High acetylcholine sets circuit dynamics for attention and encoding; Low acetylcholine sets dynamics for consolidation

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Introduction.

Extensive physiological research has demonstrated a number of effects of acetylcholine within the hippocampus, piriform cortex, neocortex and thalamus (Krnjevic and Phillis, 1963; Krjnevic et al., 1971; see review in Hasselmo, 1995). Here the review will focus on data regarding cholinergic modulation in the hippocampus and piriform cortex, but data from the neocortex suggests similar principles apply in other cortical structures.

At times the effects of acetylcholine on specific neuron types and synaptic pathways in cortical structures appear paradoxical and inconsistent. For example, why should acetylcholine simultaneously enhance pyramidal cell spiking through depolarization (Krjnevic et al., 1971; Cole and Nicoll, 1984), while suppressing excitatory glutamatergic synaptic transmission at intrinsic synapses in the hippocampus (Hounsgaard, 1978; Valentino and Dingledine, 1981; Dutar and Nicoll, 1988; Hasselmo and Bower, 1992; Hasselmo and Schnell, 1994) and neocortex (Brocher et al., 1992; Gil et al., 1997; Hsieh et al., 2000)? Similarly, why should acetylcholine in the hippocampus simultaneously depolarize interneurons (Frazier et al., 1998; McQuiston and Madison 1999a,b; Alkondon and Albuquerque, 2001) while suppressing hippocampal inhibitory synaptic transmission (Pitler and Alger, 1992; Patil and Hasselmo, 1999)? A unifying theoretical framework is required for understanding these disparate physiological effects.

Computational modeling offers a unifying theoretical framework for understanding the functional properties of acetylcholine within cortical structures (Hasselmo, 1995; Hasselmo, 1999). This article will provide a description of how the different physiological effects of acetylcholine could interact to alter specific functional properties of the cortex. In particular, acetylcholine enhances the response to afferent sensory input while decreasing the internal processing based on previously formed cortical representations. These same circuit level effects can be categorized with different colloquial terms at a behavioral level, sometimes being interpreted as an enhancement of attention, sometimes as an enhancement of memory encoding. But the same change in circuit level dynamics could underlie all these behavioral effects. In this article, we will present the basic theoretical framework of enhanced response to input, with reduced feedback processing. We will then discuss individual physiological effects of acetylcholine in the context of this framework. Finally, we will discuss how the loss of cholinergic modulation will shift network dynamics toward those appropriate for the consolidation of previously encoded information.

Evidence for diffuse modulatory state changes caused by acetylcholine

The computational models described here assume that acetylcholine causes diffuse modulatory state changes within cortical structures. This assumption is based on the following evidence: 1.) microdialysis studies show dramatic changes in acetylcholine level in cortex during different stages of waking and sleep; 2.) anatomical studies of cholinergic fibers suggest diffuse modulatory influences on cortical function, and 3.) the slow transition between different states is supported by data showing a relatively slow time course of changes in physiological effects of acetylcholine.

1.) Microdialysis studies of acetylcholine

The physiological effects of acetylcholine on cortical circuits will change in magnitude as the extracellular concentration of acetylcholine changes within cortical circuits. Microdialysis studies demonstrate striking changes in the levels of acetylcholine within the cortex during different behaviors (Giovanninni et al., 2001) and during different stages of waking and sleep (Jasper et al., 1971; Kametani and Kawamura, 1990; Marrosu et al, 1995;). In particular, acetylcholine levels are higher during active waking in freely moving rats (Kametani and Kawamura, 1990) and cats (Marrosu et al., 1995), as summarized in Figure 1. In experiments on rats, active waking is defined as periods of time during which the rat is actively exploring the environment, scurrying along the walls or across the floor, sniffing novel objects and rearing up extensively. In EEG recordings from hippocampus and entorhinal cortex, this period is characterized by large amplitude oscillations in the theta frequency range (Buzsaki, 1989; Bland and Colom, 1993; Chrobak and Buzsaki, 1994) , whereas the neocortex displays high frequency, low-amplitude activity with local synchronization (Steriade et al., 1996) and some periods of theta in certain regions (Maloney et al., 1997). The increase in acetylcholine during waking is particularly strong when a rat is initially exposed to a novel environment, apparently in association with both the increase in fear elicited by such an environment, as well as the increase in attention to stimuli within the environment (Giovanninni et al., 2001). Cortical acetylcholine levels rise dramatically during performance of tasks requiring sustained attention for detection of a stimulus (Himmelheber et al., 2000; Arnold et al., 2002).

In contrast, acetylcholine levels decrease during periods of “quiet waking” during which animals are immobile or performing consummatory behaviors such as eating or grooming (Marrosu et al., 1995). Recordings of the EEG in this phase of behavior shows irregular EEG activity with periodic appearance of brief, large amplitude events

termed sharp waves (Buzsaki, 1986; Chrobak and Buzsaki, 1994). Acetylcholine levels decrease even more dramatically during slow wave sleep, to levels less than one third of those observed during active waking (Jasper et al., 1971; Kametani and Kawamura, 1990; Marrosu et al., 1995). Slow wave sleep is defined by the characteristic EEG phenomena occurring during this phase of sleep, particularly the large amplitude, low frequency oscillations found in neocortical structures and commonly termed slow waves (Steriade, 1994; Steriade, 2001). Thus, there are striking changes in acetylcholine levels within cortical circuits which are correlated with striking changes in behavior and electroencephalographic dynamics within these structures. Computational modeling can help to elucidate how the changes in acetylcholine concentration could contribute to the change in EEG dynamics and functional properties of cortical circuits during these different periods.

2.) Anatomical support for volume transmission

In the computational modeling work presented here and previously (Hasselmo et al., 1992; Hasselmo and Schnell, 1994; Patil and Hasselmo, 1999; Linster and Hasselmo, 2001), we model acetylcholine effects as being diffuse and relatively homogeneous within cortical circuits. That is, we assume that volume transmission provides a general activation of cholinergic receptors at a number of receptor sites, rather than focused effects localized at individual synaptic contacts (Descarries et al., 1997). Anatomical evidence supports this concept of volume transmission for acetylcholine. In particular, the axonal varicosities on cholinergic fibers predominantly are not accompanied by specific post-synaptic densities (Umbriaco et al., 1994; 1995), suggesting that the release sites of acetylcholine are not associated with specific clusters of cholinergic receptors. For example, in the hippocampus, only 7 percent of the axonal varicosities on cholinergic fibers are associated with junctional specialization, whereas all GABAergic varicosities showed synaptic specializations (Umbriaco et al., 1995). In the parietal cortex, less than 15% of cholinergic varicosities were associated with post-synaptic junctions (Umbriaco et al., 1994). This data supports the concept of volume transmission for acetylcholine within the hippocampus and neocortex.

In addition to this anatomical data, functional considerations support the concept of volume transmission. The number of cholinergic neurons within the basal forebrain is relatively small, on the order of 10^5 in the rat (Mesulam et al., 1983a, 1983b). These cholinergic neurons innervate cortical structures containing many orders of magnitude more pyramidal cells and interneurons. These structures mediate encoding of a large number of different patterns of activity in semantic memory. This large discrepancy in number of neurons raises serious doubts about the

ability of the basal forebrain to selectively regulate activity associated with specific memory patterns in cortical structures. Even if each stored pattern were being regulated by only a single basal forebrain neuron, the number of stored patterns in semantic memory would far exceed the capacity of the basal forebrain for selective regulation. In contrast, this relatively small number of neurons could work in a more cohesive manner to set different functional properties during longer functional stages of waking and sleep. There are sufficient numbers of cholinergic neurons to regulate transitions between active waking and quiet waking, and the numbers are sufficient to allow these functional stages to be regulated separately for larger cortical regions.

3.) Slow time course of modulatory changes caused by acetylcholine

The large scale regulation of functional state via volume transmission is also supported by the relatively long time course of cholinergic modulatory effects. Experimental data demonstrates that activation of muscarinic cholinergic receptors causes physiological changes which take several seconds to reach their maximum, and persist for a minimum of 10-20 seconds, both for measurements of membrane potential depolarization (Krjnevic et al., 1971; Cole and Nicoll, 1984) and for cholinergic modulation of excitatory synaptic transmission (Hasselmo and Fehlau, 2001). This slow time course means that even weak, temporally variable diffusion of acetylcholine within the extracellular space will build up over many seconds to cause strong and tonic changes in functional state within broad cortical regions. Thus, these considerations support the modeling of acetylcholine as a diffuse and relatively homogeneous regulation of circuit properties.

Acetylcholine enhances input relative to feedback

This review focuses on a single general framework for interpreting effects of acetylcholine within cortical structures. As summarized in Figure 2, acetylcholine appears to enhance the strength of input relative to feedback in the cortex. The physiological effects of acetylcholine serve to enhance the influence of feedforward afferent input to the cortex, while decreasing background activity due to spontaneous spiking and the spread of activity via excitatory feedback connections within cortical circuits. Thus, by enhancing the response to sensory input, high levels of acetylcholine enhance attention to the environment, making cortical circuits more responsive to specific features of sensory stimuli. Likewise, by enhancing the response to external input, high levels of acetylcholine enhance the

encoding of memory for specific stimuli, by making cortical circuits respond to the specific features of sensory stimuli, allowing more effective and accurate encoding of sensory events.

This basic theoretical framework will be applied in discussing a number of effects of acetylcholine within cortical structures. The change in dynamics results from three primary sets of effects on a physiological level: i.) modulation of intrinsic properties of pyramidal cells, ii.) modulation of inhibitory neuron depolarization and synaptic transmission, and iii.)selective modulation of excitatory synaptic transmission; ii. The physiological effects of acetylcholine will be described within this functional framework in the following sections.

Acetylcholine enhances spiking response to afferent input.

The physiological effects of acetylcholine on cortical pyramidal cells act to enhance the spiking response to excitatory afferent input, consistent with the enhanced response to input summarized in Figure 2. Early studies using single unit recordings from the neocortex showed that application of cholinergic agonists to the cortex would cause a strong increase in firing rate of neurons (Krnjevic and Phillis, 1963; Krjnevic et al., 1971; Krnjevic, 1984). This increase in firing rate was demonstrated to result from a slow depolarization of cortical pyramidal cells due to blockade of a potassium current, causing the membrane potential to move away from the reversal potential of potassium (Krnjevic et al., 1971). Subsequent research in brain slice preparations of cortical structures have consistently demonstrated depolarization of pyramidal cells with application of cholinergic agonists (Benardo and Prince, 1982; Cole and Nicoll, 1984; Barkai and Hasselmo, 1994). This slow depolarization of membrane potential will enhance the spiking response to excitatory synaptic input (see Figure 3).

Another physiological effect which enhances the spiking response to afferent input is the suppression of spike frequency accommodation, also shown in Figure 3. Pyramidal cells normally respond to a sustained current injection with a high initial firing rate which gradually slows down. This results from activation of a voltage-sensitive potassium current (the M current) and also from voltage-dependent calcium influx causing activation of calcium-sensitive potassium currents (the AHP current) (Constanti and Galvan, 1983; Constanti and Sim, 1987; Madison and Nicoll, 1984; Madison et al., 1987; Schwindt et al., 1988). Activation of muscarinic receptors decreases activation of both of these potassium currents, allowing neurons to fire in a more sustained manner in response to input. This

reduction in spike frequency accommodation appears in neocortical structures (McCormick and Prince, 1986) as well as the piriform cortex (Tseng and Haberly, 1989; Barkai and Hasselmo, 1994) and hippocampal region CA1 (Madison and Nicoll, 1984). This effect allows neurons to continue to generate spiking responses to sustained afferent input, which could be very important for maintaining responsiveness to sensory input in attentional tasks. In particular, behavioral accuracy in continuous performance tasks requires neurons to remain responsive to subtle sensory input over extended periods of time. Suppression of spike frequency accommodation could prevent spontaneous background activity from reducing the sensitivity of cortical pyramidal cells to afferent input. Similarly, more sustained spiking activity would be important for maintaining responses necessary for encoding new memories.

Cholinergic modulation of inhibitory interneurons suppresses background activity while enhancing response to input

Acetylcholine also regulates the functional properties of cortical circuits through modulation of inhibitory interneurons. On first inspection, some of the data on these modulatory effects of acetylcholine appear contradictory and paradoxical, but they make sense when analyzed computationally, as shown in Figure 4. Experimental data in the hippocampus demonstrates that acetylcholine simultaneously depolarizes inhibitory interneurons, while suppressing the evoked release of GABA at inhibitory synaptic terminals (Pitler and Alger, 1992; Behrends and ten Bruggencate, 1993). Cholinergic agonists have been shown to suppress inhibitory synaptic potentials in the hippocampal formation In whole cell clamp recordings, the cholinergic agonist carbachol suppresses spontaneous $GABA_A$ inhibitory synaptic potentials, suggesting a direct suppression of the release of synaptic vesicles containing GABA (Pitler and Alger, 1992). However, carbachol also increases the number of miniature synaptic potentials presumed to result from the spontaneous spiking of inhibitory interneurons (Pitler and Alger, 1992). This coincides with other evidence showing that application of acetylcholine causes direct increases in spiking activity of inhibitory interneurons (McCormick and Prince, 1986). This evidence includes recordings from inhibitory interneurons in cortical structures which demonstrate direct depolarization of inhibitory interneurons by activation of cholinergic receptors in the hippocampus (Frazier et al., 1998; McQuiston and Madison, 1999a,b; Chapman and Lacaille, 1999). The activation of muscarinic receptors causes depolarization in many individual interneurons (McQuiston and Madison, 1999b). Similarly activation of nicotinic receptors depolarizes interneurons with different receptor properties in different neurons. In the

hippocampus, neurons which responded with both fast nicotinic alpha-7 receptor responses and slow non-alpha-7 responses had cell bodies in oriens and projected to lacunosum-moleculare, while another set of neurons were depolarized by only alpha-7 receptors and appeared spread through many layers (McQuiston and Madison, 1999a). The direct depolarization of interneurons is consistent with the fact that nicotinic receptor activation causes an increase in GABA currents in hippocampal pyramidal cells and interneurons (Alkondon and Albuquerque, 2001). Similarly, in the neocortex, there is a selective nicotinic depolarization of specific interneurons, including neurons containing vasoactive intestinal protein (Porter et al., 1999). Depending on the magnitude of this direct depolarizing effect on interneurons, it can result in periods of apparent enhanced inhibition after cholinergic application in slices (McCormick and Prince, 1986) or the enhancement of inhibition upon awakening (Steriade and Deschenes, 1974).

Thus, acetylcholine appears to increase spiking activity in inhibitory interneurons, while decreasing synaptic transmission from these neurons. These effects appear somewhat paradoxical, but as demonstrated in Figure 4, computational modeling provides a framework for understanding such a combination. The influence of these two effects was analyzed in a circuit model evaluating the steady-state response to different levels of afferent input A. The cholinergic depolarization of interneurons has the effect of reducing the background firing rate of pyramidal cells during weak afferent input. In contrast, the cholinergic suppression of GABAergic transmission has the effect of enhancing the steady-state response to strong afferent input. Thus, these cholinergic effects reduce background activity, but heighten the response to suprathreshold stimuli. Overall, these modulation effects on inhibition could enhance the sensitivity of cortical circuits to specific sensory input, important for performance in attention tasks as well as encoding tasks. The reduction in background firing could enhance the detection of subtle sensory input (assuming that the input strongly activates a subset of cells). In addition, this reduction in background firing activity would prevent activation of the calcium-dependent potassium currents underlying spike frequency accommodation. Thus, depolarization of interneurons could enhance the ability of cortical circuits to maintain responses to sensory input over extended periods, while the suppression of inhibitory transmission would reduce inhibition when a signal activates the cortex.

Evidence for selective cholinergic regulation of cortical circuitry has also been demonstrated in rat visual neocortex circuits In particular, nicotinic depolarization of low threshold spiking interneurons could inhibit activity in upper layers (and dendritic inputs to layer V pyramidal cells), while muscarinic hyperpolarization of fast spiking

interneurons could release inhibition at the soma of layer V pyramidal cells and increase spiking activity (Xiang et al., 1998, 2002). Acetylcholine also causes suppression of inhibitory synaptic potentials in visual cortex, while simultaneously depolarizing pyramidal cells (Murakoshi, 1995). These combined effects could play a similar role in reducing background activity while enhancing responses to suprathreshold stimulation. Acetylcholine has selective effects on inhibitory synaptic transmission within other structures as well. For example, stimulation of mesopontine cholinergic nuclei causes suppression of inhibitory potentials elicited in the anterior thalamus by cortical stimulation, while enhancing inhibitory potentials elicited by mammillary body stimulation (Curro-Dossi et al., 1992). These studies emphasize the potential importance of selective modulation of different network properties.

Acetylcholine selectively suppresses excitatory feedback but does not suppress afferent input

Acetylcholine appears to reduce the internal processing of information by cortical structures, due to suppression of excitatory synaptic transmission at excitatory feedback connections within cortical circuits. This suppression of excitatory glutamatergic transmission contrasts with the depolarization of excitatory pyramidal cells in the same manner that the suppression of inhibitory GABAergic transmission contrasts with the depolarization of inhibitory interneurons. In the framework of computational modeling, these competing effects of acetylcholine make sense when it is emphasized that the cholinergic suppression of excitatory transmission is selective for the excitatory feedback connections. As described below, acetylcholine allows afferent input to maintain a strong influence on cortical circuits.

