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EU ADVANCED COURSE IN COMPUTATIONAL NEUROSCIENCE

An IBRO Neuroscience School

(30 July - 24 August 2001)

"Neuromodulation"

presented by:

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Neuromodulation - 1 - Can it be defined?

* Spatial distribution: neuromodulators often arise from brain nuclei that project widely to large numbers of brain regions

* Time course of action: the actions of neuromodulators are often considered to be slower than those of classic neurotransmitters

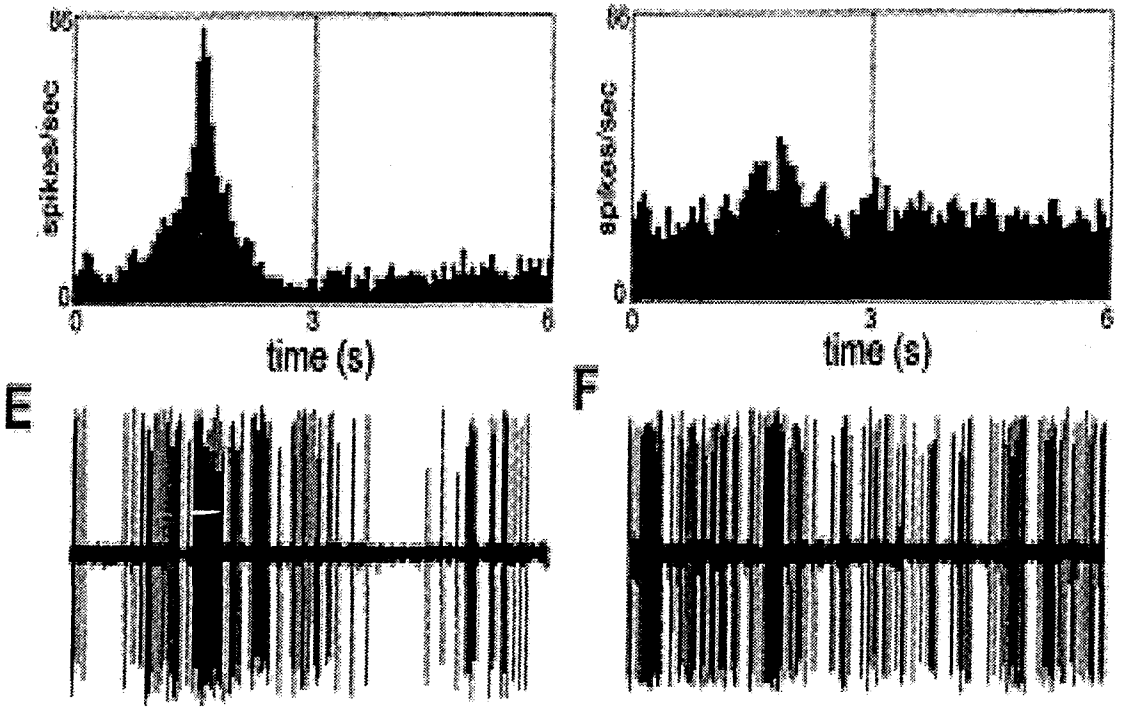
* Functionality: absence of presence of neuromodulators in given behavioral situations; modulation of existing neural function

* Neuromodulators have a large variety of effects: they change intrinsic neural properties; modulate synaptic events; modulate learning and many others.

* Some neurotransmitters, like GABA or Acetylcholine can be regarded as neurotransmitters or as neuromodulators depending on the nature of the receptors they act on.

Neuromodulation - 3 - Observations

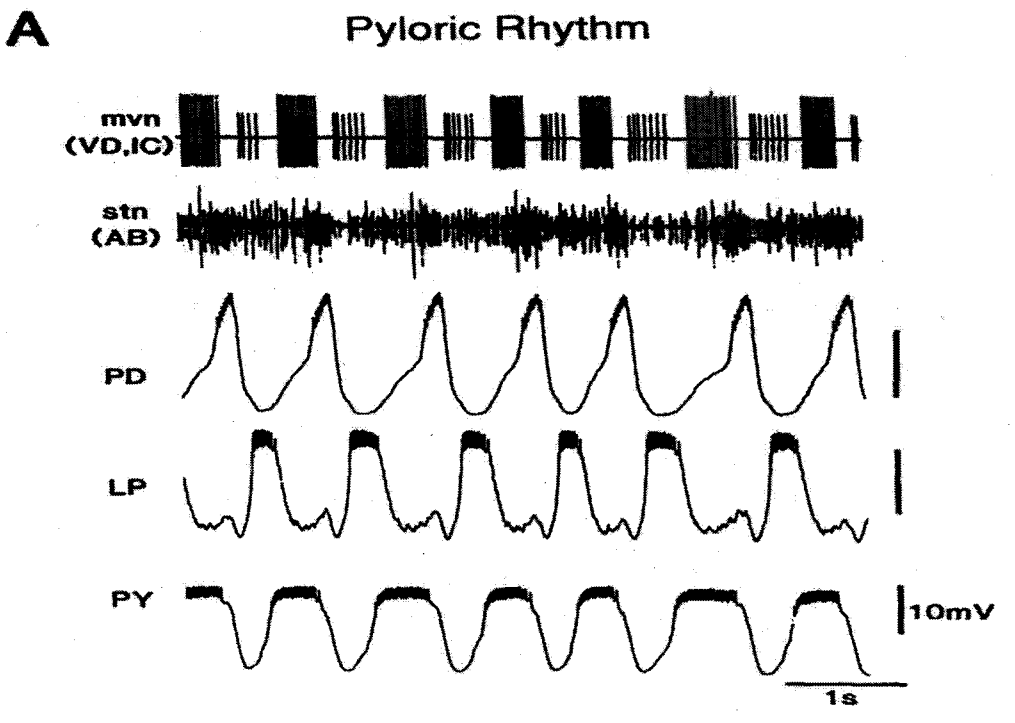
Modulation of signal-to-noise ratio (noradrenaline)

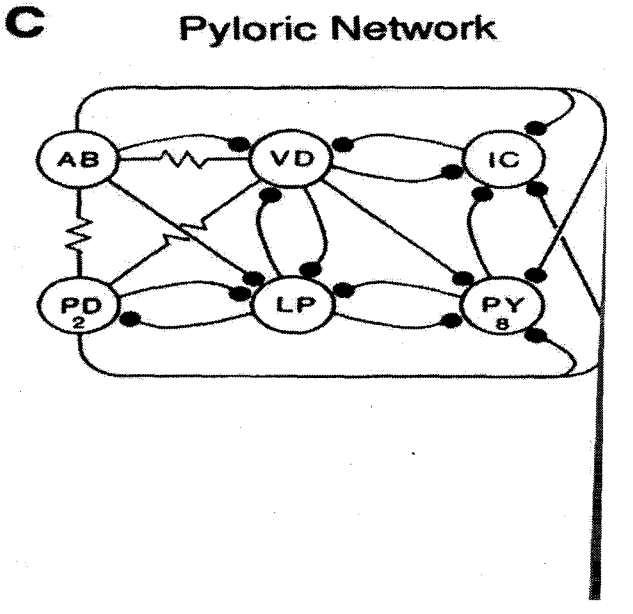


NA present

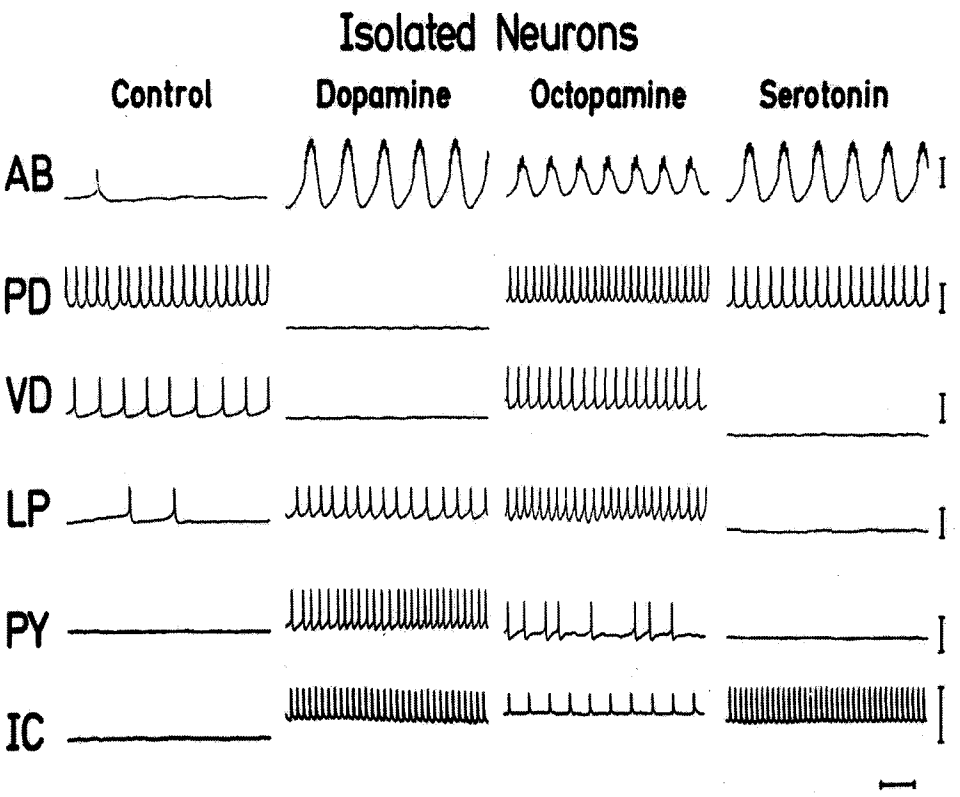
NA absent

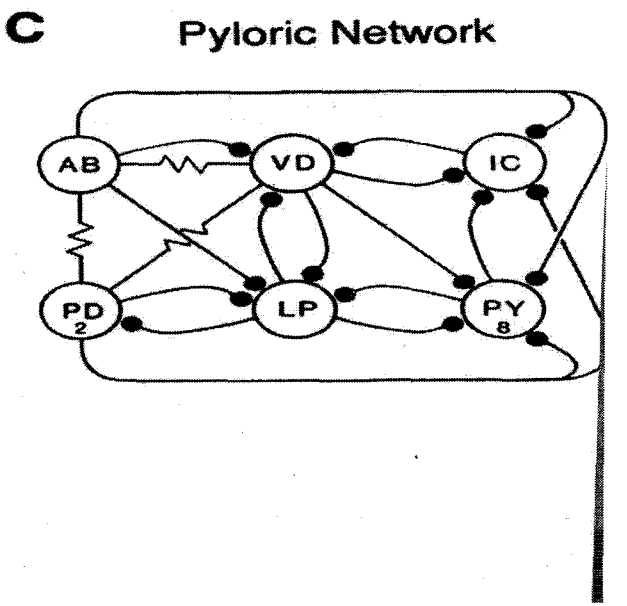
Stomatogastric ganglion (STG)



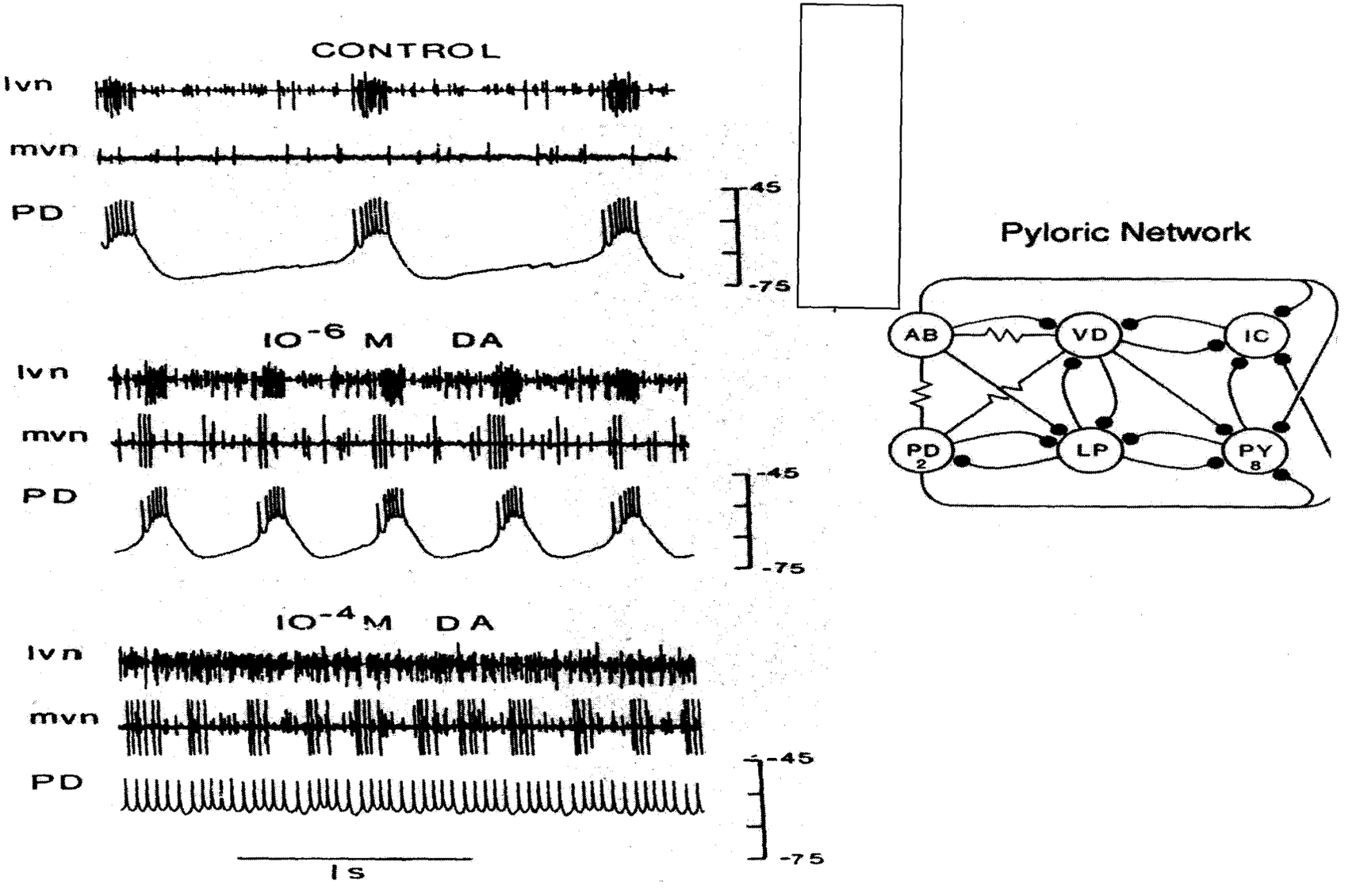


Stomatogastric ganglion (STG)





Stomatogastric ganglion (STG)



Other commonly observed neuromodulatory effects:

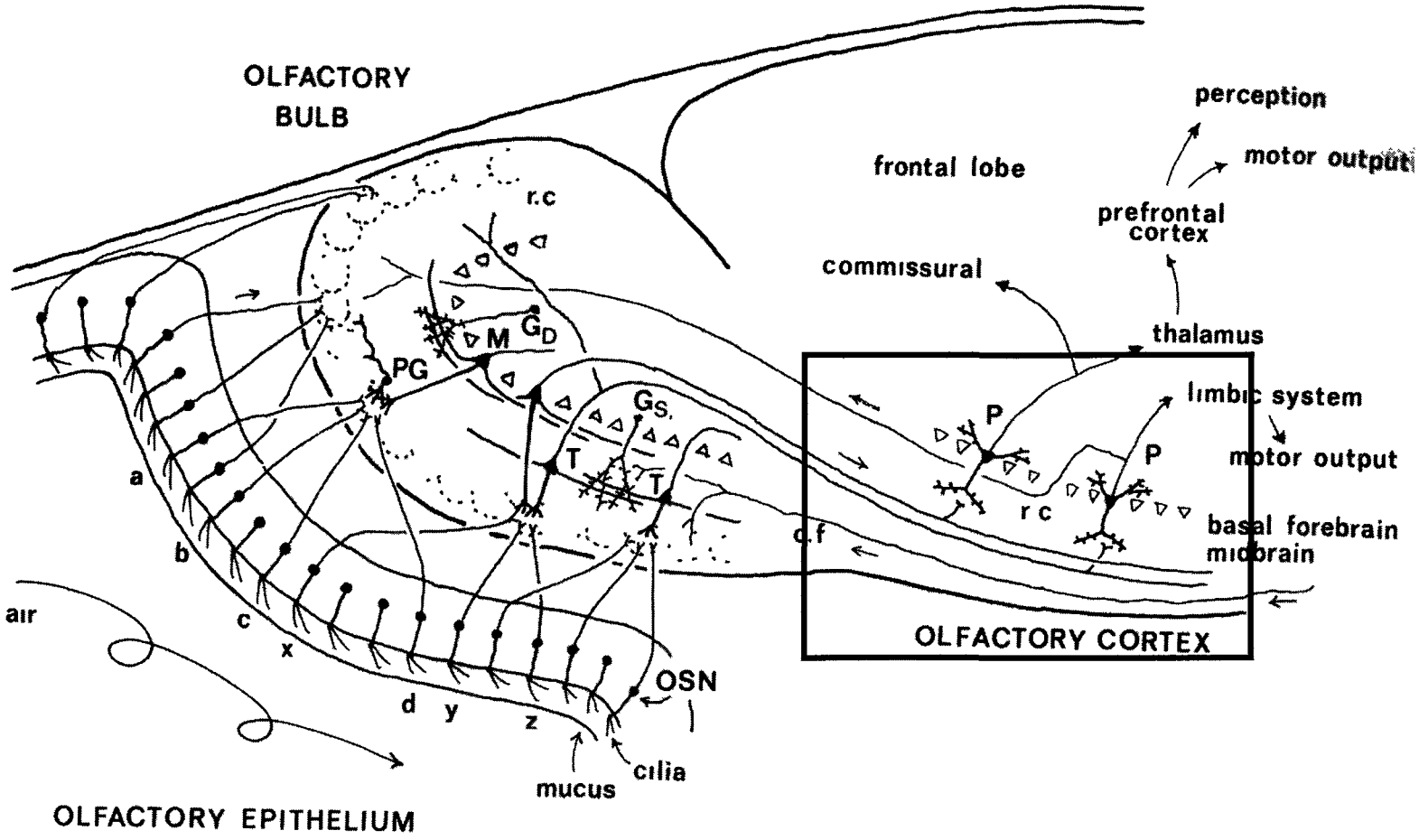
* Cholinergic agonists can evoke oscillatory activity in hippocampal slices
* Oscillatory activity in the hippocampus of behaving rats depends on cholinergic inputs
* Pyramidal cells in hippocampus and cortex are often depolarized by ACh and NA
* Synaptic potentials can be modulated (increased or decreased) by ACh or NA
* Long term potentiation is modulated by ACh and NA

and many others ..

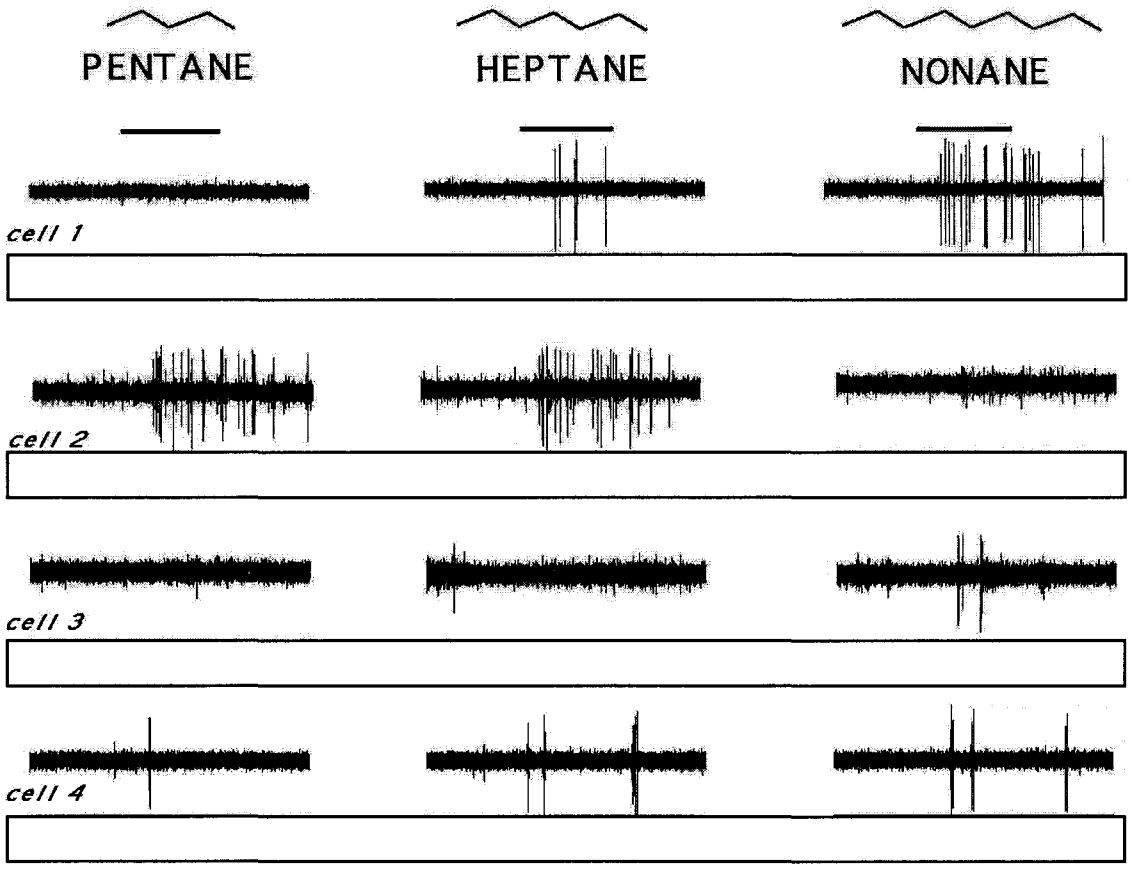
* Rats are impaired in long-term and short term memory experiments when certain neuromodulatory effects are blocked
* Rats show attentioanl deficits when cholinergic modulation is decreased

etc …

Neuromodulation - 4 - An example: cholinergic modulation of associative memory in olfactory cortex

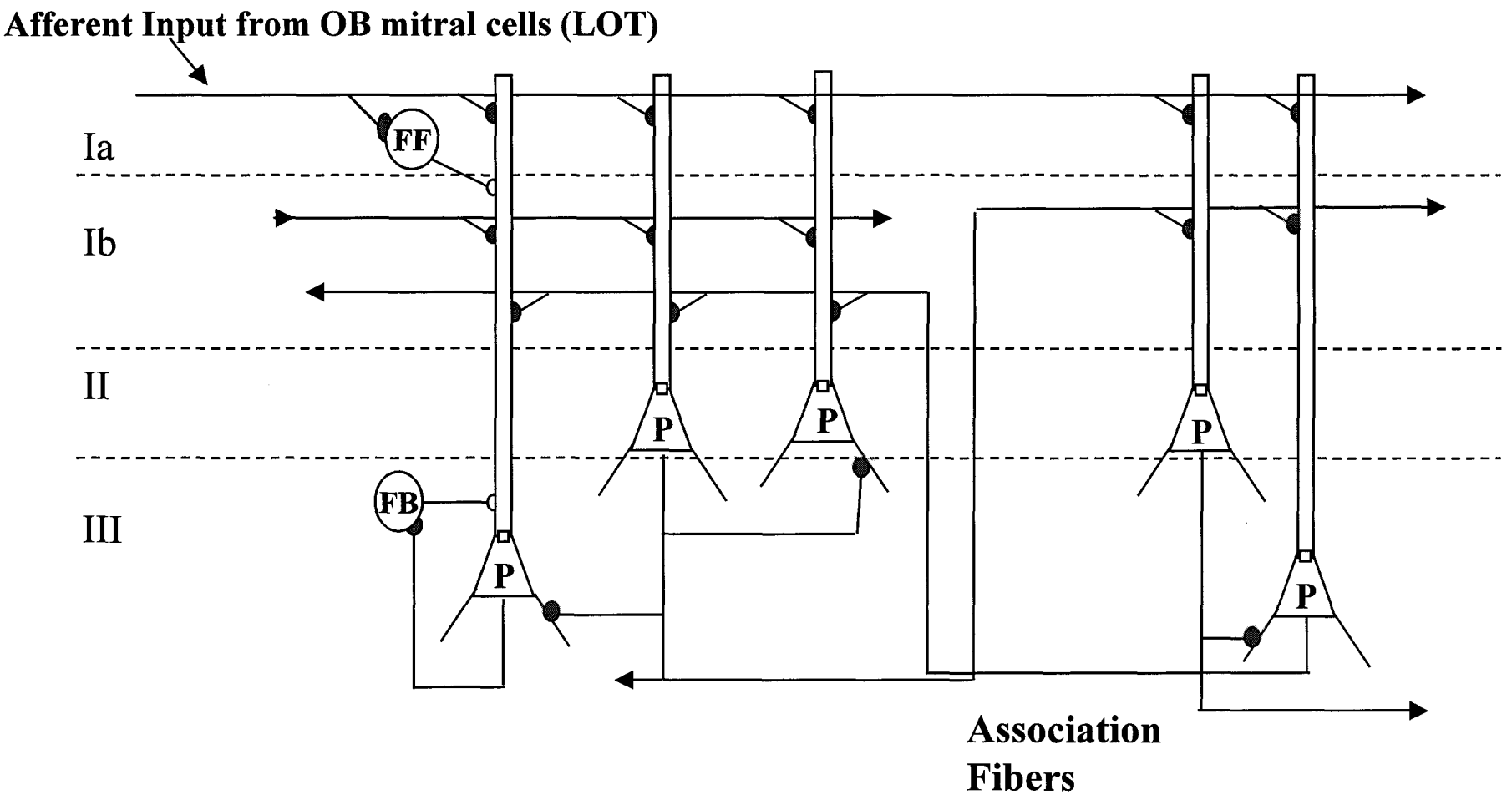


Odor responses of olfactory cortex pyramidal cells



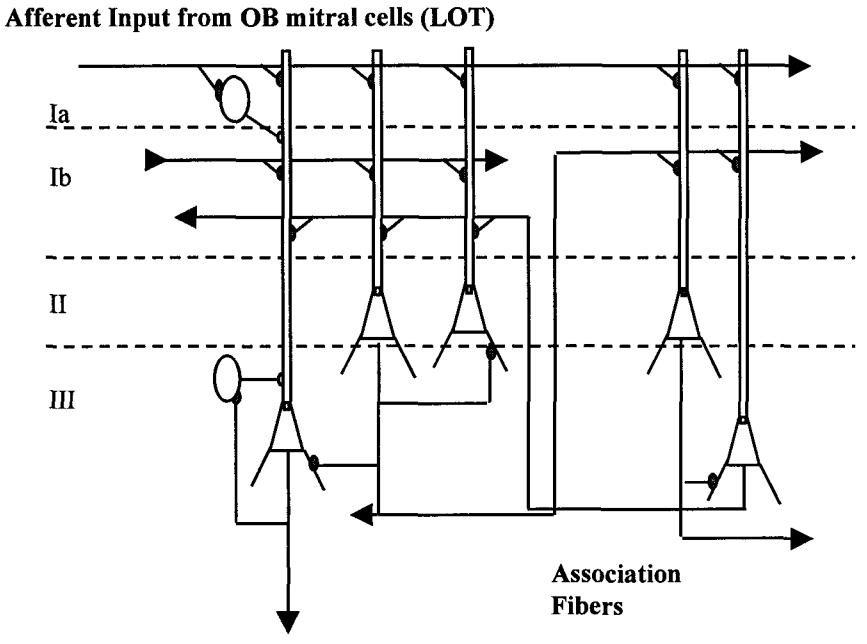
Wilson, D.A. J. Neurophys. 84(6): 3036-42 (2000)
Wilson, D.A. AChemS meeting, 2001

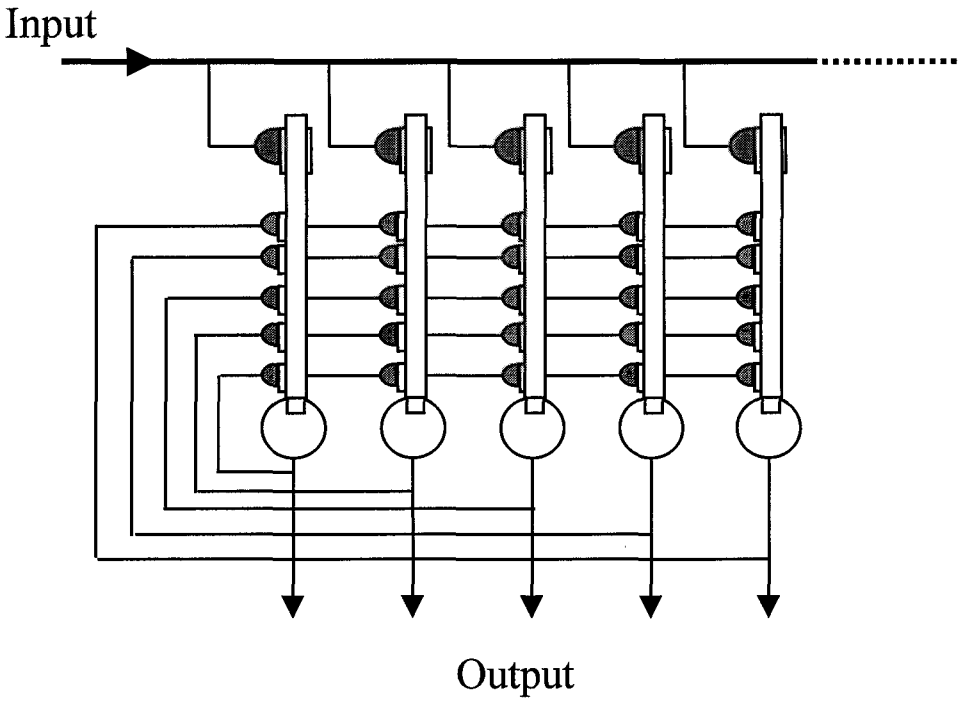
Piriform cortex circuitry



Haberly, L.B. Chem. Senses, 10: 219-38 (1985)

Piriform cortex =? associative memory network

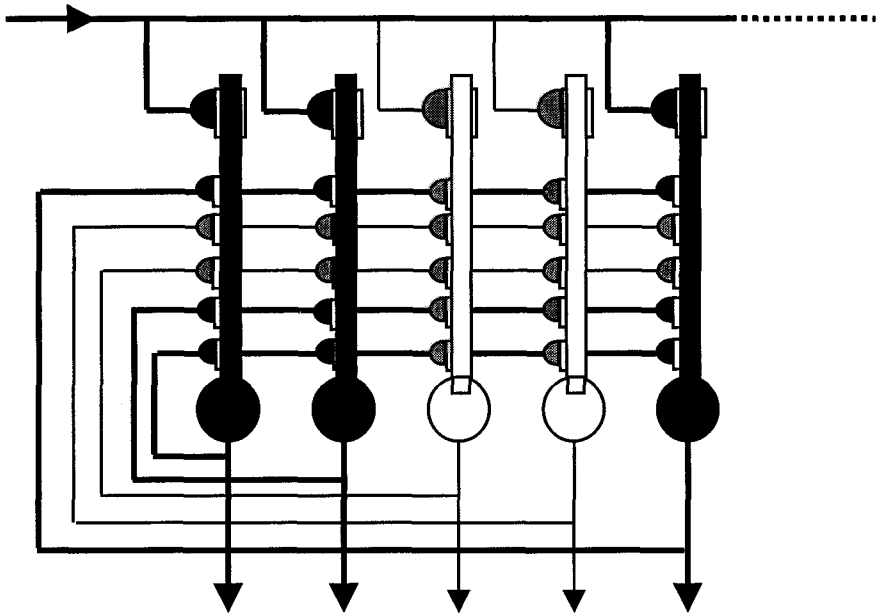




Haberly, L.B. Chem. Senses, 10: 219-38 (1985)
Haberly & Bower, TINS, 12: 258-64, (1989)

Associative memory function

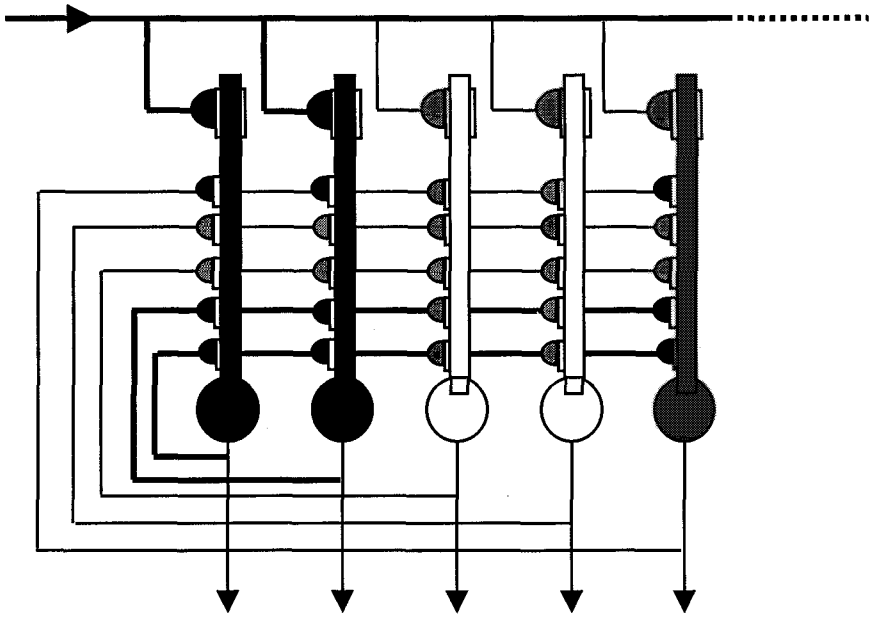
Learning



Output

Synapses are strengthened according to some "Hebbian" learning rule

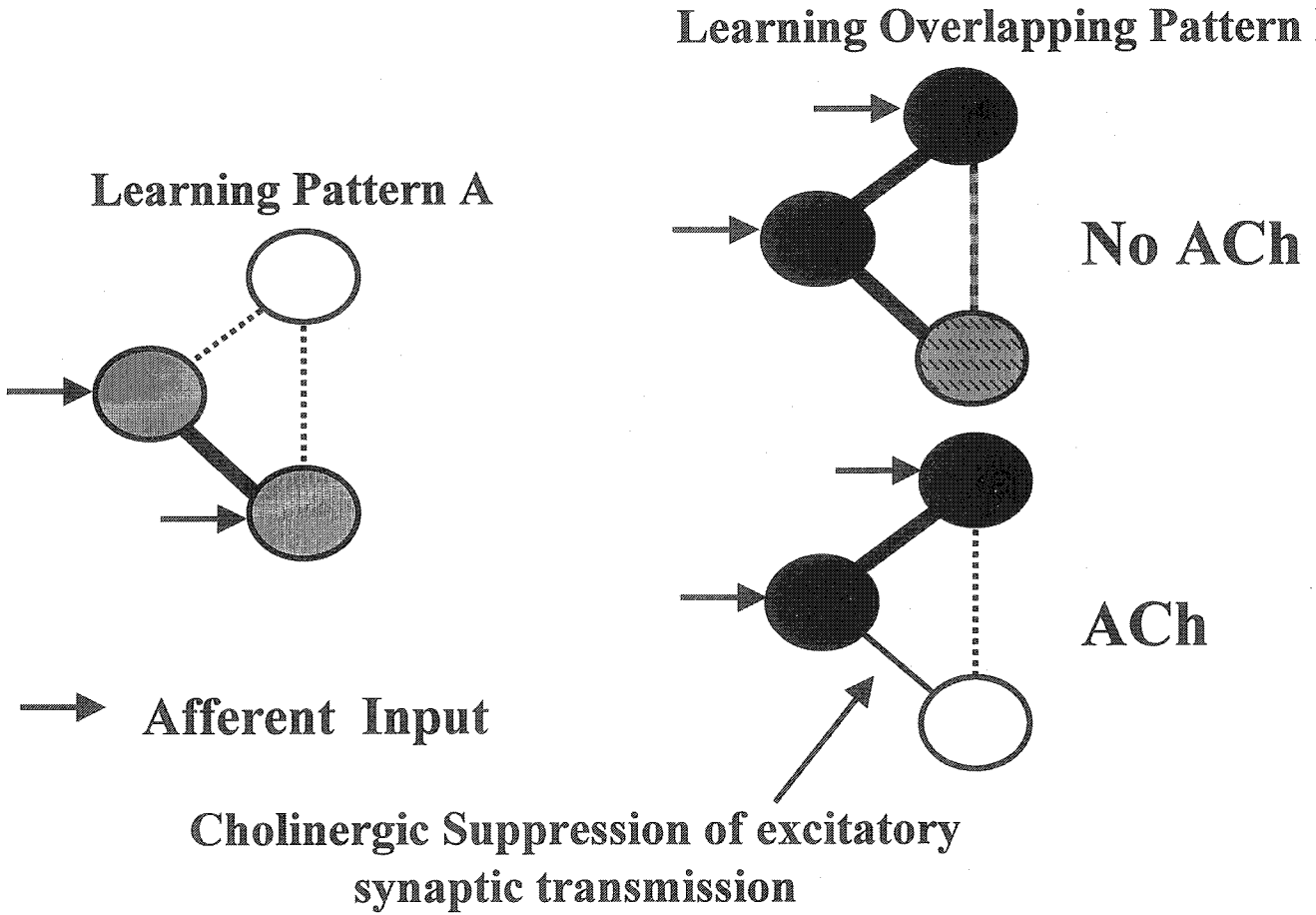
Recall



Output

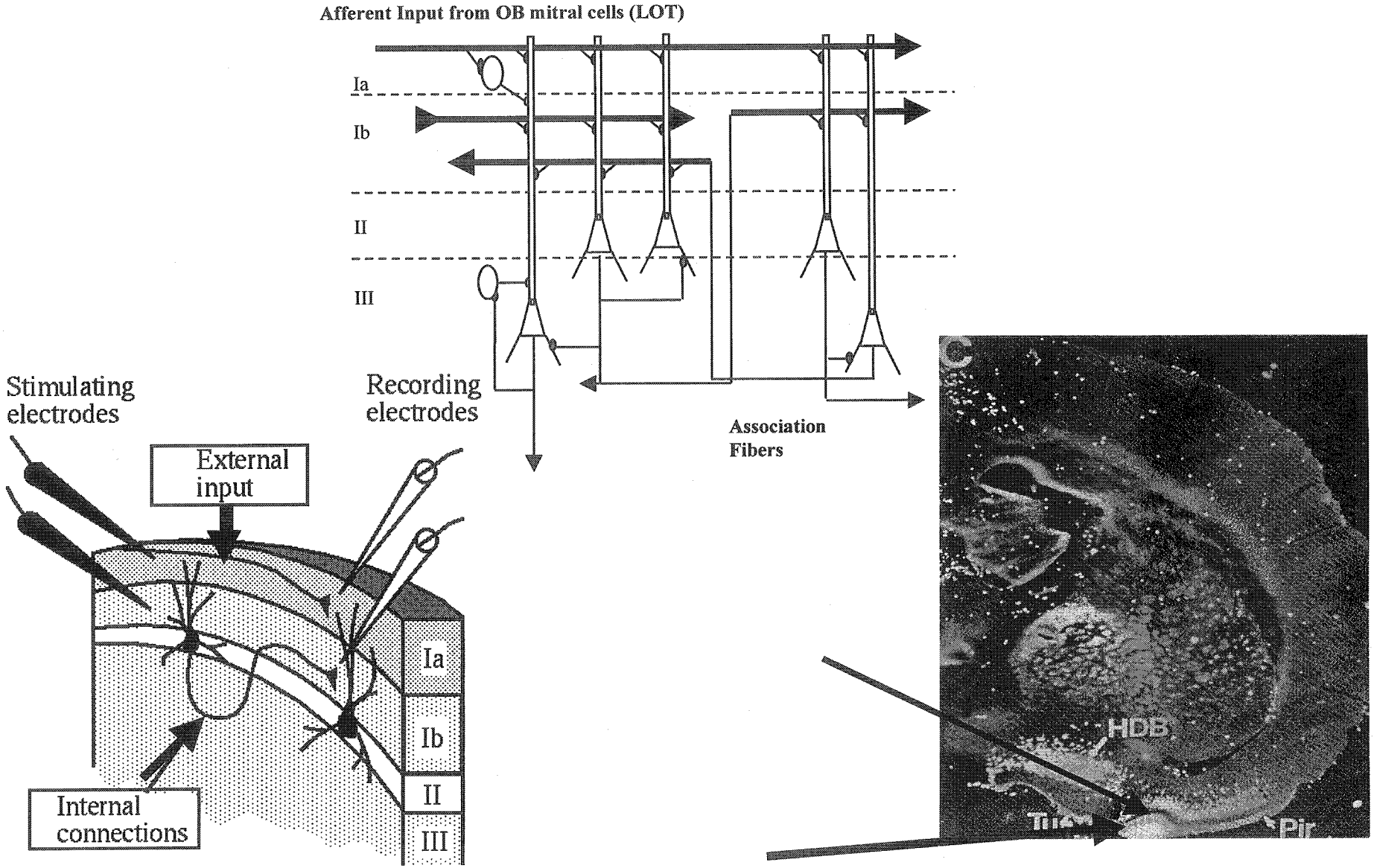
Incomplete input pattern is reconstructed

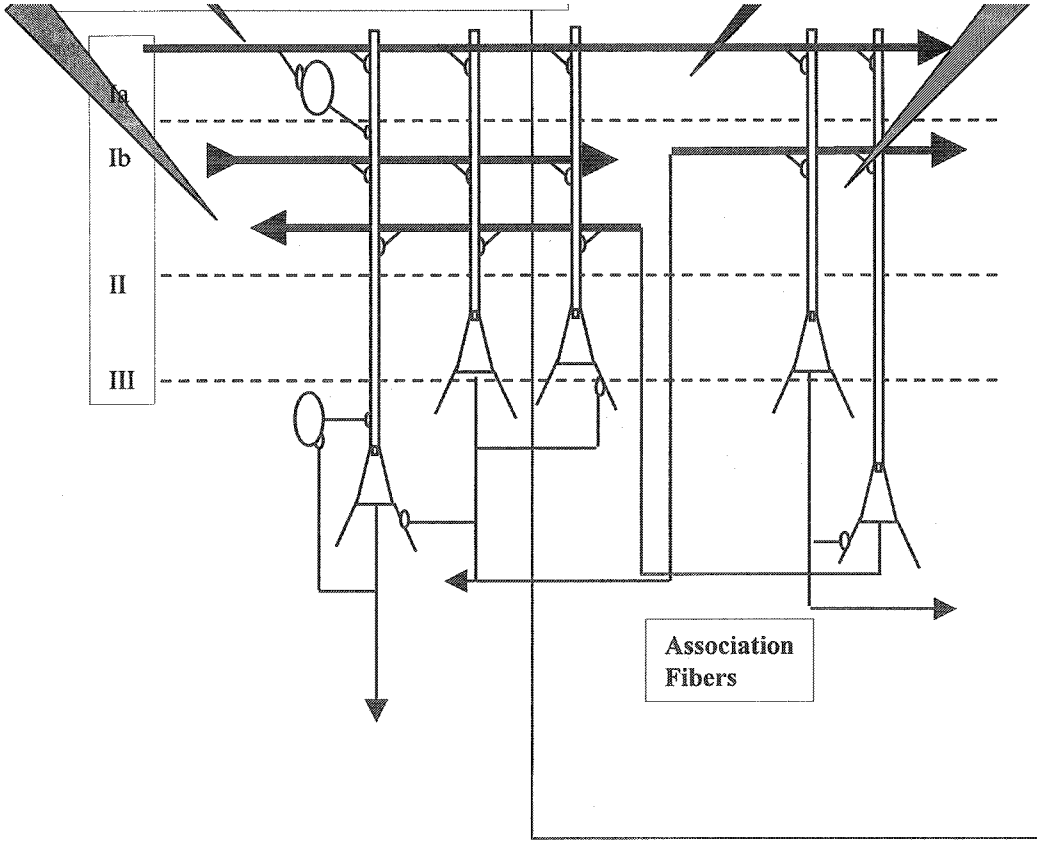
Cholinergic suppression of association fibers during learning reduces interference between overlapping patterns

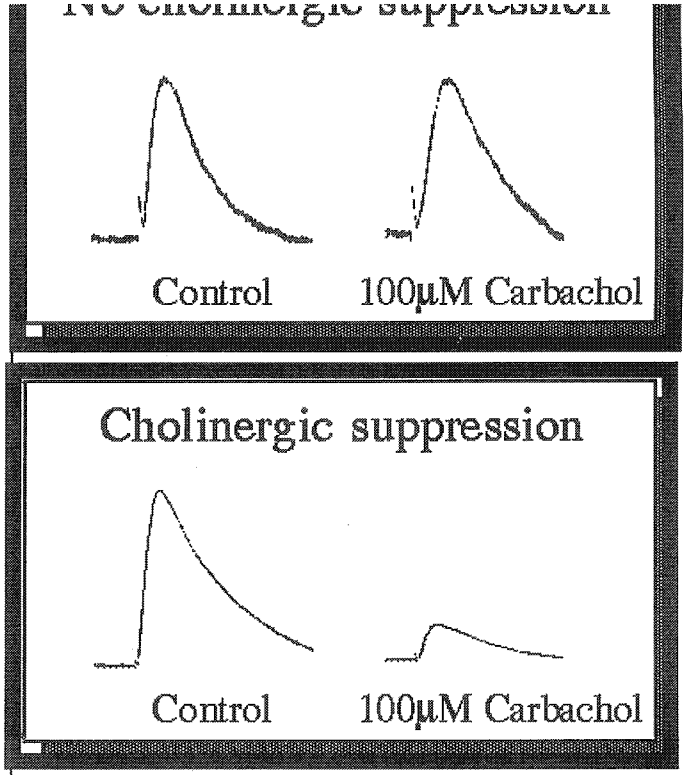


Hasselmo M.E. Neural Computation. 5(1): 32-44 (1993).
Hasselmo M.E. and Bower J.M. J. Neurophysiol. 67: 1222-1238 (1992).

Cholinergic suppression of association fibers recorded in a brain slice preparation

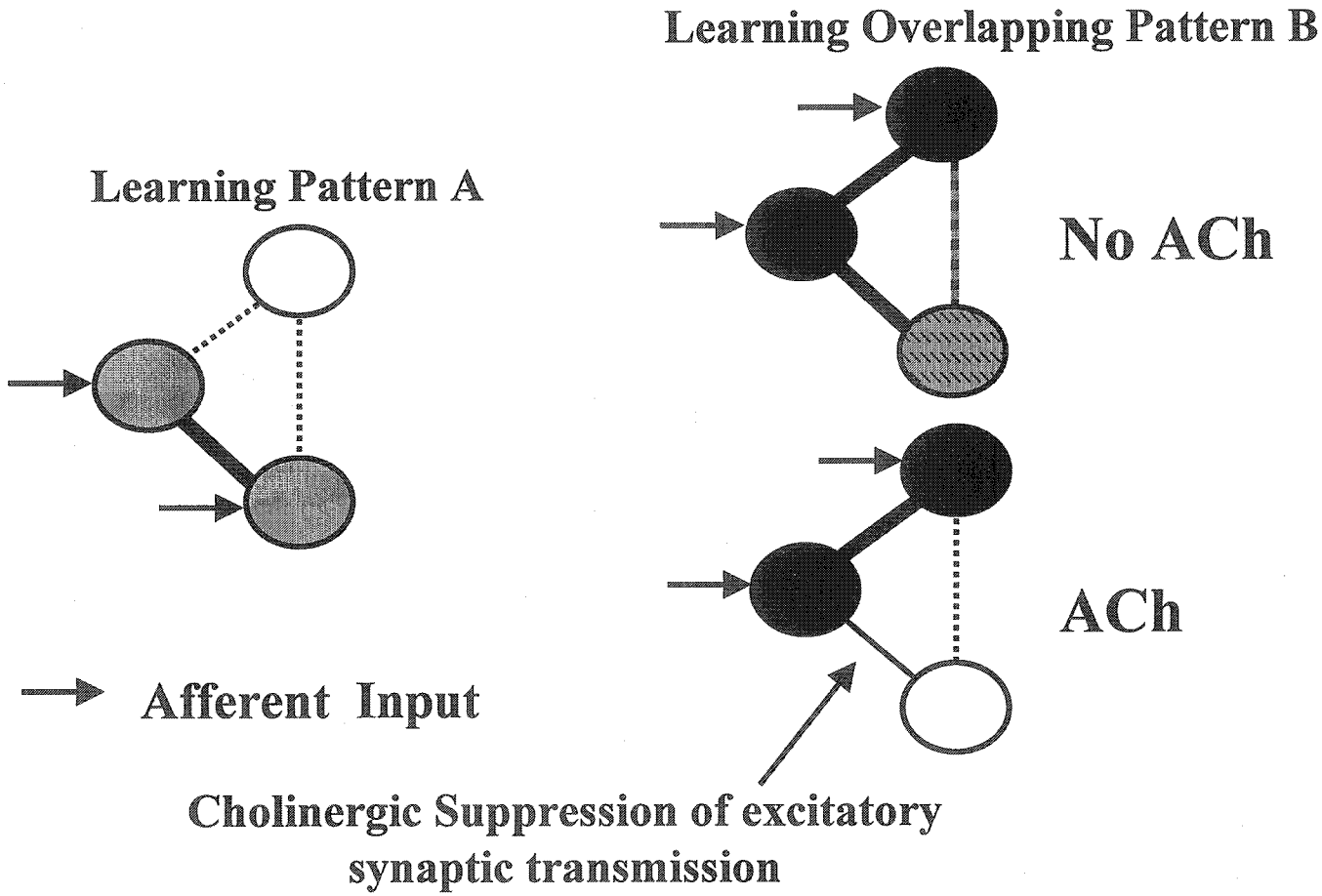






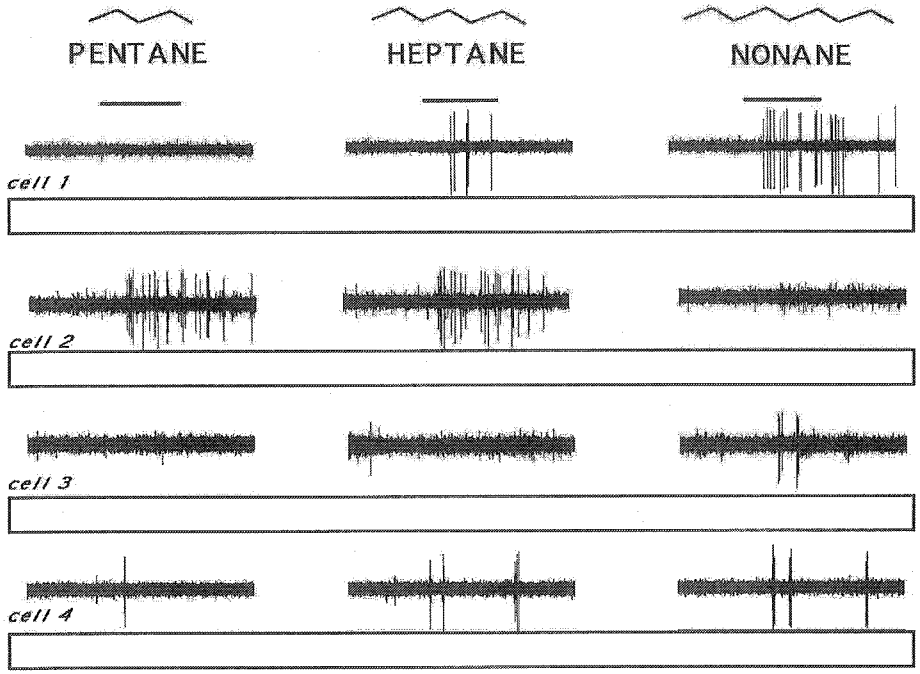
Layer 1b: intrinsic

Cholinergic suppression of association fibers during learning reduces interference between overlapping patterns

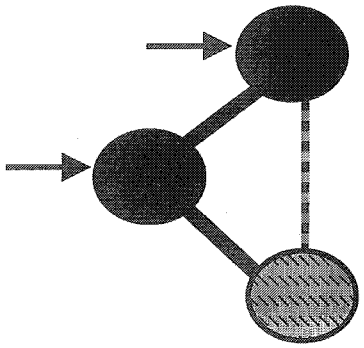


Hasselmo M.E. Neural Computation. 5(1): 32-44 (1993).
Hasselmo M.E. and Bower J.M. J. Neurophysiol. 67: 1222-1238 (1992).

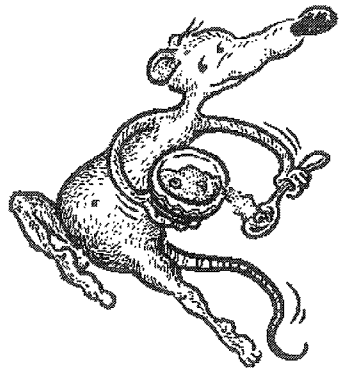
ACh important for processing of overlapping stimuli?



Learning Overlapping Pattern B

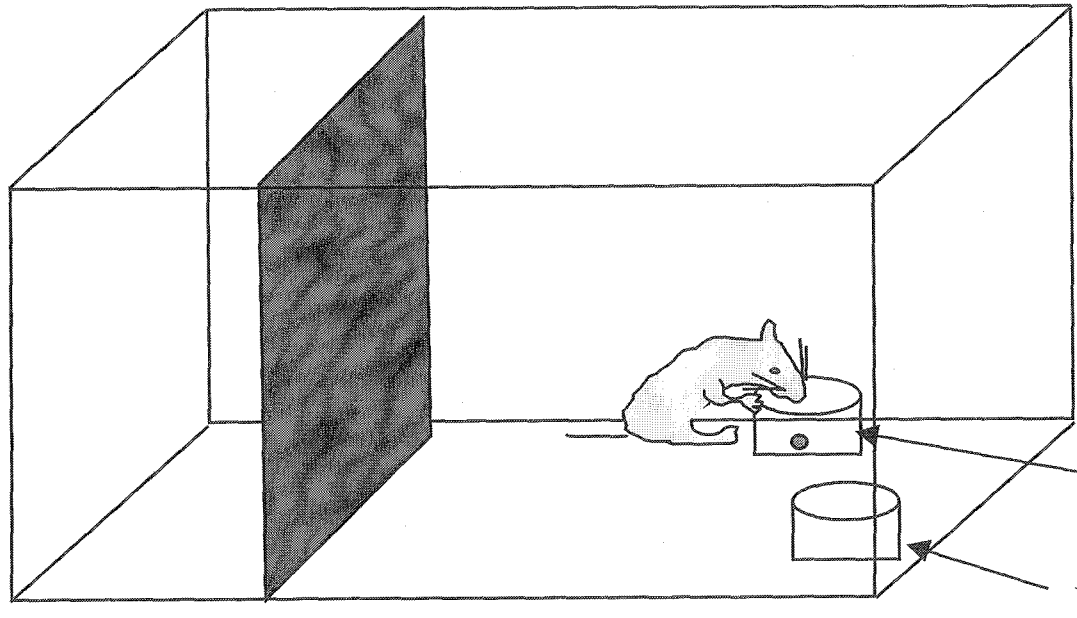


A behavioral aside ...



- Behavioral paradigm that measures perceptual similarities between odorants
- paired with selective lesions of the cholinergic neurons projecting to the olfactory system

Behavioral Paradigm

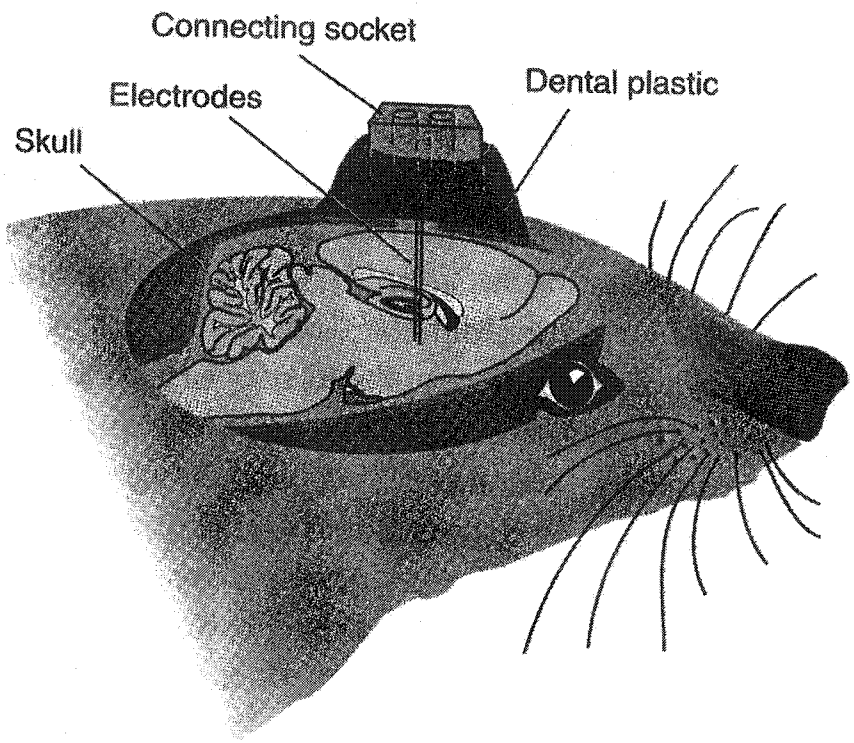


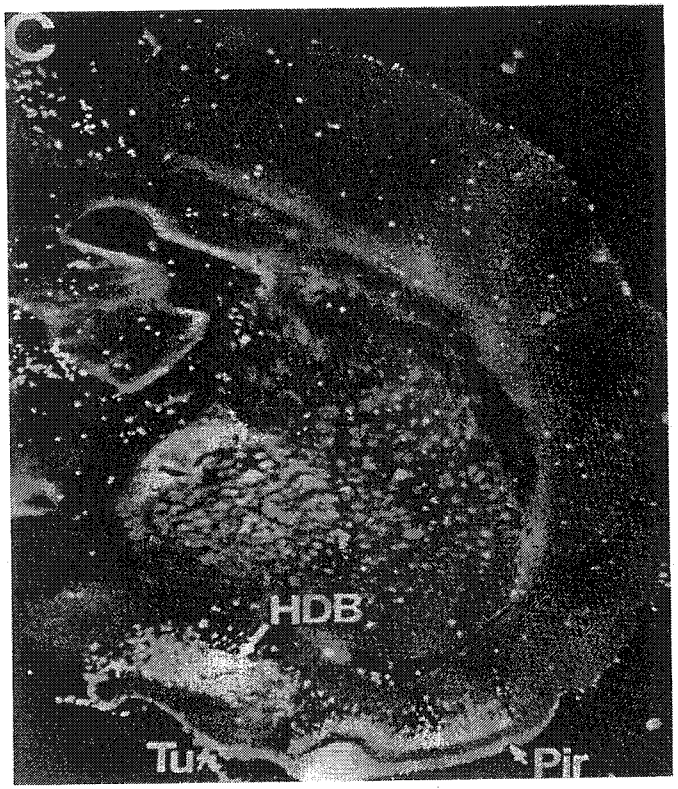
Odor	**A1 . . .**	**A1**	**Test***	**A1**	**Test***	**A1**	**A1**	**Test***
Reward	**x . . .**	**x**	**0**	**x**	**0**	**x**	**x**	**0**

**A1, A2 and X are tested in randomized order*

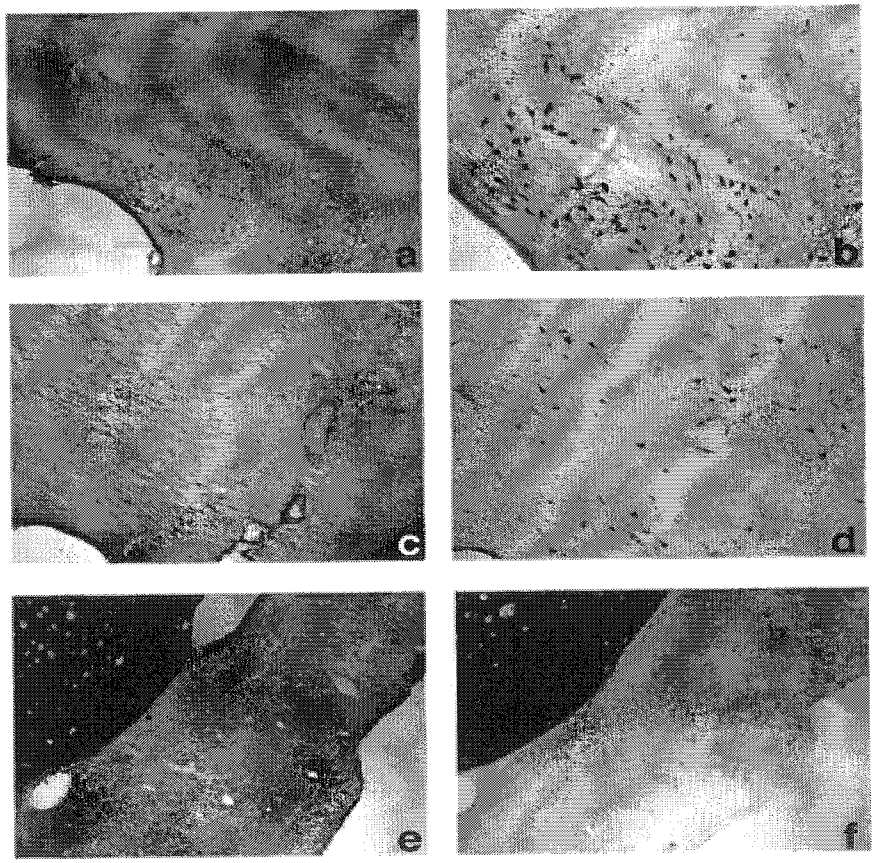
Linster, C. and Smith, B.H. (1999) Physiology and Behavior, 66 (4): 701-707.

Blocking of cholinergic modulation in the behaving animal:
* Injection of antagonists block cholinergic receptors
* Lesioning of brain nuclei which contain cholinergic neurons
* Selective, local, lesions of cholinergic neurons





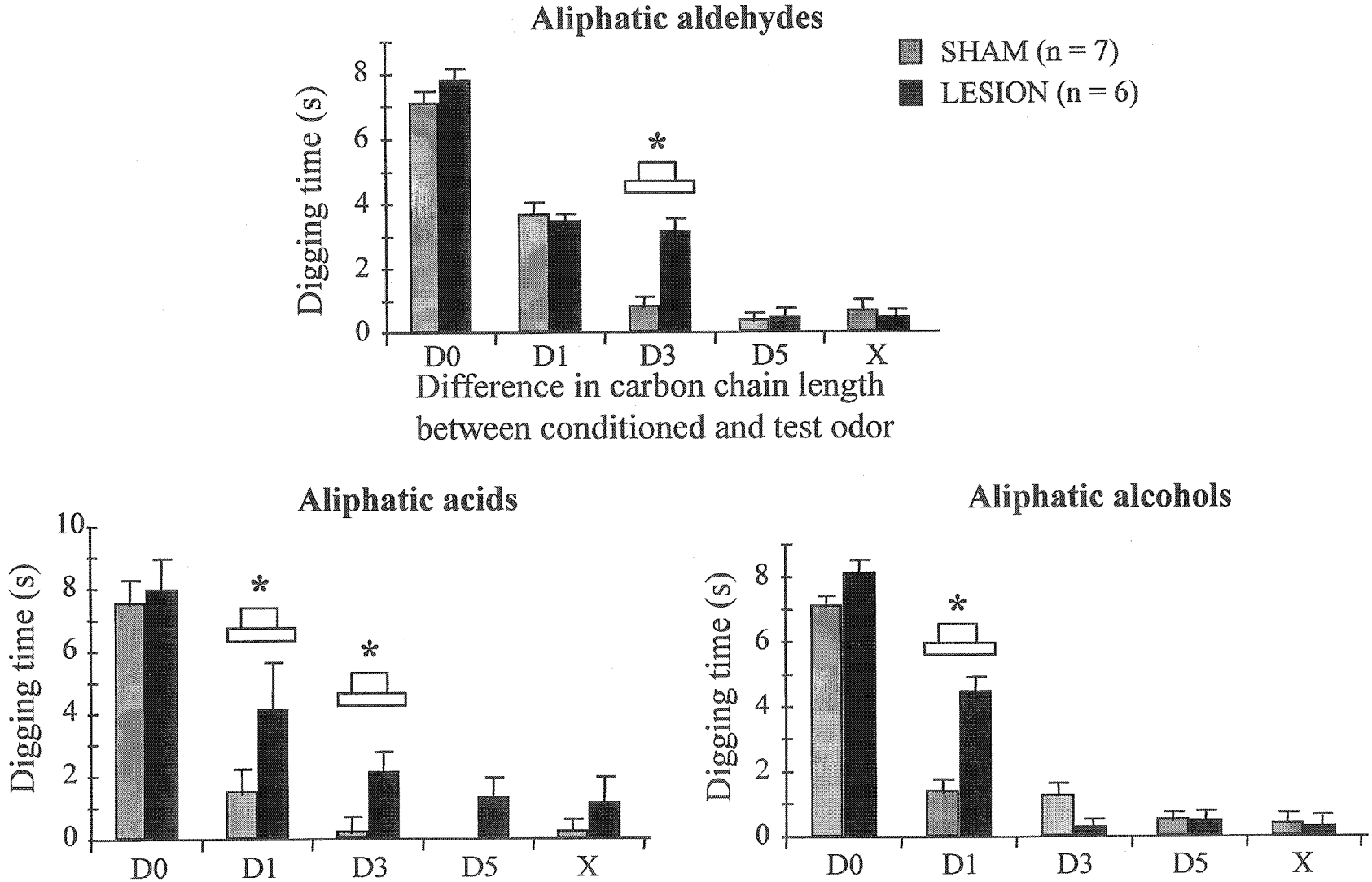
Saporin lesions only the cholinergic neurons in the horizontal limb of the diagonal band of Broca



a, b: Immunostaining for ChAT staining of HDB in control brain
c: Immunostaining for ChAT in the HDB of a lesioned rat.
d: Parvalbumin immunostaining in the HDB of a lesioned rat
e: AChE histochemistry in the PC of a control rat.
f: AChE histochemistry in the PC of an HDB-lesioned rat

Linster et al. Behavioral Neuroscience (in press)

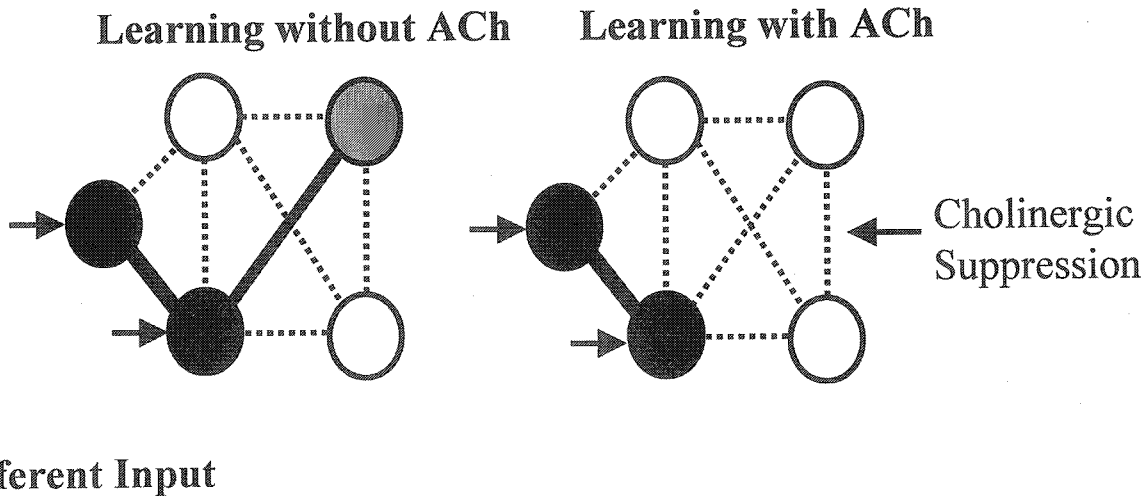
Lesions of cholinergic neurons increase generalization between similar odorants



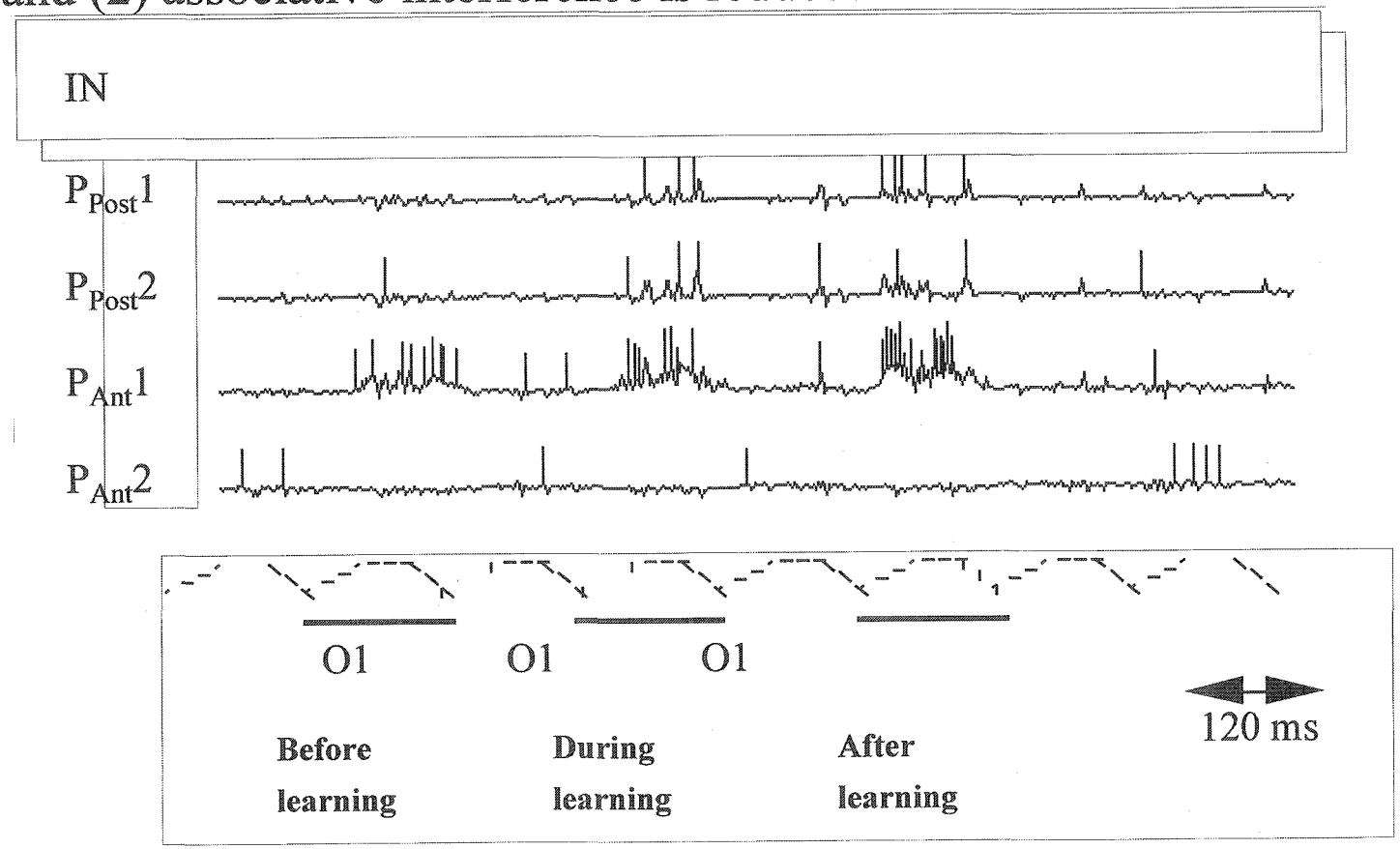
BUT ...

- In a computational model incorporating sparse synapses from the olfactory bulb (OB) to posterior piriform cortex (PC), activation of pyramidal cells in posterior PC depends on the spread of activation from anterior regions.

- The cholinergic suppression of association fibers during learning impairs the recruitment of neurons that do not receive direct afferent input.

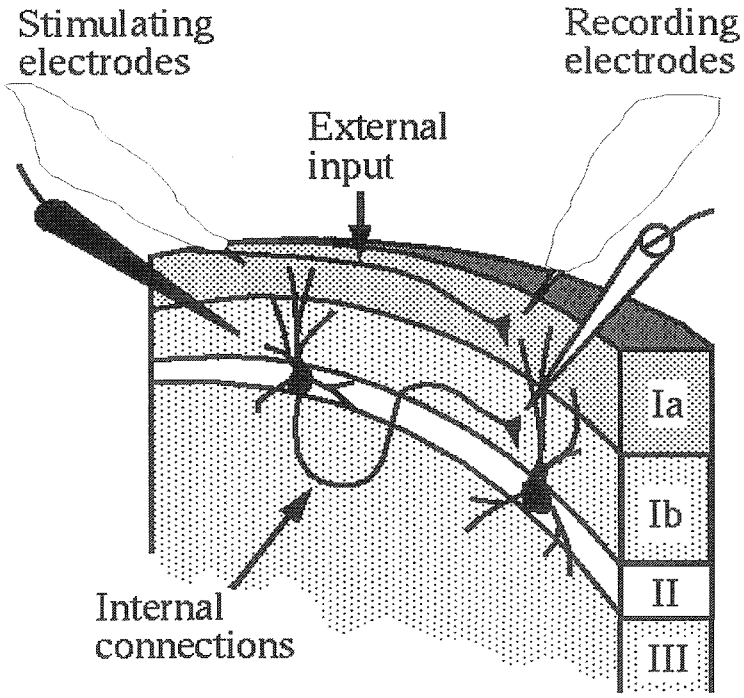


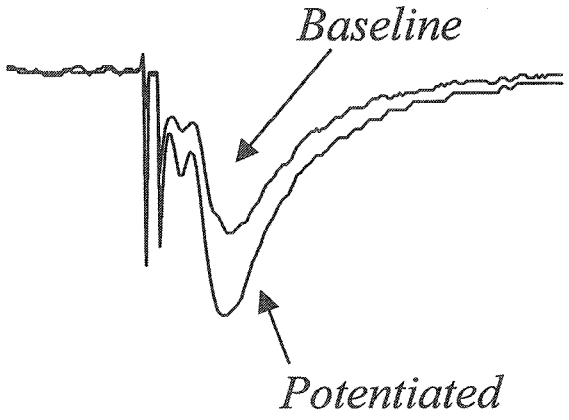
If selective cholinergic suppression of pre-strengthened association fibers is used, then (1) odor evoked activity spreads from anterior to posterior PC during odor learning and (2) associative interference is reduced.



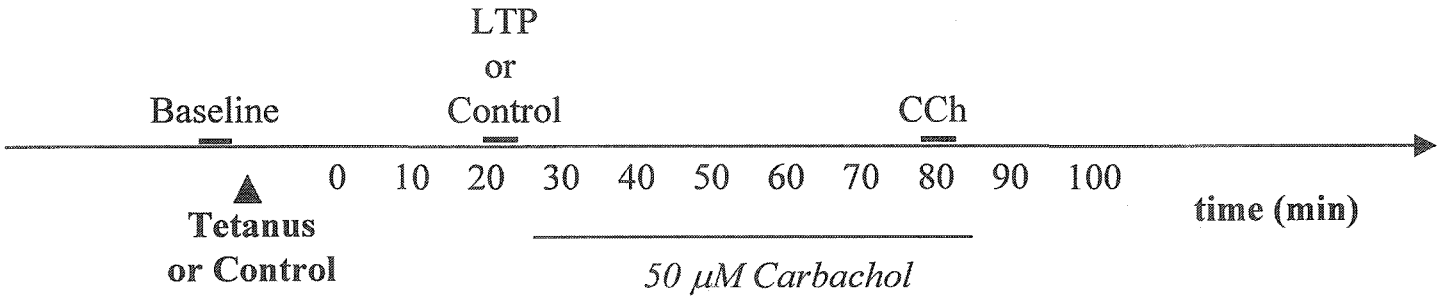
Linster, C. and Hasselmo, M.E. (1997) Computation and Neural Systems, Bower, J.M. (ed), Plenum Press.

Brain slice preparation

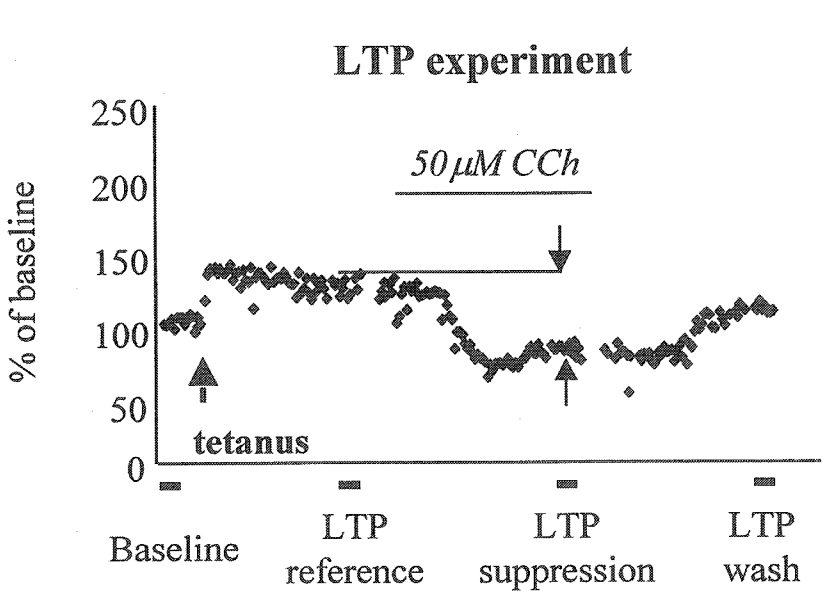


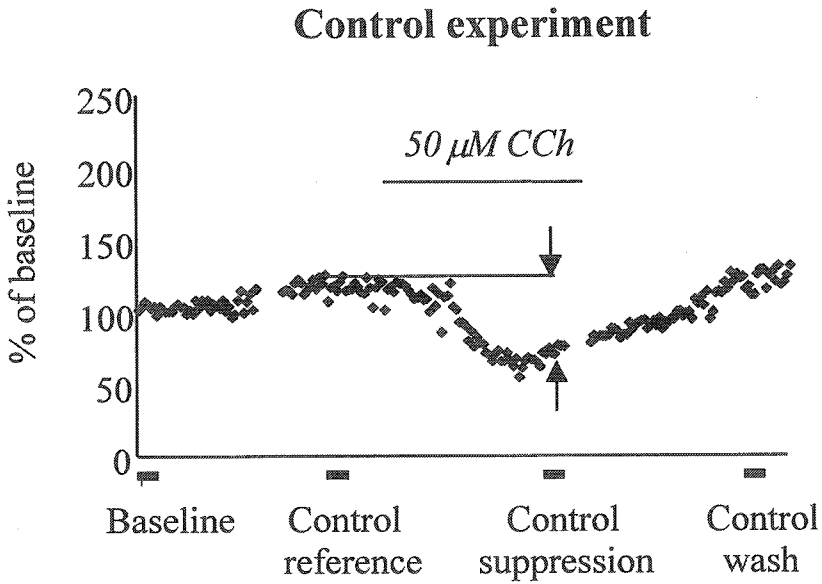


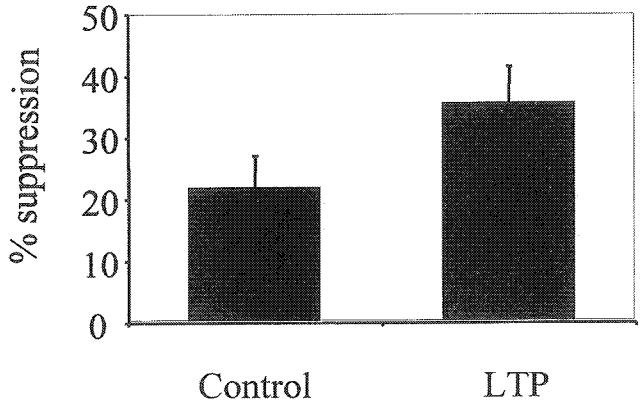
Protocol

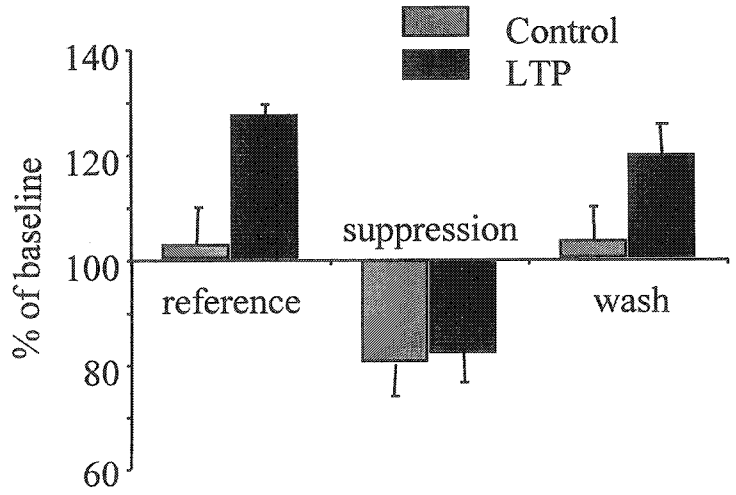


Potentiated fibers are proportionally more suppressed than unpotentiated fibers

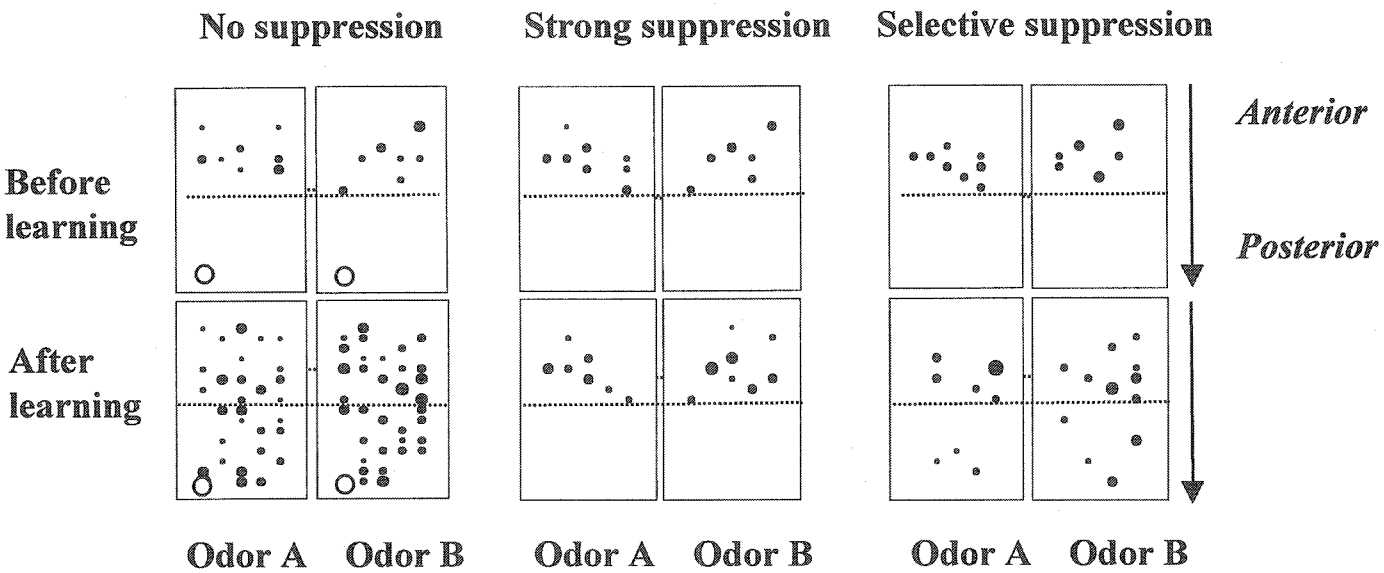


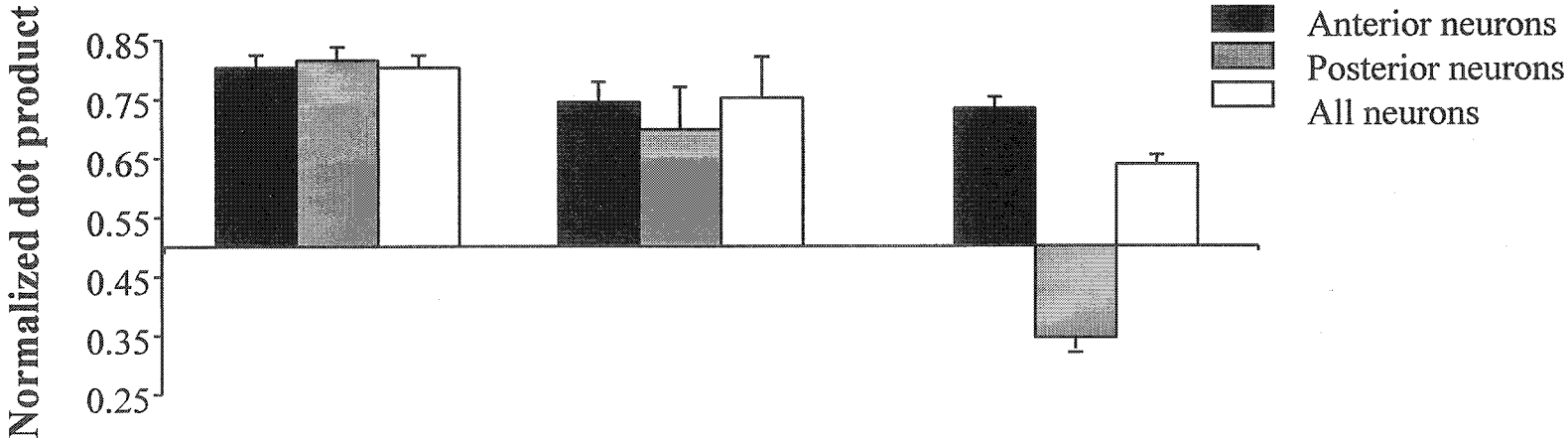






In the model, selective suppression of previously strengthened synapses can reduce the overlap between similar input patterns





Chem. Senses 26: 585–594, 2001

Neuromodulation and the Functional Dynamics of Piriform Cortex

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Acetylcholine and norepinephrine have a number of effects at the cellular level in the piriform cortex. Acetylcholine causes a depolarization of the membrane potential of pyramidal cells and interneurons, and suppresses the action potential frequency accommodation of pyramidal cells. Acetylcholine also has strong effects on synaptic transmission, suppressing both excitatory and inhibitory synaptic transmission. At the same time as it suppresses synaptic transmission, acetylcholine enhances synaptic modification, as demonstrated by experiments showing enhancement of long-term potentiation. Norepinephrine has similar effects. In this review, we discuss some of these different cellular effects and provide functional proposals for these individual effects in the context of the putative associative memory function of this structure.

Introduction

Numerous anatomical studies have described the structure of the olfactory system [for a review see Haberly (Haberly, 1985)]. Anatomical data demonstrate neuromodulatory innervation of these regions, including cholinergic and GABAergic innervation arising from the horizontal limb of the diagonal band (HDB) (Luskin and Price, 1982; Brashear *et al.*, 1986; Zaborszky *et al.*, 1986) and noradrenergic innervation arising from the locus coeruleus (McLean *et al.*, 1989) [for a review see Shipley and Ennis (Shipley and Ennis, 1996)].

A number of studies have shown an important role for neuromodulatory effects in olfactory memory function. These include data showing impairments of odor memory induced by the muscarinic cholinergic antagonist scopolamine, as well as lesions of the cholinergic and GABAergic neurons in the HDB (Hunter and Murray, 1989; Ravel *et al.*, 1992, 1994; Paolini and McKenzie, 1993, 1996; Roman *et al.*, 1993). In addition, numerous studies have shown the importance of norepinephrine for olfactory learning (Pissonnier *et al.*, 1985; Rosser and Keverne, 1985; Brennan *et al.*, 1990; Guan *et al.*, 1993; Sullivan *et al.*, 1989, 1991, 1992).

Here we provide a review of physiological data on cellular effects of these neuromodulators, a description of computational models analyzing the behavioral role of these neuromodulators, and some behavioral data testing hypotheses derived from these computational models. The piriform cortex provides an excellent region for analysis of neuromodulatory effects, as its structure resembles a class of neural network models termed 'associative memories' (Haberly, 1985; Haberly and Bower, 1989; Hasselmo *et al.*, 1990). This provides a clear computational framework for analyzing the functional role of the changes in network dynamics induced by neuromodulatory agents (Figure 1).

Studying neuromodulatory effects in olfactory cortex

Acetylcholine and norepinephrine have a number of effects at the cellular level in the piriform cortex. Acetylcholine causes a depolarization of the membrane potential of pyramidal cells (Tseng and Haberly, 1989; Barkai and Hasselmo, 1994) and interneurons (Gellman and Aghajanian, 1993), and suppresses the spike frequency accommodation of pyramidal cells (Tseng and Haberly, 1989; Barkai and Hasselmo, 1994), as well as increasing the excitability of olfactory cortex cells *in vivo* (Zimmer *et al.*, 1999). Like norepinephrine, acetylcholine also has strong effects on synaptic transmission, suppressing both excitatory synaptic transmission (Collins *et al.*, 1984; McIntyre and Wong, 1986; Williams and Constanti, 1988; Hasselmo and Bower, 1992; Hasselmo *et al.*, 1997; Linster *et al.*, 1999) and inhibitory synaptic transmission (Patil and Hasselmo, 1999). At the same time as it suppresses synaptic transmission, acetylcholine enhances synaptic modification, as demonstrated by experiments showing enhancement of long-term potentiation (Hasselmo and Barkai, 1995; Patil *et al.*, 1998). In this review, we discuss some of these different cellular effects and provide functional proposals for them in the context of the putative associative memory function of this structure.

Selective cholinergic suppression of excitatory synaptic transmission

The piriform cortex is an excellent structure for studying the neuromodulation of synaptic transmission, as it has a clear laminar segregation of different types of synapses. As shown in Figure 1, the afferent fibers arising from the olfactory bulb terminate in the most superficial layer of piriform cortex, layer Ia, whereas the fibers arising from other pyramidal cells within the cortex terminate in the deeper layers, including layers Ib and III. Cutting brain slices perpendicular to the surface of the cortex allows separate stimulation of synaptic potentials in the two layers, with stimulating electrodes in layer Ia or Ib (Figure 2). Recording can take place either intracellularly, from the pyramidal cell bodies tightly clustered in layer II, or extracellularly, from the layer being stimulated.

Previous research had demonstrated cholinergic modulation of excitatory transmission in tangential slices of the piriform cortex (Williams and Constanti, 1988). However, the use of transverse slices allowed demonstration of striking differences in the effect of neuromodulators on the different synaptic pathways. As shown in Figure 3A (Hasselmo and Bower, 1992), perfusion of acetylcholine through the slice chamber causes a suppression of synaptic potentials elicited with stimulation in layer Ib (intrinsic fibers) while having a weaker effect on synaptic potentials elicited with stimulation in layer Ia (afferent fibers). This selectivity is supported by additional studies performed *in vivo* (Figure 3B), showing that stimulation of the horizontal limb of the diagonal band causes suppression of synaptic potentials evoked with stimulation in caudal piriform cortex and entorhinal cortex, which presumably activates primarily intrinsic fibers (Linster *et al.*, 1999). In contrast, stimulation of the horizontal limb actually enhances potentials elicited by stimulation of afferent input fibers in the lateral olfactory tract (Linster *et al.*, 1999) (Figure 3C).

The cholinergic suppression of excitatory transmission might appear somewhat paradoxical, as acetylcholine has been shown to be important for learning. Why would a substance that is important for learning cause suppression of excitatory transmission? The importance of this selective suppression of transmission has been analyzed in computational models, and recent experiments have tested behavioral predictions of these computational models. Here we will first describe the behavioral experiment, and then show a schematic model of how suppression of transmission could play a role in this experiment.

The basic experiment is shown in Figure 4. The experiment tested the learning of odor pairs presented at separate odor ports. