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Review article

Neuromodulation and cortical function: modeling the physiological basis of behavior [1]

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Abstract

Neuromodulators including acetycholine, norepinephrine, serotonin, dopamine and a range of peptides alter the processing characteristics of cortical networks through effects on excitatory and inhibitory synaptic transmission, on the adaptation of cortical pyramidal cells, on membrane potential, on the rate of synaptic modification, and on other cortical parameters. Computational models of self-organization and associative memory function in cortical structures such as the hippocampus, piriform cortex and neocortex provide a theoretical framework in which the role of these neuromodulatory effects can be analyzed. Neuromodulators such as acetylcholine and norepinephrine appear to enhance the influence of synapses from afferent fibers arising outside the cortex relative to the synapses of intrinsic and association fibers arising from other cortical pyramidal cells. This provides a continuum between a predominant influence of external stimulation to a predominant influence of internal recall (extrinsic vs. intrinsic). Modulatory influence along this continuum may underlie effects described in terms of learning and memory, signal to noise ratio, and attention.

Key words: Modulation; Neocortex; Hippocampus; Piriform cortex; Acetylcholine; Norepinephrine; Baclofen

1. Introduction

The techniques of computational neuroscience are particularly useful for analysis of the role of neuromodulators in cortical function. The effects of neuromodulators are slower, longer lasting and more spatially diffuse than neurotransmitters. Understanding the subtle and diffuse influence of neuromodulators requires the broad view of network dynamics provided by computational techniques. This review will provide an overview of physiological evidence on neuromodulators and the efforts to model this evidence. In particular, it will focus on the possible role of the neuromodulators acetylcholine and norepinephrine in shifting the dynamics of cortical function from a predominant influence of external stimulation (appropriate for learning new representations of the environment) to a predominant influence of intrinsic activity (appropriate for recall of previously learned representations).

An illustration of the respective role of neurotransmitters and neuromodulators in cortical activity is provided in Figs. 1 and 2, which summarize evidence from the piriform cortex. Sensory information arriving in the cortex from various peripheral structures commonly enters the cortex via fast, presumably glutamatergic or aspartergic synapses (see [43] and [94] for review). Release of glutamate elicits excitatory postsynaptic currents due to activation of AMPA and NMDA receptors [43,122]. Similarly, the rapid spread of activity within and between cortical structures (along intrinsic and association fibers) is mediated by glutamatergic synaptic transmission. The glutamatergic neurons mediating this interaction between cortical regions are commonly pyramidal cells which display the property of neuronal adaptation. That is, they decrease in firing rate during sustained excitatory activation [45]. In contrast, inhibitory interneurons commonly do not show adaptation.

The dynamical properties of cortical function are also strongly influenced by feedforward and feedback inhibition, mediated by GABAergic interneurons [46,224]. In contrast to excitatory neurons, these interneurons commonly have much shorter axons, remaining within a local cortical region. Feedforward inhibition is here defined as inhibition activated by afferent input or input from other cortical regions. For example, the interneurons of layer Ia in piriform cortex [224], or stratum lacunosum-moleculare

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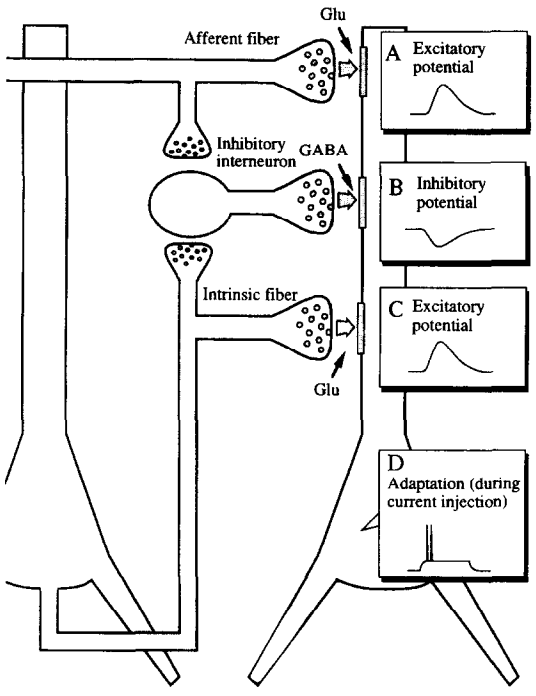

Fig. 1. Neurotransmission. Summary of neurotransmitter influences within the piriform cortex (the primary olfactory cortex). A: afferent fiber synapses from the olfactory bulb release glutamate (or aspartate), which elicits excitatory postsynaptic potentials in the distal dendrite through activation of AMPA and NMDA receptors. B: feedforward and feedback inhibitory interneurons activated by afferent or intrinsic fibers release GABA, which causes fast inhibitory potentials mediated by $GABA_A$ receptors [224]. (These potentials are hyperpolarizing only when membrane potential is depolarized above the chloride reversal potential). C: intrinsic fiber synapses arising from other pyramidal cells release glutamate (or aspartate), which elicits excitatory postsynaptic potentials in the proximal dendrite. D: current injection to a pyramidal cell elicits an initial high frequency generation of action potentials which slows and often stops due to activation of calcium and voltage-dependent potassium currents.

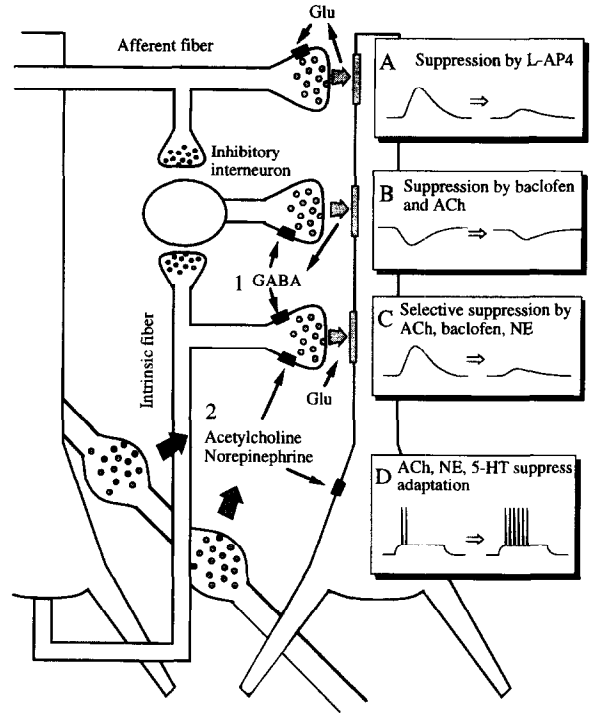

Fig. 2. Neuromodulatory regulation. 1. Local activity levels influence the release of some substances with neuromodulatory effects, including GABA, which has neuromodulatory effects at $GABA_B$ receptors, and glutamate, which has neuromodulatory effects at metabotropic receptors. 2. Neuromodulatory innervation from subcortical structures may influence function via volume transmission (release from axonal varicosities without postsynaptic densities). This includes release of substances such as acetylcholine, norepinephrine, serotonin and dopamine. Neuromodulatory effects. A: suppression of synaptic potentials at afferent fiber synapses results from decreased release of glutamate due to activation of presynaptic metabotropic receptors (experimentally induced by L-AP4). This effect is much weaker at intrinsic fiber synapses [106]. B: in the hippocampus, release of GABA appears to be blocked by activation of presynaptic $GABA_B$ receptors (tested experimentally with agonists such as baclofen) and muscarinic cholinergic receptors. Increased frequency of inhibitory chloride ($GABA_A$) synaptic potentials is observed during perfusion of substances activating noradrenergic, serotonergic, dopaminergic and cholinergic receptors [87]. C: suppression of synaptic potentials at intrinsic fiber synapses results from decreased release of glutamate due to activation of presynaptic muscarinic receptors [107], presynaptic $GABA_B$ receptors [218], and presynaptic noradrenergic receptors [228]. Activation of these receptors has almost no effect on afferent fiber synaptic potentials. Similar selective suppression is observed in the hippocampus [39,109,123,202]. D: increased spiking response to current injection is observed during perfusion of substances which activate cholinergic and noradrenergic receptors [15,225], due to suppression of potassium currents underlying adaptation [47,48].

of region CA1 [135] mediate primarily feedforward inhibition. Feedback inhibition is defined as inhibition activated by the excitatory output of neurons within the cortical region. For example, the interneurons in layer II of piriform cortex [224] or stratum pyramidale and stratum oriens of hippocampal region CA1 mediate predominantly feedback inhibition. Both feedforward and feedback GABAergic interneurons activate inhibitory currents with two different time courses [46,224]. Activation of $GABA_A$ receptors elicits rapid, short term chloride currents. Activation of $GABA_B$ receptors elicits slower, longer term potassium currents [200]. Here, the effects at $GABA_B$ receptors and metabotropic glutamate receptors will be discussed as falling in the realm of modulatory influences.

In cortical structures, substances such as acetylcholine, norepinephrine, serotonin, dopamine and the peptides appear to have a primarily neuromodulatory influence. Though some of these substances have clear neurotransmitter effects in the periphery (acetylcholine and norepinephrine within the autonomic nervous system, for instance), they do not appear to be involved in the direct transfer of information in cortical structures. Rather, they appear to alter the processing characteristics of cortical structures through influences on physiological phenomena such as synaptic transmission and pyramidal cell adaptation (see Fig. 2). Historically this difference between neuromodulators and neurotransmitters has been obscured by the tendency to describe effects of all substances as 'excitatory' or 'inhibitory', based on studies using iontophoretic application during single unit recording. But more

sophisticated intracellular and extracellular recording techniques, often in brain slice preparations, allow detailed analysis of these influences.

Sometimes the same neurochemical may have rapid transmitter type effects, followed by longer modulatory influences, suggesting that neurotransmitter and neuromodulator effects may be most effectively classified at the receptor level. In this review, activation of receptors on a protein structure directly incorporating an ion channel (an ionophore) will be defined as neurotransmission, while activation of receptors coupled indirectly to channels (e.g. via second messenger pathways) will be defined as neuromodulation. Thus, even effects of substances such as glutamate or GABA will be classified as neuromodulatory if they involve the dynamics of second messengers, as do effects at metabotropic glutamate receptors and the $GABA_B$ receptor. Here we will discuss effects of neuromodulatory substances on (1) excitatory synaptic transmission, (2) inhibitory synaptic transmission, (3) pyramidal cell adaptation, (4) resting membrane potential, (5) synaptic modification characteristics.

1.1. Anatomical constraints on neuromodulatory function

The anatomical characteristics of cortical neuromodulatory innervation suggest certain contraints on its function. In particular, neuromodulatory innervation tends to be relatively broad and diffuse, with localized nuclei in the brainstem and basal forebrain providing extensive innervation of cortical regions (see [49] for review). The axons from these subcortical nuclei run considerable distances through cortical structures, with regular axonal varicosities characterized by synaptic vesicles [85]. While some of these axonal varicosities are associated with postsynaptic densities, serial reconstruction of the varicosities of noradrenergic, dopaminergic, cholinergic and serotonergic neurons reveals that commonly over 80% are not associated with a clear postsynaptic density [60,61,206,207]. This paucity of direct synaptic contacts has led to the hypothesis that these neuromodulatory substances diffuse more broadly through cortical regions, a phenomenon referred to as 'volume transmission' and illustrated in Fig. 2 (see [85] for overview). If neuromodulatory influences have this broad, relatively homogeneous effect, then network models may be necessary to effectively understand their role in cortical function.

In general, this widespread, diffuse modulatory innervation arises from a small number of subcortical nuclei. Noradrenergic innervation of the cortex arises primarily from the locus coeruleus (for review see [79]). Dopaminergic innervation of the cortex arises primarily from the ventral tegmental area, and is strongest in prefrontal regions (for review see [138]). Cholinergic innervation of the cortex arises from a series of nuclei in the basal forebrain which have been given a range of different names [164,243]. The neocortex receives innervation from the nucleus basalis of Meynert (Ch4), the piriform cortex receives innervation from the horizontal limb of the diagonal band of Broca (Ch3) [86,231], and the hippocampus receives innervation from the vertical limb of the diagonal band of Broca (Ch2) and the medial septum (Ch1) [83,86]. In addition to cholinergic innervation, basal forebrain nuclei also provide considerable GABAergic innervation of cortical regions [81].

Neuromodulation does not necessarily only arise from sources external to the cortex, but can involve local mechanisms of control. Local cortical activity can influence the release of substances with effects which could only be classified as neuromodulatory. The influence of glutamate itself at metabotropic receptors may be more effectively classified as modulatory. As discussed below, activation of metabotropic receptors by trans-ACPD or L-AP4 can suppress excitatory synaptic transmission [106,128]. Similarly, some of the effects of GABA may be classified as modulatory, such as the suppression of excitatory and inhibitory synaptic transmission mediated by $GABA_B$ receptors (see Fig. 2), as revealed by experiments with the $GABA_B$ agonist baclofen [39,137,218]. In contrast to glutamate, however, these GABAergic influences might arise either from release of GABA by local interneurons, or GABA released from the innervation arising from the basal forebrain. GABAergic cortical interneurons may also release putative neuromodulators such as somatostatin and cholecystokinin [57]. Finally, it is possible that cortical activity directly influences the release of neuromodulators such as acetylcholine and norepinephrine from axonal varicosities, without requiring a long feedback loop through subcortical structures.

2. Physiology of neuromodulation

2.1. Historical perspective

Descriptions of the effects of neuromodulatory substances have been influenced by terminology derived from specific electrophysiological techniques – either single unit recording or electroencephalography. While the data obtained from these techniques is useful and should be considered in analyzing the role of neuromodulators in cortical function, classifying neuromodulators primarily in terms of these effects often obscures their influence on cellular physiology.

In particular, too often clinical researchers refer to the neuromodulatory influences of substances such as dopamine or norepinephrine as 'excitatory' or 'inhibitory'. This

terminology appears to have primarily arisen from studies in which the influence of iontophoretic application (or even systemic application) of agonists and antagonists was analyzed in terms of the firing rate of cortical neurons. Increases in firing rate led to the label 'excitatory', while decreases in firing rate led to the label 'inhibitory'. What these categories neglect is that an increase in firing rate could result from any or all of a number of sources, including direct depolarization, suppression of currents mediating adaptation, suppression of inhibitory synaptic transmission, or direct inhibition of inhibitory interneurons. Conversely, 'inhibition' in this context could arise from direct hyperpolarization, enhancement of currents mediating adaptation, suppression of excitatory intrinsic synaptic transmission, or direct excitation of inhibitory interneurons. As described below, the ambiguous results of many of these experiments could result from the fact that neuromodulators have different cellular effects which would lead to both increases and decreases in the firing rate of individual cortical neurons during iontophoretic application of a neuromodulator.

A more complex classification scheme comes from analyzing the influence of neuromodulators (usually systemic) on the properties of evoked potentials or the EEG (frequently quantified in terms of influences on separate components of the power spectra). Again, these influences are ultimately due to neuromodulatory effects at the cellular level influencing the dynamical properties of cortical networks. This review will emphasize the analysis of neuromodulatory effects at the cellular level, which allows a more direct mapping to the processing units commonly used in computational models of the cortex.

2.2. Modulation of excitatory synaptic transmission

One of the clearest modulatory effects is the suppression of excitatory synaptic transmission in cortical structures, as shown in Fig. 2. This effect has been most extensively analyzed in the hippocampus and piriform cortex, where the laminar segregation of fiber pathways and excitatory synapses allows isolation of synaptic field potentials and discrete stimulation of specific fiber pathways during intracellular and extracellular recording.

2.2.1. Acetylcholine (muscarinic)

In early tangential slices of the dentate gyrus, Yamamoto and Kawai [246] described suppression of synaptic potentials evoked in stratum moleculare during perfusion with carbachol. Suppression of synaptic transmission by acetylcholine was later described in stratum radiatum of region CA1 of the hippocampus [72,117,227]. Cholinergic suppression of field potentials has also been described in tangential slices of the piriform cortex [239,240] and in brain slice preparations of the prefrontal cortex [229] and primary visual cortex [29].

Recent experiments have demonstrated a clear laminar selectivity of the cholinergic suppression of synaptic transmission in cortical structures [107–109,123]. Many of the earlier studies appeared to assume that the suppression of excitatory synaptic transmission was uniform at different sets of synapses in cortical structures [227], though the functional value of such uniform suppression is unclear. However, even in tangential slices of the dentate gyrus, differences in the amount of suppression were noted depending upon the side of the slice being studied [246]. Later experiments in transverse slices revealed that cholinergic agonists have little effect in the outer molecular layer (receiving afferents from the lateral entorhinal cortex), but more strongly suppress synaptic transmission in the middle molecular layer (receiving input from the medial entorhinal cortex) [123]. A similar pattern of laminar selectivity appears in the piriform cortex, where acetylcholine and cholinergic agonists strongly suppress synaptic transmission at intrinsic and associational fibers in layer Ib, while having little effect on afferent fiber synaptic transmission in layer Ia [107]. Laminar selectivity for suppression of synaptic transmission also appears in hippocampal region CA1, where cholinergic agonists more strongly suppress synaptic transmission in stratum radiatum compared to stratum lacunosum-moleculare [109]. This common pattern of effects in different cortical regions suggests that the selective suppression of synaptic transmission may represent a basic principle of cortical function.

2.2.2. Norepinephrine (alpha)

As described below, norepinephrine has postsynaptic effects similar to acetylcholine, yet its influence on excitatory synaptic transmission is less clear. Some studies in hippocampal region CA1 have found no effect of norepinephrine on the slope of excitatory synaptic potentials [148,168]. However, norepinephrine has been shown to suppress excitatory synaptic transmission in cultures of region CA3 of the rat hippocampus [202], in the piriform cortex [228], and in neocortical slices [65] through activation of alpha receptors. It is surprising that norepinephrine does not suppress excitatory transmission in stratum radiatum of CA1 [148], since these synapses arise from CA3 pyramidal cells which show suppression at other synapses, including the excitatory synapses in stratum radiatum of CA3 [202] and excitatory synapses on inhibitory interneurons in CA1 [69]. Norepinephrine suppresses synaptic transmission with laminar selectivity similar to acetylcholine in brain slice preparations of the piriform cortex [228]. The possible selective suppression of intrinsic but not afferent synaptic transmission by norepinephrine might be enhanced by the apparent specificity of no-

radrenergic innervation for layers other than layer IV in the neocortex [170]. The possible suppression of synaptic transmission by norepinephrine is consistent with its capacity for decreasing spontaneous activity of hippocampal pyramidal neurons in vivo [54,55,205] for suppressing seizure activity in the piriform cortex and hippocampus [174] and decreasing population spikes in the hippocampus in vitro [177].

2.2.3. Dopamine and serotonin

There have been no reports of suppression of synaptic transmission in cortical structures by serotonin. Dopamine has been shown to have mixed influences on synaptic transmission in tangential slices of the piriform cortex [44], and has also been shown to enhance the NMDA component of synaptic potentials in the striatum and to modulate gap junctions in the retina [68].

2.2.4. GABA ($GABA_B$)

The $GABA_B$ agonist baclofen has been shown to suppress excitatory synaptic transmission in the molecular layer of the dentate gyrus [137], in hippocampal regions CA3 and CA1 [12,39,123,201] and in the piriform cortex [42] [218]. This suppression of synaptic transmission has a laminar selectivity similar to that caused by cholinergic modulation, with much stronger suppression in stratum radiatum than in stratum lacunosum-moleculare [12,39] and stronger effects at intrinsic and associational synapses than at afferent synapses in piriform cortex [218]. This similarity of effect suggests that the cholinergic and GABAergic innervation arising from the basal forebrain may have similar modulatory influences on synaptic transmission.

2.2.5. Glutamate (metabotropic)

Suppression of excitatory synaptic transmission has also been demonstrated with activation of a metabotropic glutamate receptor. The glutamate analogue, L-AP4, was shown to suppress synaptic transmission in the molecular layer of the dentate gyrus [128]. That study demonstrated laminar specificity of the modulation of synaptic transmission, showing much stronger effects of L-AP4 in the outer molecular layer (note that this contrasts with the effect of cholinergic agonists). L-AP4 suppression of synaptic transmission has also been reported in region CA1 [80], though AP4 effects in this region were previously attributed to postsynaptic antagonism [127]. More recently, L-AP4 has been demonstrated to have the same laminar specificity in the piriform cortex, more strongly suppressing afferent synaptic transmission in the superficial layer (layer Ia) [106,116]. Again, this contrasts with the laminar specificity of cholinergic and $GABA_B$ suppression of excitatory synaptic transmission.

2.2.6. Other

Excitatory synaptic transmission is also suppressed by adenosine in the piriform cortex [171] and hippocampal region CA1 [71,167,201,247]. Neuropeptide Y has been shown to suppress synaptic transmission in hippocampal region CA1 [126]. The source of these neuromodulatory influences are as yet unclear, but like the influences at metabotropic receptors, the endogenous source of these effects is probably due to intrinsic activity within a cortical region, rather than innervation from subcortical neuromodulatory nuclei.

2.3. Modulation of pyramidal cell adaptation

Perhaps the bulk of research on neuromodulatory agents has focused on the modulation of neuronal adaptation or accommodation. Pyramidal cells in the cortex respond to sustained current injection or excitatory synaptic input with an initial high firing rate which decreases over time [15,45,50,76,145–147,157,158,203,204]. This decrease is termed adaptation or accommodation, and appears to result from the activation of voltage- and calcium-dependent potassium currents [15,47,48,136,146,203,204]. The calcium-dependent potassium current also causes a long-lasting hyperpolarization of the membrane potential after calcium influx caused by action potentials, a phenomenon termed the slow afterhyperpolarization (AHP). These properties of pyramidal cells contrast with the ability of inhibitory interneurons to respond with sustained firing in response to current injection [45,157]. A number of neuromodulatory agents influence the voltage- and calcium-dependent potassium currents underlying adaptation and hyperpolarization.

2.3.1. Acetylcholine

Early recordings from cortical structures in vivo demonstrated an increase in firing activity of cortical neurons during application of cholinergic agonists [132–134]. This effect could be partly due to direct influences on pyramidal cell membrane potentials, and partly due to modulation of adaptation. Cholinergic agonists have been shown to suppress the adaptation of pyramidal cells in brain slice preparations of region CA1 of the hippocampus [146] of the cingulate cortex [158] and of the piriform cortex [15,225]. This effect has also been demonstrated during in vivo intracellular recording from cat somatosensory cortex [203] and motor cortex [242] This suppression of adaptation appears due to decreases in the conductance of the voltage-dependent M current [47,144] and calcium-dependent potassium currents [48,144]

2.3.2. Norepinephrine

The effects of norepinephrine on neuronal adaptation are very similar to acetylcholine. Acting at beta receptors,

noradrenergic agonists appear to shut down the calcium-dependent potassium current, thereby decreasing adaptation in response to sustained current injection [145,147]. This appears to be an influence on the same channels influenced by cholinergic modulation, though mediated via a different second messenger pathway (see [181] for review). Coupled with the evidence for noradrenergic modulation of excitatory synaptic transmission, this suggests that acetylcholine and norepinephrine have very similar influences on cortical dynamics. The beta-adrenergic suppression of neuronal adaptation, followed by the alpha-adrenergic suppression of synaptic transmission could explain the initial increase followed by the decrease in population spikes during noradrenergic modulation [173, 177].

2.3.3. Dopamine

Dopamine has been reported to both enhance the afterhyperpolarization [20,21,24,63] and suppress the afterhyperpolarization potential in hippocampal pyramidal cells [150]. The suppression of afterhyperpolarization with high doses of dopamine has been attributed to cross reactivity of dopamine with β-noradrenergic receptors, since this effect can be blocked by propranolol [150]. This latter study reported slight hyperpolarizations induced by dopamine, but did not see an increase in hyperpolarization at any concentration of dopamine. Despite the strong influence on the AHP current, no change in number of action potentials was reported in that study. A recent study suggested that activation of D1 receptors enhances and activation of D2 receptors suppresses the afterhyperpolarization currents [24].

2.3.4. Serotonin

Similar to acetylcholine and norepinephrine, serotonin has been shown to suppress the adaptation of cortical pyramidal cells, thereby increasing excitability. Serotonin decreases pyramidal cell adaptation in current clamp recording [11,41,209], and voltage-clamp recording suggests that as with acetylcholine and norepinephrine this is due to suppression of the calcium-dependent potassium current underlying long-term afterhyperpolarization [41,209]. In contrast to acetylcholine, however, serotonin simultaneously causes hyperpolarization of the membrane potential through activation of a calcium-independent potassium current [11,41,209].

2.3.5. GABA ($GABA_B$)

The $GABA_B$ agonist baclofen has strong effects on membrane potential, but has not been reported to influence adaptation characteristics of cortical pyramidal cells [179,180]. This is also the case for the metabotropic glutamate receptor agonists such as *trans*-ACPD.

2.4. Modulation of inhibitory synaptic transmission and inhibitory interneuron excitability

In addition to the regulation of excitatory synaptic transmission, neuromodulators appear to regulate inhibitory synaptic transmission. These effects are more difficult to characterize experimentally for a variety of reasons. Inhibitory synaptic potentials are difficult to distinguish with extracellular recording. Inhibitory synaptic potentials can be more effectively detected with intracellular recording, but these potentials are usually disynaptic, i.e. stimulation activates excitatory synapses on inhibitory interneurons, which subsequently causes inhibitory potentials in the neuron impaled by the recording electrode. Thus, suppression of inhibitory potentials could have resulted from suppression of the excitatory input to the inhibitory neuron, or of the inhibitory potentials themselves. Finally, inhibitory interneurons are considerably more difficult to impale, preventing discrete activation of these neurons. However, considerable evidence has been gathered showing modulatory effects on inhibitory interneurons.

2.4.1. Acetylcholine

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 [191]. Surprisingly, carbachol also increases the number of miniature synaptic potentials presumed to result from the spontaneous spiking of inhibitory interneurons [191], this coincides with other evidence suggesting a direct excitation of inhibitory interneurons by acetylcholine [158]. Thus, acetylcholine appears to simultaneously increase spiking activity in inhibitory interneurons, while decreasing synaptic transmission from these neurons. Ultimately, this is similar to the influence on cortical pyramidal cells.

2.4.2. Norepinephrine

Many studies have focused more on the noradrenergic suppression of inhibition than on noradrenergic suppression of excitatory synaptic transmission. Suppression of inhibition by NE was first reported in the olfactory bulb [121] and in that structure appears to involve direct suppression of the release of GABA [223]. Suppression of inhibition has also been reported in the hippocampus [148,168] in the form of increased size and numbers of population spikes. However, this noradrenergic disinhibition in the hippocampus appears to be due to a suppression of excitatory synaptic transmission onto inhibitory interneurons [69]. Despite this suppression of synaptic

input, norepinephrine also appears to enhance the spontaneous activity of these interneurons [69,87,148].

2.4.3. Dopamine and serotonin

Both dopamine and serotonin appear to directly enhance the activity of inhibitory interneurons in the piriform cortex [87,209], based on striking increases in spontaneous inhibitory potentials in the presence of these modulatory agents.

2.4.4. GABA ($GABA_B$)

Similar to its suppression of excitatory synaptic transmission, the $GABA_B$ agonist baclofen suppresses inhibitory synaptic transmission in brain slice preparations of the hippocampus [124] and neocortex [118]. While the $GABA_B$ mediated suppression of inhibitory synaptic transmission could be interpreted as feedback regulation of inhibitory synaptic transmission, in the manner that metabotropic receptor effects on glutamatergic synaptic transmission have been interpreted, the influence of baclofen on excitatory synaptic transmission seems incompatible with this interpretation. Perhaps a more plausible explanation would be that inhibitory synaptic transmission must be modulated in a manner proportional to excitatory synaptic transmission.

2.4.5. Other

Endogenous opiates such as the enkephalins suppress inhibitory influences in a number of structures. In the hippocampus, the enkephalin analogue DALA blocks pure monosynaptic IPSPs (revealed in presence of CNQX and AP5) via hyperpolarization of inhibitory interneurons [37]. Adenosine does not block inhibitory synaptic transmission in hippocampal region CA1 [247].

2.5. Modulation of resting membrane potential

There is a gray area in the categorization of a substance as a neurotransmitter or neuromodulator. Many neuromodulatory substances can influence the resting membrane potential of neurons, causing slow depolarizations or hyperpolarizations which are frequently referred to as synaptic potentials, despite their much slower time constant in comparison to glutamatergic or $GABA_A$ synaptic potentials. Again, it may be more accurate to classify effects with regard to receptor subtypes, distinguishing between ionophore receptors and receptors coupled indirectly to ion channels. In this context, it is easy to distinguish between the more rapid effects of glutamate at AMPA and NMDA ionophore receptors, and the slower effects at metabotropic receptors; the rapid effects of GABA at $GABA_A$ receptors, vs. the slower effects at $GABA_B$ receptors; the rapid effects of acetylcholine at nicotinic receptors, vs. the slower effects at muscarinic receptors, and so on. Here we will describe only changes in resting membrane potential which appear to be due to receptors coupled indirectly to ion channels, with primary influences on potassium currents. These effects are usually smaller and longer-lasting than ionophore effects, and may have a more modulatory influence on cortical dynamics.

2.5.1. Acetylcholine

Application of cholinergic agonists consistently causes a slow depolarization of the resting potential of cortical pyramidal cells [22,40,146], after both iontophoretic application or bath application in brain slice preparations This effect appears to be due to suppression of a tonically active potassium current [144], thereby causing movement away from the reversal potential of potassium, which usually lies below resting potential.

2.5.2. Norepinephrine

Though norepinephrine suppresses adaptation currents in the same manner as acetylcholine, norepinephrine differs from acetylcholine in that it has commonly been reported to cause hyperpolarization of membrane potential [147].

2.5.3. Dopamine

Dopamine has been reported to occasionally cause a small hyperpolarization of membrane potential [150], but this has been attributed to action at noradrenergic or serotonergic receptors.

2.5.4. Serotonin

While its effect on adaptation and afterhyperpolarization is the same as acetylcholine, serotonin differs in that it has a clear hyperpolarizing effect on resting membrane potential [10,11,41,209]. This appears to be due to direct activation of a membrane potassium current via $5\text{-}HT_{1A}$ receptors. The potassium current appears to be the same current activated by $GABA_B$ receptors [9]. Thus, during initial perfusion of serotonin in slice preparations, the response to low current intensities is decreased due to hyperpolarization, while the response to high current intensities is increased due to the suppression of adaptation [10].

2.5.5. $GABA_B$

The most familiar effect of $GABA_B$ receptor activation is probably the slow hyperpolarization of membrane potential due to activation of potassium currents. In addition to the suppression of excitatory and inhibitory synaptic transmission discussed above, the $GABA_B$ agonist baclofen causes hyperpolarization of pyramidal cell mem-

brane potentials [179,180]. This effect is most commonly observed after synaptic stimulation, when activation of $GABA_B$ receptors induces the slow, potassium-dependent component of the synaptic potential [118,224], which follows the fast, chloride-dependent $GABA_A$ potential.

2.5.6. Other

Adenosine also hyperpolarizes pyramidal cell membrane potential through increases in potassium conductance [90], but neuropeptide Y has no observed effect on resting membrane potential [126].

2.6. Modulation of synaptic modification (long-term potentiation)

Many neuromodulatory substances have been implicated in memory function. Because of this, considerable work has focused on how neuromodulatory substances influence synaptic modification, especially long-term potentiation.

2.6.1. Acetylcholine

A number of studies have demonstrated that, at the same time as they suppress excitatory synaptic transmission, cholinergic agonists enhance the relative amplitude of long-term potentiation phenomena in the dentate gyrus [31] region CA1 of the hippocampal formation [26,119], the piriform cortex [16], and in neocortical structures [29,142]. In the hippocampus, this potentiation may be related to the induction of theta frequency oscillatory dynamics [119]. This cholinergic effect on synaptic modification may be due to a direct enhancement of the mechanisms involved in long-term potentiation, such as the enhancement of NMDA currents [151,152]. It may also be due to indirect effects of the cholinergic modulation of activation dynamics, such as the suppression of neuronal adaptation [15].

2.6.2. Norepinephrine

Considering its similarity with other effects of acetylcholine, it is perhaps not surprising that considerable evidence supports the notion that norepinephrine enhances long-term potentiation in hippocampal region CA1 [115] the dentate gyrus [215] and in the neocortex [29].

2.6.3. Serotonin

Serotonin has been reported to suppress the induction of long-term potentiation at commissural synapses in stratum radiatum of hippocampal region CA3 [230]. Induction of long-term potentiation has been reported to be decreased by both agonists and antagonists of dopamine.

2.6.4. $GABA_B$ receptors

The $GABA_B$ agonist baclofen has been shown to enhance long-term potentiation in the hippocampal formation [13,32,172,183], possibly through the disinhibitory influence of the suppression of inhibitory synaptic transmission [13]. This suppression of inhibition may in particular play a role in the greater capacity of theta-frequency (3–10 Hz) stimulation for inducing long-term potentiation. Suppression of inhibition by baclofen aids in the induction of LTP with theta-frequency stimulation [172].