Selective suppression of intrinsic but not afferent fiber transmission in olfactory cortex. The selective cholinergic suppression of excitatory feedback, but not afferent input to the cortex has been demonstrated in a number of different regions, using a number of different techniques. This differential cholinergic modulation was first demonstrated in slice preparations of the piriform cortex (Hasselmo and Bower, 1992). Earlier studies had demonstrated cholinergic suppression of excitatory synaptic transmission in tangential slices of the piriform cortex (Williams and Constanti, 1988), but those slices did not allow comparison of different synapses in different layers. As shown in Figure 5, the use of transverse slices allowed direct comparison of the cholinergic effects on excitatory afferent input synapses from the olfactory bulb in layer Ia of piriform cortex, versus excitatory feedback connections in layer Ib (Hasselmo and Bower, 1992). As summarized in Figure 5, acetylcholine and muscarine caused selective

suppression of excitatory feedback potentials in layer Ib, while having a much weaker effect on afferent input in layer Ia (Hasselmo and Bower, 1992). This effect has been confirmed in anesthetized preparations in vivo, in which direct stimulation of the cholinergic innervation of piriform cortex suppresses feedback from posterior piriform cortex to anterior piriform cortex, but does not influence the afferent input to piriform cortex from the lateral olfactory tract (Linster et al., 1999; Linster and Hasselmo, 2001).

Selective suppression of intrinsic but not afferent fiber transmission in neocortex. Subsequently, a similar selectivity of cholinergic suppression has been demonstrated in the neocortex. In particular, in slice preparations of somatosensory cortex, cholinergic modulation causes suppression of excitatory transmission at feedback connections from higher order somatosensory cortex, while having less effect on synaptic potentials elicited in layer IV by stimulation of subcortical white matter (Hasselmo and Cekic, 1996). The differential regulation of different pathways was demonstrated further in thalamocortical slice preparations (Gil et al., 1997), where activation of nicotinic receptors enhanced thalamic input to the neocortex, while that of muscarinic receptors suppressed both intracortical and thalamocortical synaptic transmission. Similarly, in the primary auditory cortex, acetylcholine suppressed intracortical synaptic potentials (Hsieh et al., 2000) while having no effect on or enhancing thalamocortical connections (Metherate and Ashe, 1993; Hsieh et al., 2000). Cholinergic modulation has also been demonstrated to suppress intracortical synaptic transmission in primary visual cortex (Brocher et al., 1992) and frontal cortex (Vidal and Changeux, 1993). In studies of visual cortex using optical imaging, cholinergic modulation appeared to regulate the intracortical spread of activity, while having a much weaker effect on thalamic input (Kimura et al., 1999; Kimura, 2000). The nicotinic enhancement of thalamic input to the neocortex has also been demonstrated for the medial dorsal thalamic input to prefrontal cortex (Vidal and Changeux, 1993; Gioanni et al., 1999). Thus, the differential suppression of intracortical feedback connections with sparing of afferent input connections which was demonstrated in piriform cortex appears to generalize to most neocortical regions, supporting the functional framework illustrated in Figure 2.

Selective suppression of intrinsic but not afferent fiber transmission in hippocampus. The selective suppression of excitatory synaptic transmission at feedback but not feedforward synapses has also been demonstrated at connections within the hippocampal formation, as described in a recent review (Hasselmo, 1999). The suppression of excitatory synaptic transmission by acetylcholine was described in a number of early studies in slice preparations of

the hippocampal formation. Muscarinic suppression of excitatatory transmission was reported at connections including the medial entorhinal input to the middle molecular layer of the dentate gyrus (Yamamoto and Kawai, 1967; Kahle and Cotman, 1989) as well as the Schaffer collaterals projecting from hippocampal region CA3 to region CA1 (Hounsgaard, 1978; Valentino and Dingledine, 1981). Similar suppression of Schaffer collateral synaptic potentials was obtained in anesthetized animals with microintophoretic application of acetylcholine (Rovira et al., 1982), with stimulation of the medial septum (Rovira et al., 1983), and with sensory stimulation which activates hippocampal theta rhythm (Herreras et al., 1988a, b). Cholinergic modulation has also been demonstrated to suppress excitatory synaptic transmission in the amygdala (Yajeya et al., 2000).

The differential modulation of excitatory synaptic transmission has been explicitly demonstrated in slice preparations of the hippocampal formation. Within the dentate gyrus, the synaptic inputs to the outer molecular layer from lateral entorhinal cortex show little decrease in the presence of cholinergic agonists (Yamamoto and Kawai, 1967; Kahle and Cotman, 1989). Within hippocampal region CA1, there is strong suppression of excitatory transmission in the stratum radiatum, where Schaffer collateral inputs terminate (Hounsgaard, 1978; Valentino and Dingledine, 1981; Hasselmo and Schnell, 1994), but there is a much weaker suppression of synaptic potentials in the stratum lacunosum-moleculare, where input from entorhinal cortex layer III terminates (Hasselmo and Schnell, 1994). In hippocampal region CA3, excitatory recurrent connections in stratum radiatum are strongly suppressed (Hasselmo et al., 1995; Vogt and Regehr, 2001), whereas the effect at synapses from dentate gyrus terminating in stratum lucidum appears much weaker (Hasselmo et al., 1995). There was some evidence for suppression of the mossy fiber input from dentate gyrus, but this appeared to be due to secondary cholinergic activation of inhibitory interneurons, as there was no cholinergic suppression of mossy fiber input in the presence of GABAB receptor blockers (Vogt and Regehr, 2001).

The selectivity of the cholinergic suppression of synaptic transmission is summarized in Figure 5. This general suppression of excitatory feedback would act to reduce feedback within the hippocampus and from hippocampus to other cortical areas during high acetylcholine levels. But none of these papers show total suppression -- the influence of hippocampus is reduced but not removed; there is still sufficient feedback to allow retrieval of relevant stored information.

These specific data are consistent with recordings showing changes in feedback transmission in awake, behaving animals. Recordings from the entorhinal cortex suggest that during active waking the influence of hippocampus on entorhinal cortex is weak, as determined by the low rates of spiking activity in deep layers of entorhinal cortex, which receive output from the hippocampus, in contrast to the higher rates of activity in the superficial layers of entorhinal cortex which send input to the hippocampus (Chrobak and Buzsaki, 1994). In contrast to this weak hippocampal feedback during active waking, the spiking activity in deep entorhinal layers is much higher during quiet waking and slow wave sleep (Chrobak and Buzsaki, 1994). In addition, stimulation of entorhinal input pathways causes very small amplitude evoked potentials in the entorhinal cortex during active waking, whereas the same stimulation amplitude will evoke much larger evoked potentials in the entorhinal cortex during slow wave sleep (Winson and Abzug, 1978; Buzsaki, 1986). A weaker cholinergic influence on perforant path input to the dentate gyrus is supported by the fact that EPSPs evoked in the dentate gyrus by angular bundle stimulation are larger during the high acetylcholine levels of active waking than during the lower acetylcholine levels of slow wave sleep (Winson and Abzug, 1978). In anesthetized animals, sensory stimulation activating theta rhythm appears to increase the sensory response within the dentate gyrus (Herreras et al., 1988b), though this may be due to a cholinergic increase in postsynaptic excitability, because stimulation of the medial septum causes increases in population spike activity in the dentate gyrus, but does not have a systematic effect on EPSPs (Mizumori et al., 1989). Cholinergic modulation influences synaptic transmission in the thalamus as well. In particular, stimulation of the cholinergic laterodorsal nucleus enhances excitatory synaptic potentials in the anterior thalamus induced by mammillary body stimulation (Pare et al., 1990) as well as ventrolateral thalamic EPSPs induced by cerebellar stimulation (Timofeev et al., 1996). It is not clear if these effects can be described within the same functional framework presented here.

Functional data

The theoretical framework presented in Figure 2 raises the question: What is the functional purpose of the alteration in circuit dynamics induced by cholinergic modulation? Why would it be necessary to selectively enhance the afferent input relative to feedback excitation? This section will review behavioral evidence demonstrating the potential role of this change in circuit dynamics, showing how acetylcholine effects may enhance attention to external stimuli, and may enhance encoding of new input. This raises another question: If this enhancement of attention and

encoding is important, then why should circuit dynamics not remain in this state at all times? The existence of a selective modulator for changing these dynamics suggests that the absence of these dynamics are important for some function. The last section here will review how the low acetylcholine state may be important for a separate function. In this state, excitatory feedback is strong, whereas afferent input is relatively weak. Additional physiological and behavioral data suggests that low levels of acetylcholine may set appropriate dynamics for the consolidation of previously encoded information.

Acetylcholine and the enhancement of attention

Behavioral data supports the functional framework presented here for the role of acetylcholine within cortical structures. In particular, the enhancement of afferent input relative to internal processing could enhance performance in attention tasks. The performance in attention tasks often depends on the sensitivity to specific weak stimuli over an extended period of time. Performance in these tasks will be enhanced if the neuronal response to the stimulus is strong (allowing rapid and accurate behavioral responses), whereas the background noise in neural systems should be relatively weak (thereby preventing generation of incorrect responses at inappropriate times in the task).

The cholinergic influence on circuit dynamics illustrated in Figure 2 has the net effect of enhancing the response to external sensory stimuli relative to background noise. This can be seen in Figure 6, which shows the results of a spiking network simulation of piriform cortex (Linster and Hasselmo, 2001). This model implements selective suppression of excitatory feedback synaptic transmission, as well as modulation which reduces feedback inhibition (analogous to the suppression of GABAergic transmission shown experimentally). These effects serve to enhance the response of the network to the pattern of input, while reducing the amount of background spiking activity (Linster and Hasselmo, 2001). These effects are analogous to what has been reported in single unit recordings from neurons in the primary visual cortex, which shows that local application of acetylcholine enhances the response of neurons to visual input (Sato et al., 1987) and enhances the direction selectivity of individual neurons (Murphy and Sillito, 1991). Thus, the change in network dynamics enhances response to sensory stimulation relative to background noise.

