifically, they found that systemic infusions of scopolamine induce significant decreases in both the spatial and temporal periodicity of entorhinal grid cells. As such, spatial information processing in the hippocampus is subject to both local influences of acetylcholine (as shown by Brazhnik et al., 2004) and to the influences of cholinergic modulation on the entorhinal grid cells which are believed to serve as a source of spatial information that is ultimately reflected in the spatial correlates of CA1 and CA3 place cell activity (Moser et al., 2008).

Theta may mediate role of acetylcholine in spatial processing

The precise mechanism by which acetylcholine contributes to the tuning of place cells and grid cells is not clearly understood. A promising hypothesis is that the spatial tuning of such cells is affected by cholinergic modulation through an intermediary: theta rhythms (e.g., O'Keefe and Recce, 1993; Blair et al., 2007; Burgess et al., 2007; Hasselmo et al., 2007). Unit recordings of both place cells and grid cells provide compelling support for an intimate relationship between theta and the function of these cells. The spiking of both place cells and grid cells exhibits theta rhythmicity and theta phase locking, demonstrating a clear interaction between the two (e.g., O'Keefe and Recce, 1993; Hafting et al., 2005). Additionally, the existence of phase precession (i.e., the precession of spiking from late phases of theta to progressively earlier phases as a rat runs through a firing field) in both place cells and layer II and V grid cells further suggests an intimate relationship between theta and the representation of space in the

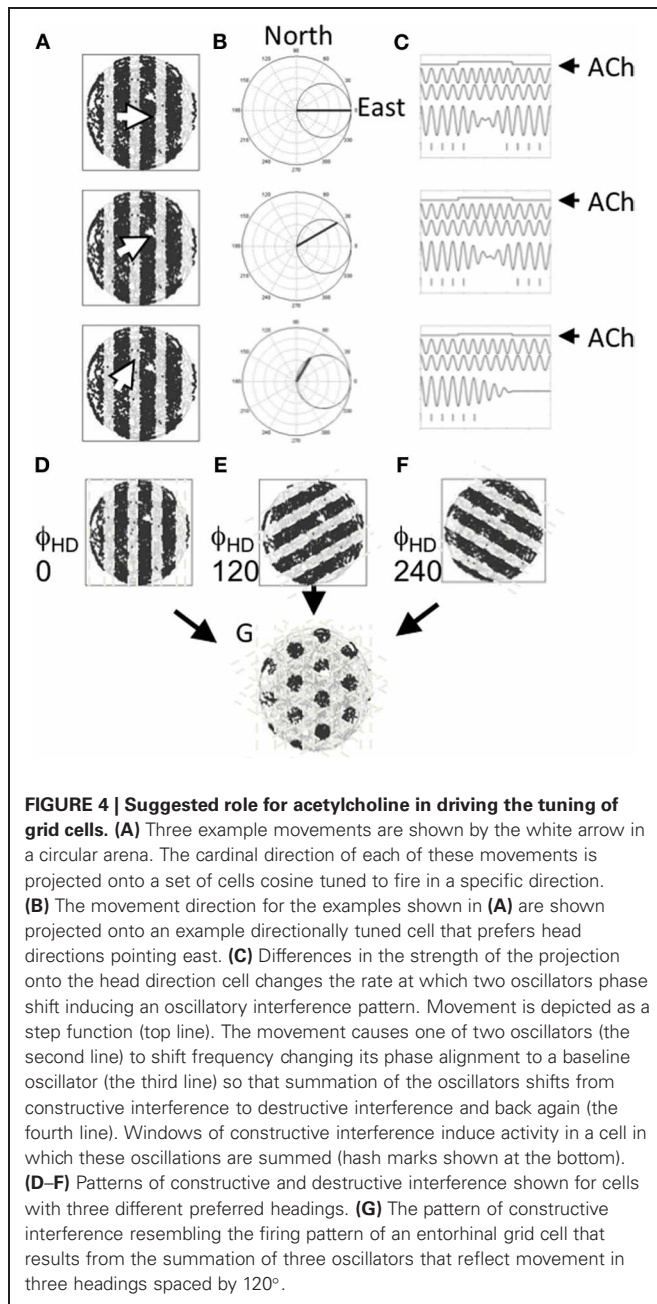
hippocampus and medial EC (O'Keefe and Recce, 1993; Hafting et al., 2008).

It is possible that the correspondence between the activity of spatially tuned cells and theta does not reflect a functional link, but rather, results from a shared involvement in medial temporal lobe processing. To test this, Brandon and colleagues (2011) tracked the spatial and temporal periodicity of entorhinal grid cells as they temporarily blocked theta oscillations in the hippocampus and EC via infusions of muscimol (a GABA(A) agonist) into the medial septum. They found that both the spatial tuning and theta rhythmicity of the grid cells was significantly reduced following the inactivation of the medial septum. Further, they found that the time course of the recovery of the spatial tuning paralleled the time course of the recovery of theta amplitude. A similar pattern of results was also found by Koenig et al. (2011). These findings strongly support the hypothesis that the spatial tuning of grid cells is functionally linked to theta rhythms.

Inactivation of the medial septum also influences hippocampal place cells (in both CA1 and CA3), but in a less robust fashion. Koenig et al. (2011), for example, found a significant but modest (relative to the grid cells) reduction in the correlation of the spatial tuning of place cells following the inactivation of the medial septum. Similarly, Shapiro et al. (1989) found that the spatial tuning of place cells on a radial arm maze becomes more dispersed and more easily disrupted following lesions of the fornix (see also Miller and Best, 1980). Interestingly, Shapiro et al. (1989) also found that the fornix-lesion induced changes were partially reversed following intrahippocampal grafts of fetal basal forebrain tissue rich in cholinergic neurons, reinforcing the hypothesis that diffuse release of acetylcholine facilitates the tuning of place cells.

Oscillatory interference model

Mechanistically, Burgess et al. (2007) suggested that theta may drive the formation of the spatial tuning pattern observed in entorhinal grid cells as a result of multiple oscillators coming into and out-of phase with each other as a rat moves. At its essence, the model suggests that grid cells fire when the sum of at least two oscillators crosses a threshold. Importantly, the frequency of each oscillator is determined by the speed of the animal in a particular heading (e.g., north)—that is, when the rat is moving in the preferred direction (north in this example) the frequency of that oscillator increases proportional to the speed of the animal. If however, the animal moves in a direction orthogonal to the preferred direction (e.g., west), the oscillator returns back to a baseline frequency, assumed to be in the theta band, to indicate a zero magnitude projection on the preferred direction. The preferred direction of the two oscillators is assumed to differ by an integer multiple of 60°. When two such velocity controlled oscillators are summed and thresholded, the interference pattern closely resembles the spatial tuning pattern of entorhinal grid cells. This is summarized in **Figure 4**. Several variants of this oscillatory interference model of grid cell formation have since been described to address challenges faced by the first version of this model (e.g., Blair et al., 2008; Burgess, 2008; Hasselmo, 2008, 2009; Hasselmo et al., 2009; Zilli and Hasselmo, 2010).



Oscillatory interference models have provided a number of testable predictions that have since been supported by empirical evidence. Most clearly, the model predicts that grid cell tuning requires an intact theta rhythm. The findings of Brandon et al. (2011) provide clear support for this prediction in that medial septal inactivation both significantly reduced the amplitude of theta oscillations and significantly decreased the spatial tuning of grid cells. Additionally, the model predicted that shifts in firing field spacing observed along the dorsal-ventral axis of the hippocampus should correspond to differences in the frequency of intrinsic oscillators along the same axis (Burgess et al., 2007). Consistent with this hypothesis, Giocomo and Hasselmo

(2007) found that the frequency of subthreshold membrane oscillations in stellate cells (putative grid cells) was significantly faster in dorsal medial EC (3.8 and 4.9 mm below the dorsal surface of the brain) than ventral medial EC (between 4.9 and 7.1 mm below the dorsal surface of the brain, see also Giocomo and Hasselmo, 2008, 2009; Yoshida et al., 2011). Finally, Jeewajee et al. (2008) found that the rhythmic firing of grid cells increased with running speed as was further predicted by the model.

The central role of theta oscillations in the oscillatory interference models, by proxy, instills an important role for acetylcholine in the regulation and maintenance of the spatial tuning of grid cells. For example, given the purported role of acetylcholine in modulating theta frequency (e.g., Givens and Olton, 1995), it is likely that environmental factors that alter acetylcholine release would impact the grid cell network. For example, novelty triggers increased acetylcholine release (e.g., Acquas et al., 1996; Giovannini et al., 2001) and decreased theta frequency (e.g., Jeewajee et al., 2008). As such, the oscillatory interference model suggests that novelty should result in the expansion of grid field spacing. This result was supported by a unit recording study performed by Barry et al. (2009, 2012), in which, they found that the spacing of grid cells expanded by as much as 40% when rats were first placed in a novel testing enclosure. As the rats gained experience with the enclosure, the size of the fields gradually decreased their spacing. Also consistent with this prediction, Heys et al. (2010) demonstrated that, *in vitro*, bath application of carbachol reduced the resonant frequency of layer II stellate cells.

SYNTHESIS AND SUMMARY

Our goal, in this review, was to highlight the important role that computational models have played in linking the empirical work that has been done on the physiological and cognitive influences of acetylcholine. The symbiotic relationship between computational theory, physiology, and behavior is particularly strong in the case of acetylcholine due to the multitude of influences that acetylcholine has, particularly at the physiological level. These influences frequently appear contradictory (e.g., ability to cause both enhanced LTP and acute presynaptic inhibition of synaptic potentials) but can be shown to have a coherent cognitive function through simulation (e.g., allow for stimuli to be clearly represented without previously formed memories obscuring the perception). In each case, the models first provide a coherent framework to account for existing data but then serve their true function second: to provide testable hypotheses that serve to focus new empirical explorations. A wide variety of models were described in this review, each offering a distinct view on acetylcholine and each with different implications for future research. Thus, by way of synthesis, the remainder of this manuscript will aim to catalog these views and implications as well as to highlight important unanswered questions in the empirical and theoretical domains. Because the connection between cholinergic function and spatial memory, in particular, remains poorly understood, we focus on drawing points of potential contact between each of the previously described mechanisms and spatial processing.

Persistent spiking

Acetylcholine activates a calcium-sensitive non-specific cation current (I_{CAN}) in some medial EC neurons that allows for these cells to spike persistently following a single pulse of stimulation in slice preparations (e.g., Klink and Alonso, 1997). Although already discussed in the context of working memory, it is possible that this mechanism additionally contributes to spatial information processing. For example, persistent spiking cells have been proposed to play the role of the velocity controlled oscillators in a variant of the oscillatory interference model of grid cell tuning (Hasselmo, 2008). As such, the degraded spatial tuning of grid cells observed following systemic infusions of scopolamine may result from the disruption of the firing of persistent spiking cells in the absence of cholinergic activation of I_{CAN} . Additional investigation, specifically on the influences of local infusions of scopolamine, into the medial EC, on grid cells is required before strong conclusions can be drawn on this hypothesis.

Gating of extrinsic afferent projections

Acetylcholine simultaneously boosts the strength of afferent projections while depressing the strength of intrinsic projections (e.g., Hasselmo and Bower, 1992). Modeling has shown that these effects serve to enhance the encoding of new representations to support processing of environmental stimuli (e.g., Hasselmo et al., 1992) or to allow contextual cues to disambiguate perceptual processing (Yu and Dayan, 2005). Both processes are likely to play important roles for spatial information processing. Empirically, this can be explored through analyses of inter regional coherence of local field potential signals. Several exciting recent studies employing these techniques have revealed insights into the means by which anatomically distinct areas communicate (Buschman and Miller, 2007; Colgin et al., 2009), however, none have yet to investigate the influence of cholinergic modulation on such interregional coherence metrics.