3. Neuromodulation in computational models of cortex

Most models of cognition are ultimately models of cortical function. Therefore, the processing characteristics of these models must eventually correspond in a one-to-one manner to the physiological properties of cortical structures. By using the anatomical and physiological evidence available on cortical function, we can more rapidly obtain this one-to-one correspondance between model and reality. Research will only converge on a satisfactory model of cognitive function when work is simultaneously constrained by anatomy and physiology as well as behavioral experiments.

Currently, even most neural network models of cortical function are very highly simplified representations. Neural network models have tended to focus on the linear summation of rapid excitatory or inhibitory effects of neurotransmitters, neglecting the intermediate time course of neuromodulatory influences. The spread of activity in these models primarily matches the effects of ionophore receptors (such as the AMPA and the $GABA_A$ receptor) in time course. Nonetheless, the effects of neuromodulatory substances can be analyzed within the theoretical framework provided by these models, as described below. By modeling the effects of neuromodulators in cortical networks, the physiological influence of these substances can be related directly to their function, without intervening levels of theoretical description which do not correspond directly to a biological substrate.

3.1. Spread of activity

Neural network models must account for the spread of activity within cortical networks. This spread of activity includes both the properties of synaptic transmission and the input/output function of individual neurons. Any model of neuromodulation must effectively represent the influence of neuromodulatory substances on these properties.

3.1.1. Synaptic transmission

In neural network models, the spread of neuronal activity across a set of synapses is commonly represented by matrix multiplication [8,93,114,129]. The firing rate of one population of neurons is represented by a vector, which is multiplied by a matrix with elements representing the excitatory or inhibitory strength of individual synapses. The resulting vector represents the summed synaptic influence on each of the postsynaptic neurons.

While modulation of synaptic transmission is a prominent effect of a number of different neuromodulators, few neural network models have analyzed the role of this modulation of synaptic transmission. Neuromodulation of excitatory and inhibitory synaptic transmission can be represented by simply multiplying the synaptic connectivity matrix by a parameter representing the strength of suppression [100–103,108,109].

Neural network models of cortical function differ with regard to the flow of activity through the network. In many models, activity flows through the network in a purely feedforward manner, giving a certain output dependent upon a specific input. Most models of the formation of feature detectors in visual cortex have this characteristic [92,143,166]. These networks have relatively simple activation dynamics, and are usually analyzed primarily in terms of learning properties. In contrast, the associative memory models described below commonly contain excitatory recurrent (intrinsic) or feedback type connectivity. These networks have more complicated activation dynamics, which are commonly analyzed with regard to settling into an attractor state [6,114]. The selective suppression of synaptic transmission by neuromodulators such as acetylcholine may play an important role in regulating the relative influence of these two different types of activation dynamics [101,108,109].

3.1.2. Modulation of inhibitory synaptic transmission

It is often difficult to draw comparisons between neural network models and cortical function because of the tendency in models to lump together different types of neurons. In particular, most attractor neural network models and backpropagation models use networks in which units can make both excitatory and inhibitory connections with other units. This is highly unrealistic, since real cortical pyramidal cells can only cause inhibitory effects on other pyramidal cells via inhibitory interneurons which are simultaneously receiving input from a large number of other neurons and sending output to a large number of neurons. An individual pyramidal cell can have a very specific excitatory effect on other pyramidal cells through direct excitatory synapses, but its inhibitory effects will be considerably less specific due to mediation by interneurons. Effective representation of the modulation of inhibition requires a separate representation of inhibitory interneurons in models.

3.1.3. Input–output functions

The input/output function of a modeled neuron describes how the output of that neuron (usually the firing rate) depends upon the synaptic input to that neuron. These input/output functions usually operate on a variable representing either the membrane potential of the neuron or the total membrane current which changes according to the sum of synaptic inputs. Most models of cortical function put this summed input through a non-linear function which attempts to replicate the firing properties of neurons. One non-linear function (the threshold-linear function) simply gives zero output for input below the threshold, and gives output directly proportional to input for input above the threshold [91,220]. Here the threshold corresponds to the physiologically determined firing threshold, and the slope of the line reflects how firing rate depends upon membrane potential.

In contrast, a larger number of neural network models use what are commonly referred to as sigmoid input–output functions, including most networks trained by back-propagation of error [155,197,248,249] and attractor neural networks [6,114]. The sigmoid input–output function increases slowly for values well below threshold, rapidly for values around threshold, and tapers off to an asymptote for values above threshold. The threshold of these functions does not correspond to the physiological threshold, but rather to the half-maximal output of the unit. Commonly, these functions contain an additional gain term which regulates the steepness of the function around its threshold. Effects of neuromodulators have been modeled as changing the gain of the sigmoid input/output function [38,208]. This change in gain will cause both an increased output for input values above threshold, and a decreased output for input values below threshold, as shown in Fig. 3.

Neither of these input–output functions accounts for the properties of neuronal adaptation, because they remain static, unchanged by the previous output of the neuron. In contrast, the majority of cortical pyramidal cells show neuronal adaptation, in which firing frequency decreases dependent upon previous spiking activity [15,45, 50,76,145–147,157,158,203,204]. As described above, a predominant influence of neuromodulators is on the adaptation characteristics of cortical neurons. This influence of neuromodulators has not been effectively modeled by changes in static input/output functions, but requires direct simulation of the adaptation characteristics of cortical neurons [14,15,105] (see Fig. 3). This can be obtained by representation of intracellular calcium concentration and the calcium-dependent potassium current in both bio-

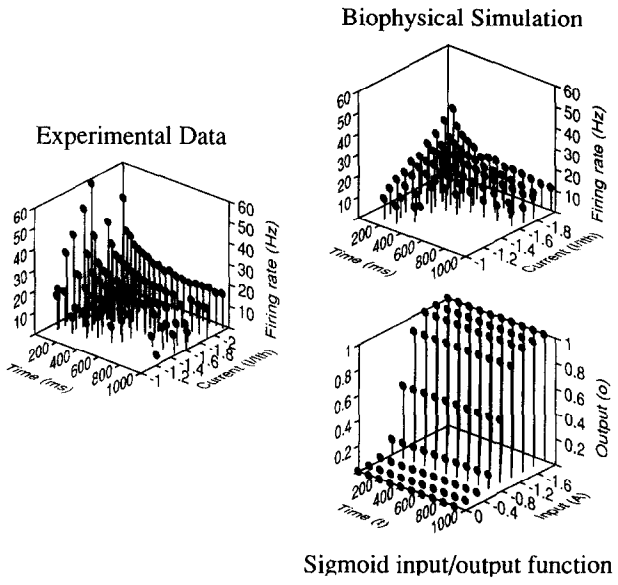

Fig. 3. Illustration of different representations of the input/output function of real and simulated neurons. Three-dimensional plots show firing frequency (computed as the reciprocal of interspike interval) vs. amplitude of injected current vs. time (during a 1 second current injection). Left: a real piriform cortex pyramidal cell shows a high initial firing rate which drops off due to adaptation as the current injection continues. Top right: a detailed biophysical representation of pyramidal cells explicitly models this adaptation [15]. Bottom right: the standard neural network representation of neuron input/output functions as a static sigmoid function does not effectively represent the adaptation characteristics of neurons.

physical simulations and more abstract representations of neuronal activity.

3.2. Learning mechanisms

Most neural network models focus on learning. These systems are required to learn new associations between input and output patterns, or form self-organized representations of input patterns. This leads to a focus on the mechanisms of synaptic modification.

3.2.1. Synaptic modification

Most neural network models implement learning through modification of synaptic strength. Thus, in addition to a rule describing the spread of activation through the network, many models use a learning rule describing how synaptic strength is modified dependent upon variables such as pre- and postsynaptic activity. Rules which depend upon the product of pre and postsynaptic activity are commonly referred to as Hebbian learning rules. Considerable physiological evidence suggests these learning rules are realistic for some types of synaptic modification [125,238]. In contrast to these rules, some of the most popular algorithms for connectionist models of cortical function involve learning rules based on the explicit computation of an error signal – i.e. the difference between actual output and desired output – and changes in synaptic connections designed to decrease this error. This includes the popular back-propagation of error algorithm [156,197]. However, it is unlikely that cortical networks explicitly compute an error signal, though the dynamical interactions within cortical structures might ultimately result in connection changes which minimize error without explicitly computing that error.

The modulation of synaptic modification phenomena such as long-term potentiation [16,26,31,115] can be represented in a number of different ways, including changes in the rate constant of learning and in the threshold of synaptic modification. More detailed physiological experiments are necessary to determine the most realistic representation of the modulation of synaptic modification.

3.2.2. Change in other parameters

Long-term changes in other cortical parameters could also affect network function, though few models have analyzed these properties. Some work has focused on how changes in the adaptation currents of pyramidal cells could be used to store information [23,193], and some experimental work supports the possibility that such changes underlie learning [50,64]. These types of models commonly make reference to the currents underlying adaptation, frequently proposing that cholinergic modulation may trigger long-term changes in adaptation in neurons which are active. The relative amplitude of the A current and AHP current in different neurons could determine the directions in which activity spreads for a given input pattern. However, the storage of information in this form has a much smaller capacity, since the learning occurs at the level of individual neurons rather than individual synapses. This suggests that long-term changes in adaptation characteristics are likely to be selective to particular subregions of the dendritic tree, or to be combined with changes in synaptic strength.

3.3. Self-organization and associative memory function

Models of cortical function which do not use error correction learning rules will be described here with reference to two basic categories: associative memory models and self-organizing systems. While individual examples of these models differ considerably, modifiable synapses in these models can be classified on the basis of a single criterion – the extent to which the spread of activity across the modifiable synapse influences postsynaptic activity during learning. As shown in Fig. 4, if the modifiable synapses are the primary influence on postsynaptic activity during learning, these synapses are self-organizing, if the modifiable synapses have no influence on postsynaptic

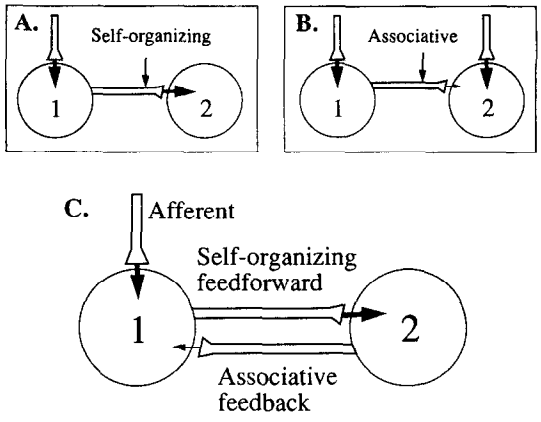

Fig. 4. Two classes of synaptic function in cortical models using Hebbian learning (strengthening of synapses dependent upon pre and postsynaptic activity). Size of arrow indicates strength of synaptic transmission during learning. A: self-organization. Modifiable synapses between region 1 and 2 undergo self-organization if these synapses are the predominant influence on postsynaptic activity during learning. This allows the formation of feature detectors or other more compressed representations of region 1 activity. Suppression of synaptic transmission prevents other postsynaptic input from guiding the synaptic modification. B: associative memory function. Modifiable synapses between region 1 and 2 store an association between pre- and postsynaptic activity if these synapses are not the predominant influence on postsynaptic activity during learning. Suppression of synaptic transmission at the modifiable synapses during learning prevents previously stored associations from being recalled, allowing other input to determine the postsynaptic activity during learning. During recall, this suppression must be removed. C: combination. Selective suppression of synaptic transmission during learning (small arrow) allows combination of self-organization and associative memory function in the same network.

activity during learning, these synapses mediate associative memory function.

3.3.1. *Associative memory models*

Synapses with associative memory function store associations between pre and postsynaptic activity patterns such that when presented with a previously learned pattern of presynaptic activity, they recall the associated pattern of postsynaptic activity. In associative memory models, modifiable synapses are not the predominant influence on postsynaptic activity during learning. The postsynaptic activity is determined by separate afferent input to the postsynaptic neuron. This ensures that the modification of the synapse stores an association between the pre and postsynaptic patterns of activity without influencing those patterns of activity.

This characteristic of associative memory models requires a change in activation dynamics between learning and recall. During learning, the modifiable synapses must store associations without spreading sufficient activity to perturb those associations, while during recall these modifiable synapses must be capable of recalling the associations without any other postsynaptic input. In these models, network activity is commonly clamped to the pattern of afferent input during learning. This technique is used in the early linear associative memories [4,7,129] and in the later attractor neural networks [1,6,114,220].

Associative memory models have commonly been described as basic models of cortical function [6,130,222]. In particular, autoassociative memory function has been attributed to the piriform cortex [94,95,100,103,105,108, 110,241] and region CA3 of the hippocampus [73,153, 162,222]. The Schaffer collaterals from region CA3 to CA1 have been proposed to underlie heteroassociative memory function [109,139,161].

Neuromodulatory influences may provide the ideal means of changing activation dynamics between learning and recall. In particular, the effects of acetylcholine within cortical networks appear to set the appropriate dynamics for learning in an associative memory [100–103,108,109]. The selective suppression of one set of synapses allows modification of these synapses to store associations, while the absence of suppression at another set of synapses allows these synapses to set the postsynaptic activity during learning. Selective suppression of synaptic transmission has been demonstrated in both the piriform cortex [107] and region CA1 of the hippocampal formation [109].

3.3.2. *Self-organizing systems*

Synapses which undergo self-organization cause postsynaptic activity to form a compressed or altered representations of input from another region. This function requires that the modifiable synapse be the predominant influence on postsynaptic activity during learning.

Self-organizing systems have been presented as models of the formation of feature detectors in the primary visual cortex [92,143,166], and the formation of topographic maps in cortical structures [166]. Neuromodulators appear to play an important role in this self-organization in biological systems, since combined blockade of the cholinergic and noradrenergic innervation of visual cortex has been shown to interfere with formation of feature detectors [18], and the response characteristics of these feature detectors are strongly influenced by cholinergic neuromodulation [165,211]. Neuromodulatory influences may therefore play an important role for making transitions between learning and recall for self-organizing systems as well. In particular, in cortical networks, intrinsic and feedback synapses appear to outnumber afferent input and feedforward synapses [66]. Modulation of synaptic transmission and neuronal adaptation may play an important role in determining whether the synapses undergoing self-organization are allowed to be the predominant influence on postsynaptic activity.

3.3.3. *A common algorithm of cortical function*

Neuromodulation may be particularly important for the combination of self-organization and associative memory

function in cortical networks. The cortex ultimately must take in a range of sensory and kinesthetic information, and guide appropriate behavioral responses. This requires the ability to form links between stimulus and behavior, but also to form more sophisticated representations of the environment to enhance the generality and accuracy of the associations. Ultimately, models of cortical function should consist of synaptic connections with the properties of both self-organization or associative memory function.

Few models have attempted to combine self-organization and associative memory function in a single network, since these types of functions involve different learning dynamics. As shown in Fig. 4, the suppression of synaptic transmission during learning provides an ideal mechanism whereby associative memory function and self-organization can be combined in the same network. This prevents synapses with associative memory function from being the predominant influence on postsynaptic activity, and also prevents associative memory synapses from interfering with the modification of synapses undergoing self-organization. The influence of acetylcholine and norepinephrine on cortical neurons is ideal for setting the appropriate learning dynamics for combining self-organization and associative memory function. Networks which combine self-organization and associative memory function without neuromodulatory influences must use different dynamical features to prevent synaptic transmission at synapses with associative memory function from interfering with their own modification or with the modification of synapses undergoing self-organization. Examples of such networks are adaptive resonance theory (ART) [35,36] and counterpropagation networks [111].

In the framework of these general functional characteristics, the following section presents a theory of the role of cholinergic modulation in the piriform cortex, hippocampus and neocortex.

4. A theory of cortical neuromodulation: shifting from intrinsic recall to extrinsic stimulation

In this section, a theory of the role of neuromodulation in cortical function will be proposed, with an emphasis on the possible role of acetylcholine in the cortex. In general, acetylcholine is proposed to switch the dynamics of cortical function from a state in which activity is determined primarily by intrinsic synapses mediating recall based on previous learning to a state in which activity is determined primarily by extrinsic stimulation arriving along afferent input fibers. This modulation is essential for both associative memory function and self-organization. For synapses mediating associative memory function, acetylcholine suppresses transmission during learning, preventing the modifiable synapse from being the predominant influence during learning. For synapses undergoing self-organization, acetylcholine allows these synapses to become the predominant influence on postsynaptic activity by suppressing other input and enhancing neuronal responsiveness. These basic functions will be described in the context of models of the piriform cortex, hippocampus and neocortex.

4.1. Neuromodulation in the piriform cortex

In modeling research, the piriform cortex has been proposed to operate as both an auto-associative memory [14,94,95,100,102,103,105,108,110,241] and as a self-organizing network for categorization of odors [5]. These two different views are not incompatible. The former requires modification of excitatory feedback synapses within this region, while the latter requires modification of afferent and feedforward synapses.

If the piriform cortex functions as an associative memory, this requires different dynamics during learning and recall, to prevent synaptic transmission at excitatory feedback synapses from interfering with the storage of new patterns. The selective suppression of excitatory intrinsic synaptic transmission by substances such as acetylcholine [107], norepinephrine [228] and baclofen [218] could provide the appropriate dynamics for learning in this network. The role of this suppression in auto-associative memory function in piriform cortex is summarized in Fig. 5, with discussion of possible feedback regulation of cholinergic modulation. This selective suppression could allow self-organization of afferent input from the olfactory bulb to proceed without interference from excitatory intrinsic synapses [101,103,110]. Previous models of the piriform cortex as a self-organizing system have focused on purely feedforward connections, without considering possible interference due to feedback [5].

4.2. Neuromodulation in the hippocampus

The hippocampus has been a focus for modeling of cortical function, due to the experimental evidence suggesting a role for this structure in learning of specific episodic information [214,250]. A large number of researchers have focused on this area, but several common themes have emerged in actual computational models of this region, as summarized in Figs. 6 and 7 and below.

1. Perforant path synapses in the dentate gyrus have been proposed to undergo self-organization to form a sparse, distributed representation of afferent input from a range of modalities [153,161–163,195].

2. The mossy fibers projecting from dentate gyrus to region CA3 have been proposed to make the dentate

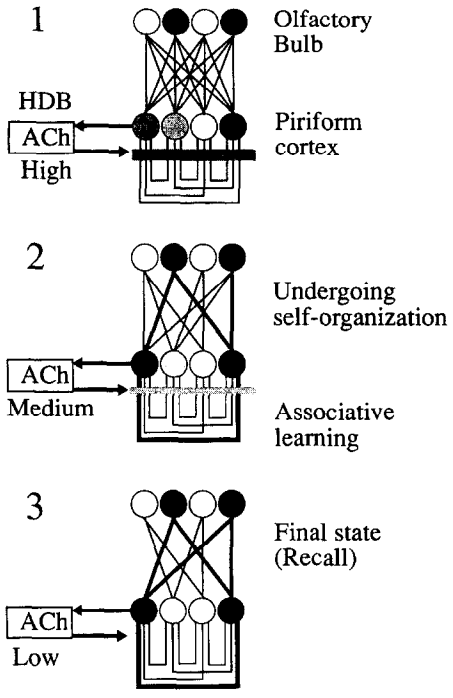

Fig. 5. Theory of cholinergic modulation in piriform cortex. Cholinergic modulation arises from the horizontal limb of the diagonal band of Broca (HDB). 1. A novel pattern of activity in the olfactory bulb initially does not elicit strong activity in the piriform cortex, because it does not match the pattern of afferent or intrinsic connectivity. Cholinergic modulation remains high. The suppression of synaptic transmission (shaded line) ensures that the spread of activity across intrinsic synapses does not interfere with learning. The suppression of adaptation enhances the response to afferent synapses, which are not suppressed. 2. As Hebbian synaptic modification takes place, afferent fiber synapses undergo self-organization, strengthening connections to activated cortical neurons and weakening connections to inactive neurons. As cortical neurons become more active, intrinsic fiber synapses are strengthened between the active neurons. Cortical activity increases and cholinergic modulation starts to decrease. 3. When cortical activity is sufficiently strong, cholinergic modulation is suppressed. This allows recall mediated by intrinsic fiber synapses to dominate the activation dynamics. The network has made the transition from learning to recall.

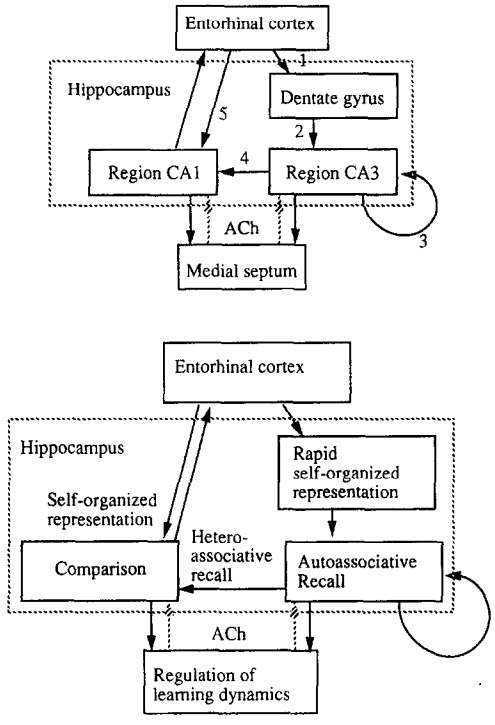

Fig. 6. Proposed function of synaptic connections within existing models of the hippocampal formation. Top: anatomical structures. 1. Perforant path synapses in the dentate gyrus undergo self-organization to form a sparse, distributed representation of input. 2. Mossy fibers from dentate gyrus to region CA3 clamp a sparse pattern of activity for auto-associative learning. 3. Excitatory feedback synapses in stratum radiatum of region CA3 mediate auto-associative recall of stored patterns of CA3 activity. 4. Schaffer collaterals from region CA3 to CA1 store associations between patterns of activity in region CA3 and the associated patterns in region CA1, allowing heteroassociative recall. 5. Perforant path inputs to region CA1 and CA3 undergo self-organization, storing simplified representations of cross-modal sensory input. Bottom: summary of function by region.

activity pattern even more sparse due to low probability of connectivity [153,161–163,195,221]. However, the strength and proximity of these synapses to the cell body are proposed to allow them to clamp activity to the desired pattern – in some cases these are referred to as 'detonator' synapses [153,161–163].

3. Excitatory feedback synapses in stratum radiatum of region CA3 have been proposed to mediate auto-associative storage of patterns of activity in region CA3 [73,104,153,162,222].

4. Schaffer collaterals from region CA3 to CA1 have been proposed to mediate heteroassociative modification, storing associations between patterns of activity in region CA3 and the associated pattern in region CA1 [109,139, 161].

5. Perforant path inputs directly to region CA1 and CA3 have been proposed to undergo self-organization, storing simplified representations of cross-modal sensory input [73,109]. These hypotheses for associative memory function and self-organization at particular synaptic connections in the hippocampus would require different dynamics during learning and recall. Cholinergic neuromodulation might set the appropriate dynamics for learning in the hippocampus by allowing activity to be dominated by afferent input rather than intrinsic recall. Without this modulatory influence, the excitatory synapses arising from region CA3 will interfere with auto-associative storage in CA3 and heteroassociative storage in the Schaffer collaterals. Thus, for these standard hypotheses of hippocampal function to work, the following neuromodulatory mechanisms appear to be necessary:

4.2.1. Appropriate dynamics for learning are set by the suppression of synaptic transmission and pyramidal cell adaptation by acetylcholine

The suppression of excitatory synaptic transmission in stratum radiatum of region CA3 and CA1 by acetylcho-

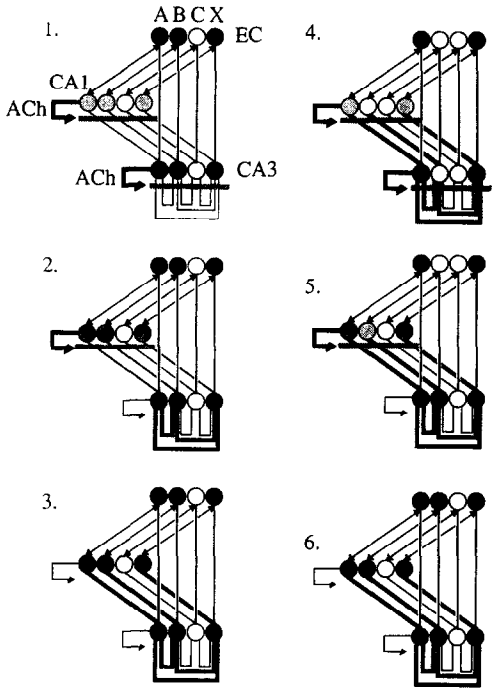

Fig. 7. A simple model of hippocampal function (note that the dentate gyrus is not shown). Parallel lines connecting regions represent broadly distributed connectivity. 1. Sensory input activates a pattern of activity in entorhinal cortex (EC). The input initially does not match the pattern of connectivity, and cholinergic modulation remains strong in CA3 and CA1. 2. As intrinsic synapses are strengthened in CA3, activity becomes stronger, decreasing cholinergic modulation and allowing recall to dominate in CA3. Activity from CA3 reaches CA1, where it is combined with the influence of EC input. The influence of CA3 activity on self-organization of the connections from EC depends upon the level of cholinergic modulation. 3. As the pattern of input from CA3 starts to match the pattern of input from EC, cholinergic modulation is decreased in CA1 and associative recall dominates. The new pattern of activity has been learned. 4. After learning, a degraded version of the pattern is presented which contains only 2 active input lines. The initial activity in CA3 is not as strong as the response to the full pattern. 5. Since the input matches the pattern of intrinsic connectivity in CA3, activity increases in that region, decreasing cholinergic modulation and allowing activity to spread to CA1. 6. The activity spreading to CA1 matches the pattern of activity coming from EC. This decreases cholinergic modulation, allowing strong CA1 activity, which spreads across feedback connections to EC, where it completes the missing components of the previously learned input pattern.

line [72,109,117,210,227] and norepinephrine [202] could play an important role in learning, changing hippocampal dynamics from being dominated by intrinsic recall, to being dominated by extrinsic stimulation. This would allow the self-organization and associative memory function described above. This suggestion is further supported by the fact that cholinergic suppression is stronger in stratum radiatum than at the synapses of the perforant path terminating in stratum lacunosum-moleculare [109]. Effects mediated by metabotropic, GABAB, adenosine and neuropeptide Y receptors might contribute to these dynamics.

4.2.2. CA1 performs a comparison function allowing self-regulation of modulation

Rapid switching between a predominant influence of extrinsic stimulation (learning) and intrinsic response (recall) requires some mechanism for the feedback regulation of neuromodulation, as shown in Fig. 7. In particular, strong activity of a few neurons may reflect an initial response to familiar input, making a switch to recall dynamics appropriate (e.g. low acetylcholine). In contrast, weak or broadly distributed activity might reflect an initial response to unfamiliar input, making a switch to learning dynamics appropriate (e.g. high acetylcholine). Simulations of region CA1 show that it might provide the basis for comparing the recall of region CA3 with the afferent input from entorhinal cortex [73,109]. A comparison function has been suggested previously for this region [73,140].

Similarly, local neuromodulators might directly respond to levels of network activity, without requiring a feedback loop. In contrast, the extrinsic neuromodulator norepinephrine might not be under such immediate control, suggesting that it provides a means for other state factors, such as fear, to determine the level of response to extrinsic stimulation vs. intrinsic recall. For example, imminent danger in a familiar environment (such as that elicited by fear of attack) might make cortical networks respond to the exact details of external stimuli, rather than operating on the basis of highly processed responses dominated by recall.

4.3. Neuromodulation in the neocortex

The ideas described for the hippocampus and piriform cortex can be extended to neocortical function as well. Most models of the neocortex have focused on the self-organization of afferent input to this region, with a primary focus on the formation of feature detectors and topographic maps in the primary visual cortex [166]. While these models frequently contain some intrinsic excitatory connectivity, they do not effectively account for the fact that on the order of 80 percent of excitatory synapses in cortical structures arise from within the cortex [66,67]. Thus, models of self-organization must account for how these intrinsic synapses are prevented from dominating the formation of representations. Selective suppression of intrinsic synaptic transmission, coupled with an enhanced response to afferent input due to suppression of pyramidal cell adaptation, could account for the predominance of external stimulation in determining cortical representations, despite the anatomical preponderance of intrinsic connectivity.

Neuromodulatory influences might also set the dynamics of learning in neocortical structures, allowing afferent input and feedforward synapses to predominate, while

suppressing recall due to intrinsic and feedback synapses. The effects of neuromodulators appear remarkably consistent across different cortical regions. For example, the cholinergic and noradrenergic suppression of pyramidal cell adaptation has been described in the hippocampus, piriform cortex, somatosensory neocortex and motor neocortex. The cholinergic suppression of excitatory synaptic transmission has been described in the dentate gyrus, hippocampus, piriform cortex and primary visual cortex. This suggests a general framework for the role of neuromodulatory agents in cortical function, as summarized in Fig. 8.

This general framework for cortical function does not construe feedforward as meaning the flow of information from sensory to motor cortices. Rather, primary cortical regions are considered to be at the input level, and feedforward synapses progress through higher association areas toward the hippocampus. As in the models of piriform cortex and hippocampus, modulation can determine where cortical dynamics fall on the continuum between learning and recall, between a predominant influence of external stimulation mediated by afferent input and feedforward synapses, and a predominant influence of intrinsic recall mediated by excitatory feedback and intrinsic synapses. The level of modulation can be determined by feedback mechanisms (see Fig. 8) which would allow cortical regions to set individual dynamics of learning and recall dependent upon the local interaction of external input and the interpretation of this input with regard to internal representations. For cholinergic modulation, this could be mediated at the highest level by the septohippocampal system, but also mediated at more primary levels by interactions between neocortical structures and the nucleus basalis of Meynert. Heterogeneous modulation of different cortical regions will allow modalities or cortical subregions in which sensory input clearly matches previously established representations to guide the establishment of representations in other regions.

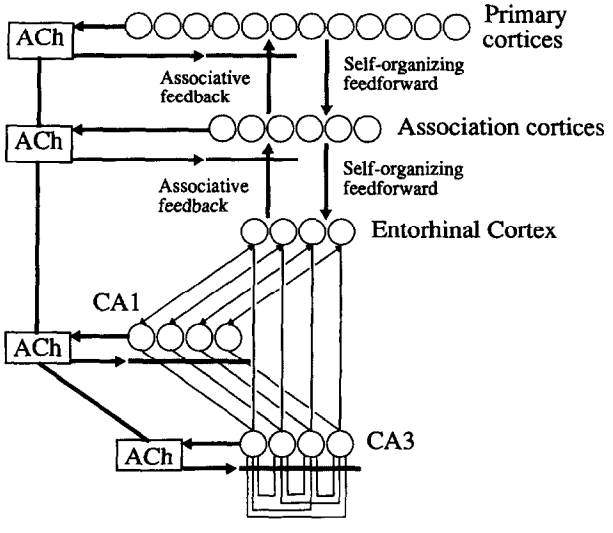

Fig. 8. Schematic representation of cholinergic modulation in the neocortex and hippocampus. In the full range of neocortical regions, the feedback regulation of cholinergic modulation is proposed to switch dynamics between recall and learning. When extrinsic input matches the pattern of recall activity within a region, cholinergic modulation is decreased and activity is dominated by recall. When extrinsic input does not match the pattern of recall, cholinergic modulation remains high, and input activity continues to dominate, setting appropriate dynamics for self-organization of input and feedforward synapses and for associative learning at intrinsic and feedback synapses.

5. Behavioral data on cholinergic neuromodulation

Here it has been hypothesized that neuromodulators such as acetylcholine may switch cortical dynamics between a predominant influence of extrinsic stimulation (learning) and a predominant influence of intrinsic response (recall). This hypothesis was developed on the basis of physiological evidence and computational modeling, but ultimately it must be tested with regard to behavioral data.

This approach to understanding cortical function explicitly seeks to avoid the use of terms such as learning, memory, attention and reinforcement. Terms derived from common language are usually ill-defined and biased by the introspective and social interpretations of behavior. Because terms like memory or attention have been used to describe certain aspects of behavior does not mean that those terms will map clearly or systematically to the actual phenomena of cortical function. A considerable body of useful behavioral data has been gathered on various neuromodulators, but the interpretation of this data is hampered by the lack of a theory accounting for the cellular influences of neuromodulators.

This section provides several examples of how behavioral data on the effects of neuromodulators can be reinterpreted in the context of computational models which incorporate the cellular effects of neuromodulators. In particular, we will show that terms like attention and memory generate spurious controversies within the field. Cholinergic modulation of the cortex has traditionally been considered to play a role in memory function. However, there have been controversies over whether this is a primary role in 'storage', in 'consolidation' or in the manner in which 'attention' influences memory function. Rather than arguing about whether acetylcholine is involved in attention or memory, we should find out how the phenomena categorized by these terms could simply be different behavioral manifestations of a common effect of neuromodulation in the cortex – regulating the level of intrinsic vs. extrinsic influences.

This is a broad initial description. Considerable further support for these proposed roles of neuromodulation must be provided by effective simulation of the behavioral func-

tion in more detailed biophysical simulations of cortical dynamics. The discussion will focus on how behavioral data corresponds to the model presented here, rather than providing a comprehensive overview of the available behavioral data. More in-depth discussion of much of the earlier behavioral data from animal research is provided in Hagan and Morris [97] and of research in humans in Kopelman [131].

Behavioral data will be discussed according to the nature of the task and the subjects used rather than the proposed function being investigated. Some of the terms used for the proposed function are provided in quotation marks.

5.1. Free recall by human subjects. 'Declarative memory'

Even at the turn of the century, physicians were aware that patients would often show no knowledge of events which occurred while they were under the influence of muscarinic cholinergic antagonists such as scopolamine ([219], cited in [97]). Subsequent controlled studies with human subjects are consistent with the notion that acetylcholine sets the appropriate dynamics for learning new information. Scopolamine impairs the recall of stimuli first learned after administration of scopolamine, while having little or no effect on recall of stimuli learned before administration of scopolamine [88,89,190]. After injections of scopolamine, impairments are found in the immediate and delayed free recall of lists of words [52,53,70,88,89, 190] or delayed recall of items from a paragraph [78]. Deficits are also observed for learning of other non-verbal stimuli. These tests include the following: learning the location of objects in a schematic house [78] (a task similar to one tested for rhesus monkeys below [17]), detection of a novel object or face in a growing list of objects or faces [78], and memory for the position of chess pieces [141] or for pictures of objects [184]. Immediate recall, as measured by digit span, does not appear to be affected [70,78].

In the context of the theory presented here, blockade of cholinergic modulation by muscarinic antagonists would block the ability to change between the dynamics of recall and the dynamics of learning [101,109]. Without such a change in dynamics, new associations cannot be stored as specific new representations, but would instead be lost in a multitude of previously recalled associations. With blockade of cholinergic modulation by scopolamine, synaptic transmission in stratum radiatum of region CA3 and CA1 is not suppressed, allowing recall of previous associations to interfere with the formation of a new representation of an association between a specific word and a specific experimental context. In addition, the blockade of the cholinergic suppression of neuronal adaptation and the enhancement of synaptic modification will contribute to poorer performance by slowing the synaptic modification necessary to form new associations. With impairments in the learning of these specific associations, the ability to recall many types of information in a specific experimental context will be impaired.

5.1.1. Intrusions after scopolamine injections and in Alzheimer's disease

An important prediction of this framework is that by blocking the suppression of synaptic transmission during learning, muscarinic antagonists would also be expected to produce increased intrusions during recall, both from stimuli presented in previous trials, and from wrong answers generated in previous trials. Subjects under the influence of scopolamine have been shown to generate increased numbers of intrusions from previous stimuli and from previous wrong answers [30], but in some studies these intrusions have not been observed [78]. In a study comparing the effects of diazepam and scopolamine (hyoscine), scopolamine impaired learning of words at the beginning or middle of the lists, suggesting increased proactive interference, but while diazepam caused increased intrusions from previous lists, scopolamine primarily increased confusions related to the current list [82]. Surprisingly, scopolamine does not induce increases in prior-list intrusions in the Brown-Peterson task [19], but this may be due to a strong decrease in learning in this task reflected by the much larger number of omissions. More intrusions might appear if subjects are tested on the Brown-Peterson task both before and after scopolamine administration. The perseveration of wrong answers has been demonstrated in Alzheimer's disease [19,84], and the absence of this perseveration in some studies of scopolamine has been used to focus on the difference between the effects of Alzheimer's disease and of cholinergic blockade [19,78]. Research has also shown that cholinergic blockade does not cause language deficits [78] and an impairment of digit span, both of which are associated with Alzheimer's disease. However, this approach to a comparison neglects the fact that Alzheimer's disease might reflect a long-term loss of modulatory influence, and the associated long-term result of interference, rather than the short-term effect associated with injections of scopolamine. The theoretical framework described here has been used to account for how interference effects due to insufficient cholinergic modulation could underlie the initiation of neuropathology in Alzheimer's disease, and how this breakdown of function could spread between cortical regions to affect functions such as language [101].

Tasks in which a subject is required to find the novel object or face in a selection of objects or faces would place

particular demands on the mechanisms of feedback regulation of cholinergic modulation. The suppression of cholinergic modulation due to a match between sensory input and intrinsic recall could be construed as 'recognition' of familiarity, while the lack of this suppression would reflect novelty. Blockade of cholinergic modulation would interfere with this shift between dynamics, setting the cortex at the normal end-state of this matching process. Without the initial sensitive state induced by cholinergic modulation, recognition memory function would be expected to be impaired, as shown experimentally [17].

5.1.2. *Basal forebrain lesions in humans*

These same experimental paradigms have been used to test the effect of lesions damaging cholinergic innervation in humans. In particular, surgery which damages the fornix will destroy much of the cholinergic innervation of the hippocampus arising from the medial septum. In subjects with these lesions, impairment on the free recall of words and paragraphs have been described [112,113,226], again suggesting an important role for the cholinergic modulation of the hippocampus in storing new associations. In some cases, no memory deficits are reported, though this may be due to preserved septohippocampal innervation through ventral pathways not involving the fornix [244].

The loss of hippocampal cholinergic innervation might be expected to cause considerable interference between different stored representations. This phenomenon has been suggested by behavioral effects of anterior communicating artery aneurysms, which cause damage to the septum. Patients with such lesions show behavioral effects often described as confabulation. This includes cases of subjects demonstrating a difficulty distinguishing events in their own life from events about which they have heard, and subjects generating answers to questions even when they clearly do not have the necessary information. This suggests that information is being stored, but is confounded with previous information such that the specific defining context cannot be recalled [56,58,59]. In the framework presented in Fig. 7, loss of cholinergic modulation in the hippocampus might also interfere with the ability to judge the validity of recalled information in the context of the current environment. The Schaffer collaterals might generate recall in response to sensory stimulation, but without cholinergic modulation this recall is not subjected to a comparison with the current input to CA1 from the entorhinal cortex.

5.2. *Stimulus detection tasks in humans. 'Attention'*

Some researchers have argued that acetylcholine is involved in 'attention' rather than 'memory', supporting this argument with separate tasks designed to exclusively test 'attention'. Subjects under the influence of scopolamine rate themselves as feeling drowsy [88,89,182] but show no deficit in detecting alphabetical sequences in series of letters [52,53] or detecting tones in white noise [33]. However, they do show deficits in other attentional tasks [33,232–234]. For example, subjects under the influence of scopolamine show reduced accuracy in counting number of tones presented at low rates (0.25 Hz) [30], in performance of a 20-min sustained rapid visual processing task [234] and in performance of stroop tasks [232].

In the framework presented here, these deficits could reflect similar effects of cholinergic blockade in different cortical regions. The efficient detection of movement or digit sequences in these tasks might require a greater influence of stimulus input on the dynamics of neocortical regions. The effects of cholinergic modulation could provide these dynamics, enhancing the influence of afferent input on the response of cortical neurons by suppressing adaptation, while decreasing the influence of recall activity through suppression of intrinsic synaptic transmission. Terms such as 'memory' and 'attention' might simply refer to the same modulatory influences in different cortical regions. The cholinergic influence on cortical dynamics could be described as 'attention' when the neocortical dynamics dominated by extrinsic stimulation are required for detection of highly learned, lower-level features, and as 'memory' when hippocampal dynamics dominated by extrinsic stimulation are required for forming a clear representation of a specific word stimulus in a specific learning context. Theoretical distinctions between 'memory' and 'attention' will only be meaningful when they can be described in terms of the dynamics of cortical function.

5.3. *Delayed non-match to sample tasks in monkeys. 'Working memory'*

Studies in non-human primates also demonstrate a greater role for acetylcholine in learning than in recall. This has been investigated in a delayed non-match to sample tasks [2,3] in which 20 trial unique object are presented sequentially, followed by sequential presentation of each of these objects paired with a novel object. Monkeys receive reward for choosing the novel object, and commonly perform at about 75% correct for 20 objects. Scopolamine injected 20 min before the initial presentation ('learning') strongly impairs performance at a range of doses, while scopolamine injected after the initial presentation, but 20 min before the paired presentation ('recall') had no effect on performance. The acetylcholinesterase inhibitor physostigmine was shown to improve performance on the task. This task has already been shown to be sensitive to lesions of the hippocampus.

In the framework presented here for hippocampus function, this deficit would be attributed to blockade of learning dynamics in the hippocampus. In the presence of scopolamine, the initial presentation of the object does not form a clear memory independent of previous learning. With dynamics dominated by recall, there may be no synaptic modification, or modification suffering from interference due to similarities between objects. Thus, during recall, the animal has no clear notion of which object is novel. Scopolamine or atropine have also been shown to impair delayed match to sample performance with repetitive use of simple stimuli such as colors at a number of recall intervals [28,188]. When learning occurs without scopolamine, feedback regulation of cholinergic modulation allows each novel object to set learning dynamics in the hippocampus, forming a new contextual representation. Subsequent administration of scopolamine does not impair function, since it locks the network into a dynamical state in which the previous presentation of the familiar objects can be clearly recalled.

Impairment of acquisition could manifest itself regardless of delay. Thus, even with very short delays (e.g. 30 s) between sample and match, the blockade of learning dynamics during acquisition should affect recall. Impairments at shorter intervals have commonly been attributed to impaired 'discrimination', leading to a focus on delay-dependent impairments to show that somehow 'forgetting' occurs more rapidly. However, the stimuli in many of these tasks [188] were simple, easily distinguished color stimuli. This use of the term 'discrimination' really refers to the ability to discriminate the presentation of an object in a specific context as a unique episode independent of other episodes – a concept akin to forming associations.

5.4. Maze tasks in rats. 'Spatial vs. non-spatial', 'working vs. reference memory'

5.4.1. Eight-arm radial maze

Cholinergic antagonists increase the number of errors by rats visiting baited arms in this task [149,198,199], consistent with the notion that feedback regulation of cholinergic modulation switches hippocampal dynamics between recall of previously learned stimuli and learning of new stimuli. After retrieving rewards from several arms, the rat must be able to observe each arm from the central platform and compare the temporal context and sensory cues from that arm with the representations formed in the hippocampus. If the temporal context and sensory cues do not match a hippocampal representation, no recall occurs. Cholinergic modulation keeps the hippocampus in a state of learning, the rat enters the new arm, and the new stimuli and context form new representations. If the context and cues match a hippocampal representation, the previous visit is recalled, and the rat turns to a different arm.

Cholinergic blockade interferes with this process, placing the hippocampus in constant recall mode. In this case, recall of previous trials occurs for each new arm, preventing effective learning of a new representation. This prevents the formation of a representation which allows an accurate choice based on sensory cues and temporal context. However, the state of permanent recall should allow the avoidance of arms which are never baited – thus, cholinergic blockade should more strongly influence what is referred to as 'working memory' than 'reference memory'. The same effect should apply in simpler tasks comparing 'working' and 'reference' memory such as the Y maze.

5.4.2. Morris water maze

In this general framework, cholinergic blockade should not eliminate the recall of a previously learned location for a hidden platform in the Morris water maze, but should interfere with the learning of a new location. Learning of platform location in the water maze is impaired by injections of scopolamine [160,217], by injections of the M1 selective antagonist pirenzepine [96] and by combined lesions of the medial septum and vertical limb of the diagonal band of Broca [98,154,185] but not by lesions of the nucleus basalis magnocellularis [98]. However, in a task involving discrimination between two platforms, one of which capsizes, injections of atropine block learning of both hidden platform location and learning of which of two visible platforms is stable [99,187]. This lack of a purely spatial deficit supports the notion that cholinergic modulation plays a role in a general process of matching external stimuli to internal recall, beyond purely spatial behavior.

While loss of modulation between learning and recall should slow learning of platform location, it should have an even stronger effect when location changes frequently. In such a study, the recall of a recent context must be distinguished from the recall of previous trials – a type of reversal requirement which should be impaired by loss of cholinergic modulation. In a study in which platform location changed each day, and recall on the second of a trial pair was compared with the first trial, clear impairments appear with systemic injections of scopolamine [235–236] and intrahippocampal injections of scopolamine [27]. Studies using microdialysis for acetylcholine in aging rats do not show a correlation between performance on the water maze and levels of acetylcholine [77]. However, baseline levels of acetylcholine may be less important than the ability to make transitions between different levels of cholinergic modulation.

Consistent with other findings, loss of cholinergic modulation impairs learning but not recall performance in

other maze tasks. Injections of scopolamine impair selectively learning but not recall on a 14-unit T maze [213]. In tasks requiring delayed non-match to position, NBM lesions have been proposed to cause 'non-mnemonic' deficits, since the effects are delay independent. The requirement for delay dependency assumes some automatically decaying store, whereas the framework presented here focuses purely on storage and subsequent effects on recall due to storage of additional information. Impairments of storage processes could affect performance of the task even with no delay between learning and recall.

5.5. *Effects of post-training injections. 'Consolidation'*

A considerable amount of work on the behavioral role of modulatory substances utilizes post-training injections of pharmacological agents ([62], for review see [159]). These injections are presumed to influence a stage of 'consolidation' of the memory trace, but these tasks commonly involve much higher doses of agonist or antagonist than injections before training, and in some cases, post-training injections do not impair performance [99]. In the framework presented here, these injections would be presumed to influence the stored representation of an event not by affecting a separate 'consolidation' process, but by altering the influence of post-trial experience. For example, if cholinergic modulation is blocked after learning of a task, the persistence of a recall state may cause retroactive interference with the previously stored event, thereby impairing subsequent recall of that experience.

5.6. *Passive and active avoidance*

Many studies of the role of cholinergic modulation in behavior use avoidance tasks in which rats or mice must avoid shock by either suppressing their exploration of a particular region of the testing chamber, or actively moving away from the region in which shock is presented. Analysis of behavioral data in these tasks must not neglect the role of muscarinic cholinergic modulation in the basal ganglia. In particular, cholinergic antagonists frequently cause increased activity which might be due to effects in this structure, and this increased activity might underlie the patterns of effect in many of these tasks (see discussion in Hagan and Morris [97]). For example, these effects could underlie the tendency for cholinergic agonists to enhance 'memory' function as shown by shorter escape latency in active avoidance tasks using two-way shuttle tasks [245], while causing impaired performance in passive avoidance tasks (as shown by shorter reentry latency) [34]. In the framework presented here, cholinergic antagonists could impair learning of passive and active avoidance by decreasing the influence of sensory features of the testing apparatus on the rats, thereby preventing effective recall of the shock stimulus when the rat or mouse is next placed in the chamber. However, the enhanced performance in some circumstances in two-way active avoidance tasks seems more likely to be due to increased activity simply allowing the rat more rapidly to discover the means of escaping shock. One manipulation using this experimental paradigm has attempted to explore 'retroactive interference', by blocking the learned avoidance behavior (tone-shock) through post-training exposure to a similar environment with a flashing light [178]. This 'interference' can be prevented by injections of atropine or methylatropine before the flashing light presentation, suggesting that cholinergic blockade actually decreases interference, rather than increasing it as proposed here. However, this makes the assumption that the 'interference' effect is only retroactive, with the flashing-light stimulation changing the representation of the previous learning. In fact, the decreased avoidance response after the flashing light environment could instead reflect an effective separate learning of that environment as not being associated with shock. Cholinergic blockade could allow recall of the previous tone–shock episode to cause *proactive* interference during storage of the flashing light–no shock episode, such that the rat continues to associate the environment with shock. The fact that a substance which does not cross the blood–brain barrier (methylatropine) has a similar effect in this task, calls into question whether this effect is cortical at all, or reflects peripheral effects of cholinergic antagonists.

5.7. *Operant conditioning*

5.7.1. *Discrimination tasks* 'Behavioral inhibition', or 'attention'.

Cholinergic antagonists have been shown to impair performance on discrimination tasks requiring different responses to different stimuli. Cholinergic antagonists more strongly impair performance on discrimination tasks when stimuli are less discriminable [74]. These types of effects of cholinergic antagonists in discrimination tasks have been interpreted as being due to effects on 'sensory processes' (usually quantified as d') or 'attention' [97] rather than 'memory'. However, in the framework presented here, the influence of acetylcholine on cortical dynamics will play a simultaneous role in all of these parameters. When acetylcholine is present, cortical activity will be more directly influenced by afferent input (stronger 'stimulus control') and less influenced by internal interpretations of the environment. These exact same effects will simultaneously enhance the rate of learning of the pattern of afferent stimulation and decrease interference from previous learning. Thus, this range of different effects can be accounted for within the same cortical model. The primary means for

distinguishing these factors may be the fact that 'stimulus control' will depend on the level of cholinergic modulation in a number of neocortical regions involved in processing of the stimulus, whereas 'memory' for the particular task may be localized in regions where activity is representative of the higher order contingencies which uniquely define the task to be performed. The cholinergic antagonist scopolamine has also been shown to increase the number of false positives (responses to unrewarded stimuli) in several behavioral tasks [51]. One interpretation of this result which is consistent with the role of acetylcholine proposed here is that these false positives reflect a greater number of spurious correlations between learned patterns. This effect also appears with tasks in which multiple or irrelevant cues as opposed to single cues are presented [237].

5.7.2. Conditional discrimination

The role of cholinergic modulation has been tested in a conditional visual discrimination task requiring left or right lever response dependent upon fast or slow flashing visual stimuli [194]. In the theoretical framework presented here, this type of conditional task should be particularly sensitive to loss of cholinergic modulation, since most of the context is similar between the two conditions, thereby allowing considerable proactive interference. Lesions of the basal forebrain impair acquisition of this task [75], but the level of impairment surprisingly does not correlate with the loss of cholinergic markers in the cortex [194]. In addition, impairments caused by injections of muscimol into the basal forebrain are not reversed by physostigmine [176] suggesting that the impairment due to lesions or muscimol injection may be due to damage to other basal forebrain projections, such as the GABAergic projection. As described above, activation of $GABA_B$ receptors causes similar effects on synaptic transmission as activation of cholinergic receptors [218], suggesting that this innervation may also decrease recall of previously learned information.

5.7.3. Multiple-choice reaction time 'Attention'

Cholinergic and noradrenergic manipulations have been investigated in a task requiring responses to brief flashes of light in one of five corridors. Impairments on this task have been demonstrated after lesions of the nucleus basalis of Meynert [175] or injections of the $GABA_A$ agonist muscimol into this region [176]. Reflecting similarities between the effects of acetylcholine and norepinephrine, deficits in this task have also been noted after lesions of the dorsal noradrenergic bundle. These deficits have been discussed as reflecting attentional impairments. Similar to the human data discussed above, this evidence can be considered to reflect a decrease in external influence on cortical activity causing decreased performance in tasks requiring sustained attention to stimulus features.

5.7.4. Negative patterning 'Configural association learning'

A particularly interesting set of experiments concerns tests of the role of cholinergic modulation in learning negative patterning – that is, learning to respond with a lever press to either tone $(T)^+$ or light $(L)^+$, but not to a combination of tone and light $(L\&T)^-$. This task requires more than simple associative memory function between existing concepts, instead requiring formation of a new, separate representation of the combined stimulus, as a 'configural' cue [196,216]. Note that negative patterning is equivalent to the XOR problem discussed extensively in the modeling literature.

Learning and performance of a negative patterning task are strongly impaired by lesions of the hippocampal formation [216], and have been tested after injections of scopolamine [169]. This provides a useful test of the model for hippocampal function presented here. In the framework presented here, formation of simple associations could be performed rapidly in hippocampal regions CA3 and CA1. Subsequent formation of configural associations would depend upon a mismatch between the reward expected on the basis of recall at the Schaffer collaterals in CA1, and the absence of reward signalled by the input from entorhinal cortex to CA1. This would let cholinergic modulation remain high, suppressing Schaffer collateral input, enhancing response to entorhinal input and allowing separate formation of a representation of the compound cue. In contrast, blockade of cholinergic modulation by scopolamine would prevent the suppression of synaptic transmission. With Schaffer collateral synapses at full strength, the recall of simple associations would dominate, preventing formation of a new representation for the compound stimulus. Thus, scopolamine should impair performance of this task.

Injections of scopolamine before each of a large number of training sessions did not impair acquisition of negative patterning [169]. However, in a separate set of animals which had already acquired the task, scopolamine impaired performance of the task, preventing the decrease in response to the compound stimulus (L&T) which normally occurs during each session. As discussed in that paper, rather than representing impaired recall, this could reflect an impairment of the relearning of the task during each session. This would more accurately match the evidence for learning impairments in primates, which involve single injections of scopolamine and training on trial unique stimuli, rather than repeated injections during learning of the same stimuli across several days. If possible, the effects of scopolamine on the learning of novel negative patterning tasks should be tested. This might be

difficult with light and tone stimuli in rats, but may be possible with olfactory stimuli.

5.8. Olfactory memory in rats

The theoretical description of the function of the olfactory cortex described above suggested that acetylcholine should play an important role in allowing independent representations of odor cues to be created. Blockade of cholinergic modulation should interfere with performance on tasks requiring learning of different odors or odor associations in different contexts. In a test using trial unique olfactory stimuli, scopolamine causes an impairment in a delayed match to sample task in which animals must choose which arm of a T-maze contains a previously presented odor [192]. In addition, previous work showed that scopolamine prevented the discrimination between novel and familiar odors as measured by time spent sniffing [120]. Scopolamine also impairs learning to recognize the odor of other individual rats [189,212]. Thus, scopolamine may interfere with the self-regulation of learning and recall dynamics in cortical structures, impairing the formation of new representations of individual odors.

6. Conclusion

The techniques of computational neuroscience are essential for linking the extensive evidence on the role of neuromodulators in behavioral tasks to the physiological evidence about effects of neuromodulators within cortical structures. As presented here, physiological data is available on the cellular effects of a large number of neuromodulatory substances, with many effects in common between different neuromodulatory substances. However, the functional significance of these cellular effects cannot be determined until they are incorporated in network models which explicitly simulate cortical function.

Computational modeling led to development of a theory of the functional role of cholinergic modulation presented here. Cholinergic modulation is proposed to change the predominant influence on cortical dynamics from recall activity dominated by intrinsic fiber synapses to learning activity dominated by afferent input to the cortex. This theory provides a general framework for considering modulation within a broad range of cortical structures, and may ultimately prove useful for linking the apparent disparate effects of cholinergic modulation in behavioral tasks. A preliminary overview of behavioral evidence suggests this possibility, but more extensive research is required to determine if behavioral data in this broad range of tasks can be effectively accounted for in simulations of the cholinergic modulation of cortical function.

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