This functional interpretation is supported by extensive data indicating a role for acetylcholine in attention processes at a behavioral level. Neuropsychological data from humans subjects has consistently suggested that neuropathology in the ascending cholinergic system underlies deficits in cognition and specifically attention (Parasuraman et al., 1992; Parasuraman and Haxby, 1993; Greenwood et al., 1997; Calderon et al., 2001). Cholinergic

effects at nicotinic receptors enhance performance in attention tasks (Wesnes and Revell, 1984; Wesnes and Warburton, 1984), whereas scopolamine impairs performance (Wesnes and Warburton, 1983). These findings have prompted neuroscientific investigations to better understand the precise role of the cholinergic system in attention.

A great deal of research has been directed at understanding the role of the cholinergic system in attention using either cholinergic drugs or a variety of lesioning techniques. These studies have been critical to the formulation of current hypotheses regarding the role of this system in attention, but the conclusions drawn were necessarily limited by the lack of selectivity of previous methods for acetylcholine (for review see McGaughy et al., 2000). Recently, the immunotoxin 192 IgG-saporin (SAP), which couples the ribosome inactivating toxin saporin to an antibody that recognizes the low affinity nerve growth factor (NGF) receptor, p75, has been developed to allow selective destruction of cortical cholinergic afferents (Wiley et al., 1991; Book et al., 1994; Wiley et al., 1995). 192 IgG-saporin also spares non-cholinergic (GABAergic and glutamatergic) neurons in the basal forebrain and permits a direct investigation of the effects of acetylcholine on cognition not previously possible using excitotoxins (Dunnett et al., 1991, 1994; Muir et al., 1995, 1996). Most cholinergic cell bodies throughout the basal forebrain, including the nucleus basalis of Meynert, medial septum (ms), vertical and horizontal limbs of the diagonal band, bear these p75 receptors and undergo apoptotic cell death following infusion of this toxin (Wiley et al., 1991; Book et al., 1994; Heckers et al., 1994; Wiley et al., 1995). In addition, this receptor is colocalized on the terminal fields of cholinergic projections in the neocortex and hippocampus, which allows neuroanatomically restricted deafferentation following retrograde transport of the toxin to the cell bodies (Wiley et al., 1991; Book et al., 1994; Heckers et al., 1994; Wiley, 1995). Cholinergic projections from the pedunculopontine and laterodorsal tegmental nucleus, which innervate the thalamic nuclei and provide a negligible contribution to the neocortex as well as those from the nucleus basalis of Meynert to the amygdala, lack the p75 receptor and are unaffected by the toxin (Book et al., 1994; Heckers et al., 1994).

Behavioral studies using this immunotoxin have provided consistent evidence of the role of acetylcholine in attention (Chiba et al., 1995; McGaughy et al., 1996; Turchi and Sarter, 1997; Bucci et al., 1998; McGaughy and Sarter, 1998; McGaughy et al., 1999). Intrabasalis infusions of the immunotoxin severely impaired sustained attention (McGaughy et al., 1996). Rats were trained to detect rare and temporally unpredictable visual stimuli and report the presence or absence of these signals via two distinct response levers (McGaughy and Sarter, 1995). The detection of signals was robustly and persistently impaired following the lesions, while the ability to respond correctly to non-signals was spared. Additionally, this impairment in signal detection was exacerbated over the

course of the testing session (McGaughy et al., 1996). The maintenance of prolonged attentional performance throughout a testing session has been previously shown to increase attentional demands (Parasuraman et al., 1987; Parasuraman and Giambra, 1991; McGaughy and Sarter, 1995) and was predicted to augment the attentional impairments produced by lesioning the nucleus basalis of Meynert. The continued ability of rats to respond to non-signal events after lesioning suggests that impairments in task performance were not confounded by a loss of memory for the rules of the task (McGaughy et al., 1996). Multiple cortical infusions of the toxin (McGaughy and Sarter, 1998) or smaller doses of the toxin into the nucleus basalis of Meynert (McGaughy et al., 1999) produced qualitatively similar though less severe impairment in sustained attention. In all studies, the degree of attentional impairment was correlated with the extent of cortical deafferentation (McGaughy et al., 1996; McGaughy and Sarter, 1998; McGaughy et al., 1999).

The framework illustrated in Figures 2, 4, 5 and 6 can be used to account for the importance of cholinergic modulation in sustained attention performance as described below (McGaughy and Sarter, 1995; Arnold et al., 2002). Effective performance in that task requires discrimination of neural activity induced by a brief light stimulus, in contrast with the activity associated with the absence of a stimulus. Cholinergic modulation of cellular and synaptic properties could contribute to this task in two ways. First, the depolarization of interneurons (Figure 4) and the suppression of excitatory feedback transmission (Figures 5 and 6) could reduce spontaneous background activity as well as any response to distractor stimuli – such as a flashing house light (McGaughy and Sarter, 1995), thereby reducing false alarms. Second, the depolarization of pyramidal cells and the suppression of GABAergic transmission could enhance the magnitude of response to sensory stimuli, which will increase the propensity of the target light stimulus for pushing network activity over threshold, resulting in correct detection of the target light stimulus (increasing hits relative to misses). Excessive cholinergic modulation could cause too much depolarization of pyramidal cells, and too strong a response to afferent input, resulting in generation of false alarms. This effect has been observed in behavioral experiments in which cholinergic modulation was enhanced by infusion of benzodiazepine inverse agonists into the basal forebrain (which reduces inhibition of cholinergic innervation, thereby enhancing acetylcholine release). This manipulation enhances the number of false alarms (Holley et al., 1995).

Cholinergic deafferentation was also found to impair divided attention (Turchi and Sarter, 1997). Rats were trained in a conditional discrimination with different response rules dependent upon the modality (auditory or visual) of the stimuli presented. Testing sessions consisted of blocks of modality-certain trials (only auditory or visual trials) followed by blocks of modality-uncertain trials (all stimulus types randomly interspersed) (McGaughy

et al., 1994). When compared to sham-lesioned rats, nucleus basalis of Meynert-lesioned rats showed greater increases in the response latencies during modality-uncertain blocks but no difference in response latencies during modality certain blocks. These data suggested that cholinergic deafferentation decreased processing capacity and produced impairments in performance only when the concurrent maintenance of both sets of response rules was required (modality uncertainty) (Turchi and Sarter, 1997).

In vivo microdialysis in rats performing various tests of attention has repeatedly demonstrated an increase in acetylcholine (ACh) efflux in the area of the frontoparietal (Himmelheber et al., 1997, 2000, 2001) or medial prefrontal cortex (mPFC) (Passetti et al., 2000; Dalley et al., 2001; McGaughy et al., 2002). In rats trained in a 5 choice serial reaction time task (5CSRTT), a test of sustained attention, intra-nucleus basalis of Meynert infusions of high doses of 192 IgG-saporin (SAP-HIGH) produced robust decreases in ACh efflux in the mPFC. This comprised efflux correlated with extensive cortical cholinergic deafferentation and severe attentional impairments (McGaughy et al., 2002). Rats infused with lower doses of the toxin (SAP-LOW), tested under standard conditions, showed no significant differences in either ACh efflux or attentional performance between lesioned rats and sham-lesioned rats. This similarity in attentional performance was hypothesized to result from neurochemical compensation in the cholinergic system following the smaller lesions, as histological analyses later confirmed that SAP-LOW rats had significant cholinergic cell loss in the nucleus basalis of Meynert (McGaughy et al., 2002). Though no differences existed under baseline conditions, attentional performance of SAP-LOW rats was more vulnerable than in sham-lesioned rats to increases in attentional demands produced by prolonged time on task or an increased event rate. Data from sham-lesioned, SAP-HIGH and SAP-LOW rats showed that cortical ACh correlated with accuracy in the task and residual cholinergic neurons in the nucleus basalis of Meynert (McGaughy et al., 2002). These data provided strong evidence that cholinergic efflux in the mPFC was dependent upon nucleus basalis of Meynert (but not vertical limb of the diagonal band of Broca) cholinergic neurons and this pathway was critical to the maintenance of sustained attention performance.

Cholinergic input to the neocortex from the nucleus basalis of Meynert is hypothesized by Sarter and colleagues to play a crucial part in activating “top-down” control of various forms of attention via the convergence of inputs from the nucleus basalis of Meynert and other sensory and associational cortices in the neocortex (Sarter and Bruno, 2000; Sarter et al., 2001). Intra-nucleus basalis of Meynert infusions of SAP impaired the ability of rats to “increment attention” in response to changes in the predictive relationship of a stimulus to a reward (Chiba et al., 1995). These attentional deficits were replicated when the immunotoxin was infused directly into the area of the

posterior parietal cortex, highlighting the specific importance of nucleus basalis of Meynert projections to this area in mediating the effect (Bucci et al., 1998). “Decremental attention”, as required to disregard previously irrelevant stimuli, was not affected by nucleus basalis of Meynert lesions (Chiba et al., 1995), but was impaired by lesions of medial septum/vertical limb of the diagonal band (Baxter et al., 1997).

Gill and colleagues have used electrophysiological methods to determine precisely what aspects of attentional performance are mediated by cortical, cholinergic afferents (Gill et al., 2000). Single unit recordings of neuronal activity in the area of the mPFC of well-trained rats performing in a test of sustained attention (McGaughy and Sarter, 1995) showed units correlated with correct responses, trial type (signal or non-signal) or the expectation of reinforcement (Gill et al., 2000). Presentation of a distractor stimulus, hypothesized to increase attentional demands, coincided with an increase in behaviorally correlated unit activity (Gill et al., 2000). This increase in unit activity was hypothesized to provide “top-down” excitation of the nucleus basalis of Meynert via glutamatergic afferents from the mPFC, thereby facilitating the processing of sensory information during conditions of heightened attentional demand (Sarter et al., 2001). Unilateral, cholinergic deafferentation produced by cortical infusions of SAP in these same animals severely attenuated event-related behavioral activity during baseline conditions, but did not impair attentional performance (this requires bilateral deafferentation). Furthermore, increases in mPFC unit activity previously associated with the introduction of a visual distractor were absent in the lesioned hemisphere (Gill et al., 2000). In summary, converging neuroscientific data continue to provide support for the hypothesis that corticopetal cholinergic afferents originating in the nucleus basalis of Meynert are critical to attentional processing.

Moreover, the role of cholinergic afferents in attention can be dissociated from that of noradrenergic afferents by both lesions and in vivo microdialysis in behaving rats. In contrast to cholinergic lesions, large noradrenergic lesions (>90% loss) produced no impairment in attentional performance in a sustained attention task, even in the presence of a visual distractor stimulus (McGaughy et al., 1997). In vivo microdialysis of the prefrontal cortex of rats performing the 5 CSRTT have shown that an unexpected change in reinforcement contingencies selectively increases noradrenergic but not cholinergic efflux. This change in efflux is found in the first but not the second exposure to these conditions (Dalley et al., 2001). In general, it has been suggested that stimuli that are sufficiently novel engage the noradrenergic system to produce a broadening of attention to context (Sarter and Bruno, 2000) and may be seen as a kind of sentry for potentially threatening stimuli.

Acetylcholine and the enhancement of encoding

As noted above, the enhanced response to afferent input with the reduction of feedback can play a role in enhancing performance in attention tasks. But this same change in dynamics could also be important for the encoding of new information in memory. Traditionally, researchers have attempted to distinguish and differentiate the role of acetylcholine in attention from the role in encoding. However, in this section we will review how these may not be separable functions. The same enhancement of afferent input relative to feedback excitation may be interpreted as enhancing attention when it occurs in neocortical structures, whereas this same effect in medial temporal structures such as the hippocampus could serve to enhance the encoding of new memories.

Numerous human memory studies demonstrate that blockade of muscarinic acetylcholine receptors by systemic administration of the drug scopolamine interferes with the encoding of new verbal information, while having little effect on retrieval of previously stored information (Crow and Grove-White, 1973; Drachman and Leavitt, 1974; Ghoneim and Mewaldt, 1975; Peterson, 1977; Beatty et al., 1986; Sherman et al., 2003; see Hasselmo, 1995; Hasselmo and Wyble, 1997 for review). Scopolamine appears to primarily affect episodic memory, while sparing semantic and procedural memory (Broks et al., 1988; Caine et al., 1981) and short-term memory phenomena such as the recency component of a serial position curve (Crow and Grove-White, 1973) and digit span (Drachman and Leavitt, 1974; Beatty et al., 1986).

A selective impairment of encoding has also been demonstrated in experiments testing memory function in animals. In particular, one series of experiments used a task with an encoding phase during which a monkey viewed a series of visual objects, followed by a later recognition phase during which they were tested for their recognition of these items (Aigner and Mishkin, 1986; Aigner et al., 1991). In these experiments, systemic injections of scopolamine impaired the encoding of new objects, while having little effect when administered during the recognition phase for objects encoded without scoplamine. These encoding effects appeared to be focused in the parahippocampal regions, because encoding of stimuli in this task was impaired by local infusions of scopolamine into the perirhinal (and entorhinal) regions but not by infusions into the dentate gyrus or inferotemporal cortex (Tang et al., 1997). Microdialysis showed a 41% increase in acetylcholine levels in perirhinal cortex during performance of this visual recognition task (Tang and Aigner, 1996).

In rats, effects of muscarinic receptor blockade by scopolamine have been observed in tasks where the rat must encode episodic memories -- events occurring at a specific place and time. For example, injections of scopolamine impaired the encoding of platform location in a task in which the platform was moved on a day by day basis (Whishaw, 1985; Buresova et al., 1986). In the 8-arm radial maze task, the encoding of previously visited

arms appeared to be impaired in a similar manner by systemic scopolamine injections, as well as by lesions of the fornix which destroys the cholinergic innervation of the hippocampus (Cassel and Kelche, 1989). The effects of scopolamine were stronger when a delay was interposed between response and test (Bolhuis et al., 1988). Scopolamine had an effect when it was present during encoding, for example the first four arm visits before a delay, but did not affect retrieval when injected during the delay (Buresova et al., 1986).

Scopolamine has also been shown to impair learning in various conditioning tasks. In eye blink conditioning tasks, the rate of learning was significantly slowed by electrolytic lesions of the medial septum (Berry and Thompson, 1979) as well as by ibotenic acid lesions of the medial septum (Allen et al., 2002). Systemic scopolamine also slowed the learning of classical conditioning in eye-blink conditioning tasks in rabbits (Solomon et al., 1983; Salvatierra and Berry, 1989) and in humans (Solomon et al., 1993). These effects have been modeled in a hippocampal simulation (Myers et al., 1998). The slowing of eye blink conditioning showed a direct correlation with reductions in hippocampal theta rhythm (Berry and Thompson, 1979; Salvatierra and Berry, 1989). The hippocampal theta rhythm appearing during alert immobility in these types of experiments was sensitive to cholinergic blockade (Kramis et al., 1975). A similar correlation with theta rhythm has been shown in experiments where presentation of the stimulus during periods of theta rhythm enhances the rate of learning (Berry and Seager, 2001; Seager et al., 2002). Scopolamine also impairs appetitive jaw movement conditioning (Seager et al., 1999), and scopolamine has also been shown to impair encoding of fear conditioning (Anagnostaras et al., 1995, 1999; Young et al., 1995), even when injected directly into the hippocampus (Gale et al., 2001), but appears to enhance consolidation of fear conditioning when injected after training (Young et al., 1995). This enhancement of consolidation by cholinergic blockade supports the hypothesis presented below that low levels of acetylcholine are important for consolidation.

Acetylcholine also appears important for encoding of sensory representations in neocortical structures such as the auditory cortex. Experimental recordings from individual neurons in auditory cortex showed a tuning curve focused on specific frequencies. These tuning curves were altered by conditioning and could also be altered by auditory stimulation combined with microiontophoretic application of acetylcholine (Metherate and Weinberger, 1990; Metherate et al., 1990). Cholinergic modulation has also been shown to cause long-term alterations in responses to somatosensory stimulation (Tremblay et al., 1990; Dykes, 1997).

Cholinergic suppression of feedback may prevent interference

The cholinergic suppression of excitatory transmission might appear somewhat paradoxical when considering encoding. Why would a substance that is important for learning cause suppression of excitatory transmission? As noted above, it is important to emphasize the selectivity of this suppression for intrinsic but not afferent fibers. The importance of this selective suppression of transmission has been analyzed in computational models of associative memory function (Hasselmo et al., 1992; Hasselmo and Bower, 1993; DeRosa and Hasselmo, 2000; Linster and Hasselmo, 2001). These models demonstrate that cholinergic suppression of transmission prevents retrieval of previously encoded associations from interfering with the encoding of new associations. For example, if an association A-B has been encoded, then subsequent presentation of an association A-C could cause retrieval of the A-B association. This would cause the new association A-C to suffer from interference from the A-B association and cause associations between C and B. Recent experiments have tested behavioral predictions of these computational models (DeRosa and Hasselmo, 2000; DeRosa et al., 2001). In one experiment, rats were initially trained to respond to odor A when presented with the odor pair A-B. Then in a separate phase of the experiment, the rat had to learn to respond to odor C when presented with odor pair A-C, and during the same period had to learn to respond to odor D when presented with odor pair D-E. In a counterbalanced design, rats received injections of scopolamine, methylscopolamine or saline after learning of A-B and before learning of A-C and D-E. Injections of scopolamine during encoding caused a greater impairment in the learning of overlapping odor pairs (A-C) than non-overlapping odor pairs (D-E). Thus, scopolamine appears to enhance proactive interference, consistent with its blockade of the cholinergic suppression of excitatory synaptic transmission at intrinsic synapses in the piriform cortex. Saporin lesions of the horizontal limb of the diagonal band, resulting in cholinergic denervation of piriform cortex, heightened the sensitivity to scopolamine in this paradigm (DeRosa et al., 2001). This model is further supported by experimental data showing that electrical stimulation of the olfactory cortex can modulate the activity of neurons in the HDB, thus providing a pathway for regulation of cholinergic activity (Linster and Hasselmo, 2000). Cholinergic blockade also increases the generalization between similar odorants seen in an odor guided digging tasks (Linster et al., 2001). Similar effects have been obtained in an experiment performed in human subjects, in which scopolamine caused greater impairments in the encoding of overlapping versus non-overlapping word pairs (Kirchhoff et al., 2000; Atri et al., 2003). These data suggest that interference effects may underlie the impairments caused by lesions of the medial septum, including impairments of reversal learning (M'Harzi et al., 1978), and delayed alternation (Numan et al., 1995). Interference effects could

also contribute to the impairment of 8-arm radial maze performance caused by scopolamine (Bolhuis et al., 1988; Buresova et al., 1986).

Acetylcholine enhances long-term potentiation

Activation of acetylcholine receptors also enhances synaptic modification in long-term potentiation experiments. This enhancement would naturally be important for the encoding of new information. Physiological experiments in brain slice preparations have demonstrated enhancement of LTP by cholinergic agonists at a number of different synaptic pathways, including the perforant path input to the dentate gyrus (Burgard and Sarvey 1990), the Schaffer collateral input to region CA1 (Blitzer *et al*. 1990; Huerta and Lisman, 1993), excitatory synaptic connections in primary visual cortex (Brocher et al., 1992) and association fiber connections in the piriform cortex (Hasselmo and Barkai 1995; Patil et al., 1998). In slice studies of region CA1, it has been shown that LTP is most strongly enhanced by stimulation in phase with spontaneous oscillatory activity (Huerta and Lisman, 1993). Drugs which block these neuromodulatory effects on LTP appear to impair memory function: muscarinic receptor antagonists such as scopolamine block the cholinergic enhancement of LTP (Burgard and Sarvey 1990; Huerta and Lisman, 1993; Patil et al., 1998) and these antagonists also impair encoding as described above. These results demonstrate that modulators could contribute to encoding of new information through enhancement of long-term potentiation.

Acetylcholine enhances sustained spiking activity

Acetylcholine also appears to influence the firing activity of cortical circuits by enhancing intrinsic mechanisms for sustained spiking activity in individual neurons. Data from slice preparations of entorhinal cortex demonstrate this cellular mechanism for sustained spiking activity. In physiological recordings from non-stellate cells in slice preparations (Klink and Alonso, 1997a, 1997b), application of the cholinergic agonist carbachol causes long-term depolarizations, which have been termed plateau potentials. If the cells generate an action potential during cholinergic modulation, either due to cholinergic depolarization or current injection, these neurons show sustained spiking activity. This sustained spiking activity appears to result from activation of a non-specific cation current (termed I_{NCM}) which is sensitive to muscarinic receptor activation, as well as the intracellular concentration of calcium (Shalinsky et al., 2002). This intrinsic capacity for self-sustained spiking activity of individual neurons could

underlie the sustained spiking activity observed during performance of delayed non-match and delayed match to sample tasks in the entorhinal cortex of rats (Young et al., 1997) and monkeys (Suzuki et al., 1997). Simulations demonstrate how these phenomena could directly arise from I_{NCM} in individual entorhinal neurons (Fransen et al., 2002). These phenomena include stimulus selective spiking activity during the delay period, as well as enhancement of spiking response to stimuli which match the previously presented sample stimulus. In addition, incorporation of these effects in a network of excitatory and inhibitory neurons can create other phenomena such as match suppression, and non-match enhancement and suppression (Suzuki et al., 1997). Recent data demonstrates that cholinergic modulation of neurons in entorhinal cortex layer V causes activation of a current capable of maintaining graded levels of spiking activity, potentially relevant to the maintenance of analog representations of external stimuli (Egorov et al., 2002).

If cholinergic activation of I_{NCM} is important to provide intrinsic mechanisms for self-sustained spiking activity, then blockade of this cholinergic activation should prevent sustained spiking activity during the delay period and match enhancement. This effect of muscarinic antagonists could underlie the behavioral impairments in delayed matching tasks seen with systemic injections of muscarinic antagonists (Bartus and Johnson, 1976, Penetar and McDonough, 1983). In addition to this role in short-term memory function, sustained activity in entorhinal cortex could also be very important for effective encoding of long-term representations through synaptic modification in the hippocampal formation. Thus, the blockade of sustained spiking activity in entorhinal cortex could contribute to the encoding impairment caused by injections of scopolamine (Aigner and Mishkin, 1986; Buresova et al., 1986; Aigner et al., 1991; Anagnosteras et al., 1995, 1999; Tang et al., 1997).

Low levels of acetylcholine set appropriate dynamics for consolidation

If acetylcholine plays such an important role in attention and encoding, then why is it not present at high concentrations at all times? Or why could the modulatory effects of acetylcholine not be maintained as the baseline parameters for cortical circuits? The ability of acetylcholine to selectively regulate these parameters suggests that the low acetylcholine state has functional importance. In this section, we review the hypothesis that low levels of acetylcholine are important for the consolidation of previously encoded information (see Hasselmo, 1999 for more detailed review). This consolidation would take place during quiet waking and slow wave sleep, when levels of

acetylcholine are low and cortical network dynamics include EEG phenomena such as slow waves (Steriade, 1994, 2001) and sharp waves (Buzsaki, 1989).

The hypothesis that consolidation occurs during slow wave sleep and quiet waking has been discussed for many years (Buzsaki, 1989; Wilson and McNaughton, 1994). This hypothesis proposes that initial encoding of memories occurs within the hippocampal formation during active waking. Subsequently, during quiet waking or slow wave sleep, in the absence of specific sensory input, random activity in the hippocampus causes reactivation of memory representations. Some research has focused on recordings of hippocampal place cells, showing that when pairs of place cells code adjacent positions during a period of active waking, these neurons show greater correlations of firing during subsequent slow-wave sleep, as compared to slow-wave sleep preceding the training session (Wilson and McNaughton, 1994). Another set of experiments have focused on the predominant flow of activity during different behavioral states (as symbolized by the arrows in Figure 7). These experiments demonstrate that during active waking, when theta rhythm is present in the hippocampus, there is extensive neuronal activity in the layer of entorhinal cortex which provides input to the hippocampus (layer II), but not in the entorhinal layers receiving output from the hippocampus (layers V and VI) (Chrobak and Buzsaki, 1994) In contrast, during quiet waking and slow wave sleep, EEG phenomena termed sharp waves originate among the strong excitatory recurrent collaterals in hippocampal region CA3 and spread back through region CA1 to deep, output layers of entorhinal cortex (Chrobak and Buzsaki, 1994). This suggests that hippocampus could be inducing coactivation of neurons in neocortical regions which could form new cross-modal associations. During this stage, slow waves are prominent in the cortical EEG arising from neocortical and thalamocortical circuits (Steriade, 2001). These slow waves include both delta waves and lower frequency oscillations which with sleep spindles are also postulated to contribute to the consolidation of memory traces acquired during the state of wakefulness (Steriade, 2001).

The sharp waves observed in the hippocampus during quiet waking and slow wave sleep could directly arise from the change in dynamics caused by a drop in acetylcholine levels during these behavioral states. As summarized in Figure 7, lower levels of acetylcholine would release glutamatergic feedback synapses from the cholinergic suppression described above (Hounsgaard, 1978; Valentino and Dingledine, 1981; Rovira et al., 1982; Hasselmo and Schnell, 1994), resulting in strong excitatory feedback. Slow-wave sleep would be characterized by a great increase in the effect of excitatory recurrent connections in region CA3 and excitatory feedback connections from CA3 to CA1 and

entorhinal cortex. This drop in cholinergic modulation could thereby underlie the increase in sharp wave activity observed during slow wave sleep (Buzsaki, 1989; Chrobak and Buzsaki, 1994). In fact, muscarinic antagonists such as atropine put the hippocampus into a sharp wave state (Buzsaki, 1986). In addition, this spread of activity should be influenced by synaptic modification during the previous waking period. Thus, the release of suppression of excitatory transmission could contribute to the greater tendency of cells to fire together during slow-wave sleep if they fired during the previous waking period (Wilson and McNaughton, 1994). The loss of cholinergic modulation during slow-wave sleep should also enhance the spread of excitatory activity in response to stimulation. This could underlie the increase in magnitude of evoked synaptic potentials during slow-wave sleep which is observed in region CA1 and entorhinal cortex after stimulation of the input connections to the hippocampal formation (Winson and Abzug, 1978).

What functional role could this enhancement of excitatory feedback have? This would provide the appropriate dynamics for the formation of additional traces within region CA3 and region CA1, and could allow the hippocampus to further strengthen internal connections and "train" the entorhinal cortex or association neocortex on the basis of previously encoded associations (Buzsaki, 1989; Wilson and McNaughton, 1994; Hasselmo et al., 1996; Hasselmo, 1999). As shown in Figure 7, the spontaneous reactivation of neurons coding an association in the hippocampus would then be able to drive cells in entorhinal cortex and neocortex without any assistance from sensory input. The reduction of cholinergic suppression might provide the opportunity for this strong feedback influence. The physiological activity during slow wave sleep has been proposed to be appropriate for modification of synaptic components (Trepel and Racine, 1998). Behavioral data suggests that slow-wave sleep may be important for the declarative component of behavioral tasks which correspond most closely to episodic memories. Subjects are better at retrieval of word lists if they learn the list before falling asleep and are tested on retrieval after being awakened in the middle of the night, than if they learn the list after many hours sleep and are tested in the morning (Stickgold, 1998).

What is the functional purpose of suppressing feedback to entorhinal cortex during active waking? To begin with, this suppression should not be total, as recently stored memories from the hippocampus are still accessible for retrieval. But the strength of connections necessary for the strong transmission of stored memories back to region CA1 and entorhinal cortex would allow them to dominate over afferent input. This could distort the initial perception of sensory information, causing interference during learning in temporal structures -- and if the retrieval activity is sufficiently dominant -- causing hallucinations such as those observed under the influence of cholinergic antagonists at

high doses (Perry and Perry, 1995). Thus, partial cholinergic suppression of excitatory feedback might allow cued retrieval without hallucinatory retrieval.

Concluding remarks

Acetylcholine has a number of different physiological effects on cortical circuits which often appear inconsistent. Computational modeling provides a unifying theoretical framework for understanding these different physiological effects, as summarized in this paper. Modeling demonstrates that the combined physiological effects of acetylcholine serve to enhance the influence of afferent input on neuronal spiking activity, while reducing the influence of internal and feedback processing. Computational models demonstrate how these network properties can be interpreted functionally as both enhancing attention to sensory stimuli and enhancing the encoding of new memories. The levels of acetylcholine in the hippocampus and neocortex change dramatically during different stages of waking and sleep. High levels of acetylcholine during active waking may set appropriate dynamics for attention to sensory input or encoding of new information. At the same time, the cholinergic suppression of excitatory feedback connections prevents interference from internal processing of previously stored information. Lower levels of acetylcholine during quiet waking and slow wave sleep may provide a release from this suppression of excitatory feedback, allowing stronger spread of activity within the hippocampus and from hippocampus to entorhinal cortex, thereby facilitating the process of consolidation of separate memory traces.

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FIGURE LEGENDS

Figure 1. Schematic representation of the microdialysis data showing changes in acetylcholine levels during different stages of waking and sleep. During active waking (exploration), animals have higher levels of acetylcholine than during quiet waking (immobility, eating, grooming). Acetylcholine levels fall to 1/3 of waking levels during slow wave sleep, but rise to levels above active waking during REM sleep (based on Jasper et al., 1971; Marrosu et al., 1995; Kametani and Kawamura, 1990).

Figure 2. General theory of acetylcholine effects in cortical circuits. This circuit diagram summarizes the predominant effect of acetylcholine within cortical circuits, an increase in the influence of afferent input relative to internal processing. This is due to three sets of effects. 1. Intrinsic properties. Acetylcholine causes depolarization of pyramidal cells, and reduction in spike-frequency accommodation, allowing pyramidal cells to respond more robustly to external afferent input. 2. Modulation of inhibition. Acetylcholine depolarizes inhibitory interneurons, decreasing background spiking activity, while suppressing inhibitory synaptic transmission, allowing a stronger response to afferent input due to reduced inhibitory feedback. 3. Modulation of excitatory synaptic transmission. When acetylcholine is present, activation of nicotinic receptors enhances thalamic afferent input, while muscarinic suppression reduces excitatory recurrent processing in cortex.

Figure 3. Intrinsic effects which enhance spiking response to afferent input. A. Acetylcholine causes direct depolarization of pyramidal cell membrane potential (Krnjevic et al., 1971; Krnjevic, 1984; Cole and Nicoll, 1984; Barkai and Hasselmo, 1994), making cells more likely to generate spikes. B. In addition, acetylcholine allows cells to generate spikes more persistently, due to cholinergic reduction in spike frequency accommodation (Madison and Nicoll, 1984; Tseng and Haberly, 1989; Barkai and Hasselmo, 1994).

Figure 4. Schematic diagram of cholinergic modulation of inhibition. A. Basic circuit diagram depicting feedback inhibition. A population of excitatory neurons (labeled by Glu) receives depolarizing afferent input A. These neurons send excitatory output to inhibitory interneurons (labeled GABA). Modulatory effects of acetylcholine include direct suppression of inhibitory synaptic transmission (H) and direct depolarization of inhibitory interneuron membrane potential (represented by depolarizing input A'). B. Analysis of this circuit demonstrates that these effects of

acetylcholine decrease background activity while enhancing the response to strong afferent input. The equilibrium (steady state) of the network is plotted for different levels of afferent input A. When acetylcholine is not present (A'=0, H=0.0018), the network responds to weak afferent input and only shows slight increases as afferent input increases. When acetylcholine is present, causing depolarization of interneurons (A'=0.09) and suppression of inhibitory transmission (H=0.0014), the network shows little response to weak afferent input, but an enhanced response to strong afferent input (Patil and Hasselmo, 1999).

Figure 5. Acetylcholine selectively suppresses excitatory synaptic transmission at feedback synapses, but not afferent input and feedforward connections. This diagram shows synaptic transmission in the piriform cortex at afferent fiber synapses on distal dendrites (top) and excitatory feedback synapses on proximal dendrites (middle). Activation of cholinergic receptors selectively suppresses glutamatergic transmission (Hasselmo and Bower, 1992; Linster et al., 1999) at excitatory feedback synapses (middle), but not excitatory afferent fibers (top). Acetylcholine simultaneously enhances the spiking response of neurons to current injection (shown) or synaptic input (Patil and Hasselmo, 1999; Linster et al., 1999).

Figure 6. Suppression of synaptic transmission at excitatory feedback synapses and inhibitory feedback synapses enhances signal to noise ratio in a simulation containing multiple integrate-and-fire neurons (Linster and Hasselmo, 2001). On the left, in the absence of modulation, there is broadly distributed background spiking activity, which makes it difficult to distinguish the response to direct afferent sensory input (arrows). The histogram on the bottom shows the number of spikes fired by individual neurons (arrows indicate afferent input). On the right, modulation of synaptic transmission enhances signal to noise, increasing the number of spikes generated by neurons receiving afferent input (arrows), while reducing the spontaneous spiking activity of other neurons in the network.

Figure 7. Schematic of cholinergic modulation of hippocampal dynamics during active waking and slow wave sleep. Left: During active waking, high levels of acetylcholine set appropriate dynamics for encoding. Sensory information from neocortical structures flows through the entorhinal cortex and dentate gyrus (DG) into hippocampal region CA3, where cholinergic enhancement of synaptic modification helps in formation of an intermediate term representation binding together different elements of an episodic memory. Feedback connections to region CA1, entorhinal cortex

and association cortex are strong enough to mediate immediate retrieval, but cholinergic suppression of these connections (ACh) prevents them from dominating over the feedforward connectivity. Right: During quiet waking or slow wave sleep, much lower levels of acetylcholine release the suppression of excitatory feedback. This strong excitatory feedback mediates reactivation of memories stored in region CA3 during EEG phenomena termed sharp waves. These waves of activity flow back through region CA1 to entorhinal cortex. This will enable the slow consolidation of long-term episodic memory in hippocampal region CA1, entorhinal cortex and association neocortex, and may underlie modification of semantic memory within circuits of association neocortex.

FIGURES

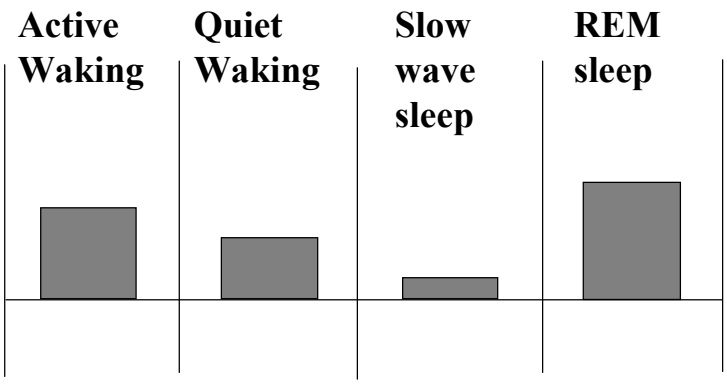

Figure 1

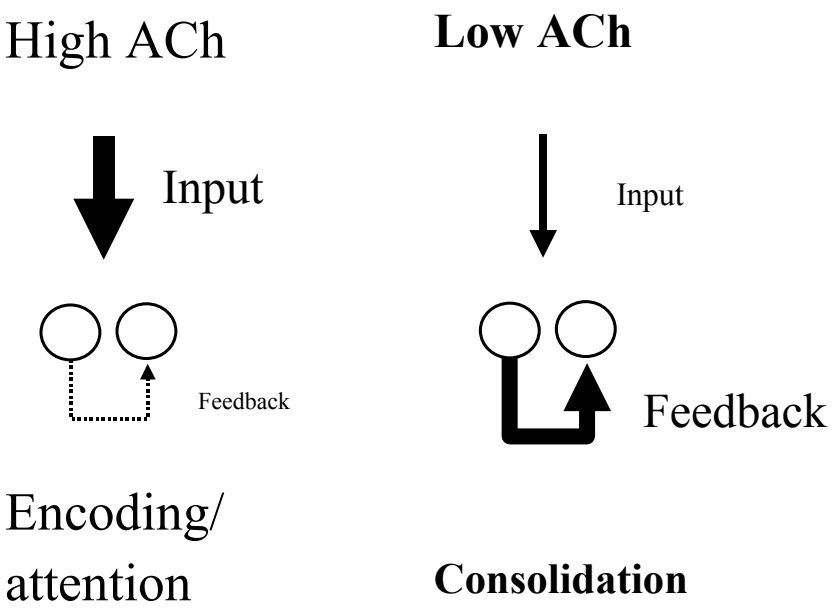
High ACh
Input
Feedback
Encoding/
attention
Low ACh
Input
Feedback
Consolidation

Figure 2

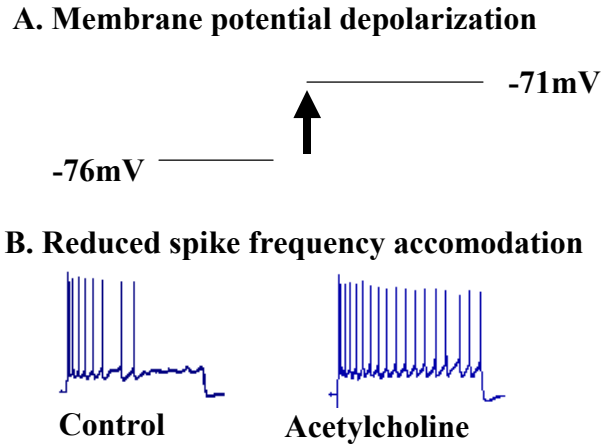
A. Membrane potential depolarization
-71mV
-76mV
B. Reduced spike frequency accomodation
Control
Acetylcholine

Figure 3

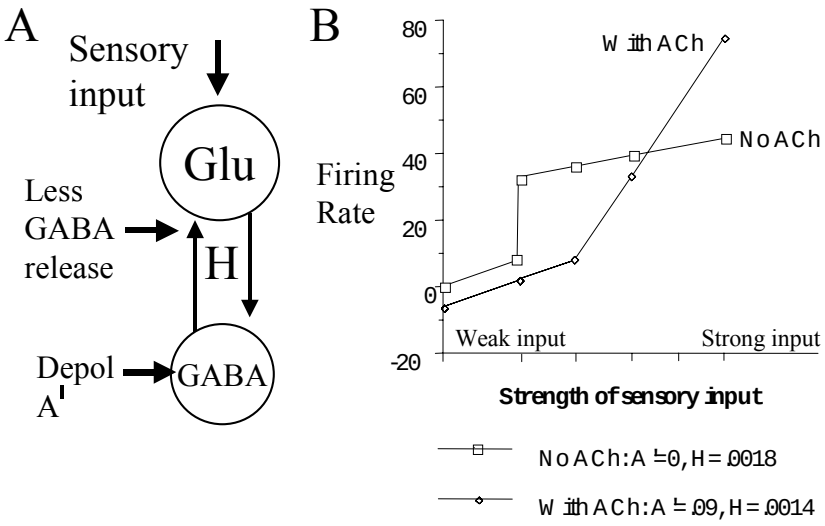
A
Sensory input
Glu
Less GABA release
H
Depol
GABA
B
Firing Rate
80
60
40
20
0
-20
With ACh
No ACh
Weak input
Strong input
Strength of sensory input
No ACh: A = 0, H = .0018
With ACh: A = .09, H = .0014

Figure 4

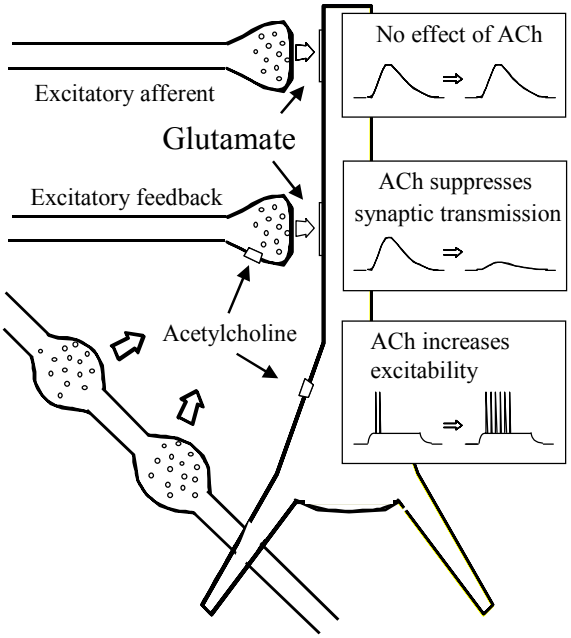
No effect of ACh
Excitatory afferent
Glutamate
ACh suppresses
synaptic transmission
Excitatory feedback
Acetylcholine
ACh increases
excitability

Figure 5

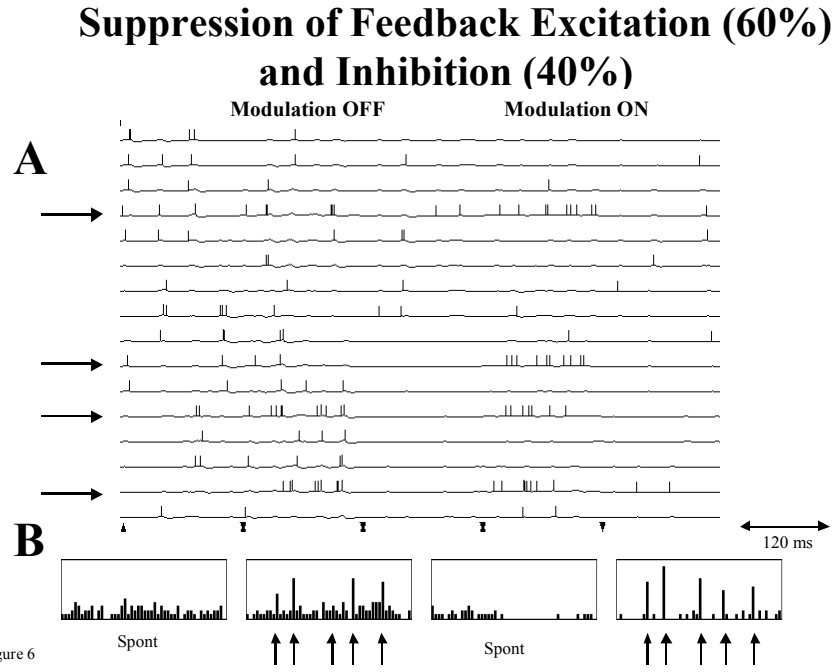
Suppression of Feedback Excitation (60%)
and Inhibition (40%)
Modulation OFF
Modulation ON
A
B
120 ms
Spont
Spont

Figure 6

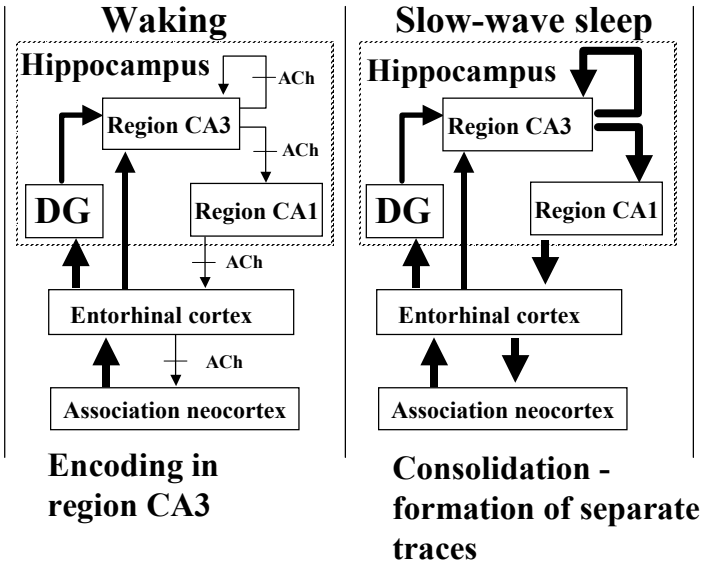
Waking
Hippocampus
ACh
Region CA3
ACh
DG
Region CA1
ACh
Entorhinal cortex
ACh
Association neocortex
Encoding in region CA3
Slow-wave sleep
Hippocampus
Region CA3
DG
Region CA1
Entorhinal cortex
Association neocortex
Consolidation - formation of separate traces

Figure 7