Gating of synaptic plasticity

In parallel to its modulation of projection strengths, acetylcholine reduces the threshold for the induction of LTP (e.g., Huerta and Lisman, 1995). An implication of these results is that, under circumstances of depleted acetylcholine, processing of environmental stimuli is likely to occur more slowly and less effectively. Further, even once stimuli are successfully represented little benefit of this processing can be reaped on subsequent encounters with the relevant environmental stimuli as a result of the high threshold for the induction of LTP. As such, cholinergic blockade is likely to elicit particularly strong deficits in the processing of new stimuli (Sarter et al., 2005). In the context of spatial memory tasks, this suggests that novel testing enclosures and task demands, for which the subject has no adequate neural representation, will be most likely to elicit strong behavioral deficits following depletion of acetylcholine.

Top-down recruitment of control

One of the few sources of regulatory input into the basal forebrain from neocortex originates in the frontal cortex (Carnes et al., 1990). This input is attributed with the function of

exerting top-down control over the cholinergic system. For example, this projection is likely to allow for top-down recruitment of attentional effort (e.g., Sarter et al., 2006). In the domain of spatial memory, this suggests that deficits are likely to be observed when the subject must exert top-down control over a maladaptive behavioral strategy. For example, systemic administration of muscarinic antagonists induces abnormal behaviors such as increased stereotypy and locomotor activity. This has been described by Schallert et al. (1980) who reported that rats can become “trapped” by simple environmental features such as corners or dead-ends of a track. They describe, for example, how rats can become stuck in a loop of stereotyped vertical or horizontal scanning movements at the dead-end of a linear track, in which they fail to ever turn around to face the open end of the track. Modification of the track to eliminate dead-ends (e.g., through the use of a circle track) can prevent trapping from occurring. Alternately, DeVietti et al. (1985) found that pre-exposure of the testing apparatus prior to infusion of atropine significantly reduced the time required to become un-trapped, for example by the dead-end.

Relatedly, Day and Schallert (1996) argued that impairments of spatial memory, as assessed in the Morris water maze, following cholinergic blockade were the result of a deficit in effective strategy selection, not in spatial processing. To test this hypothesis, they assessed the rate of learning in a Morris water maze task for animals administered a systemic injection of atropine relative to animals administered saline infusions. Critically, they employed a training protocol designed to promote the use of a spatial search strategy. Specifically, they utilized a training protocol in which the escape platform used on the first trials was almost as large as the tank. Then, over trials, the platform was replaced with smaller and smaller platforms until it had effectively shrunk into a specific quadrant of the tank. They found no difference in the rate of learning or difference in behavior on the final probe trial. They suggest that this finding indicates that cholinergic block does not impair spatial processing, but rather, the selection of a proper search strategy.

New models of cholinergic function

Amperometric monitoring of acetylcholine demonstrates that cholinergic modulation occurs at both fast and slow timescales (e.g., Parikh et al., 2007). This raises questions about the functional consequences of these different regimes. These time course effects are particularly difficult to intuit given the diversity of cholinergic receptor subtypes, each with different desensitization rates and distinct physiological influences. Thus, a fruitful avenue for future models would be to characterize the functional properties of each of these regimes.

CONCLUSIONS

We have described a number of models linking the behavioral role of acetylcholine to specific cellular effects of acetylcholine. Specifically, models of the modulation of cellular persistent spiking by acetylcholine suggest a mechanism for active maintenance in working memory that might also contribute to the path integration mechanisms underlying grid cell responses. Models of cholinergic modulation of circuit dynamics, such as

the strength of afferent input relative to recurrent feedback and threshold for the induction of LTP versus LTD, provide a framework for understanding the role of acetylcholine in enhancing attention to sensory stimuli and encoding of memories. Finally, models of network theta rhythm oscillations suggest how theta may serve as an intermediary between cholinergic regulation and episodic and spatial memory function. Unit recording studies in cortical structures serve to connect what has been learned about the physiological influences of acetylcholine *in vitro* to behavioral

effects. Such studies have provided support for existing models but additional unit recording studies will be necessary to further develop models linking behavioral function to the specific cellular effects of acetylcholine in cortical structures.

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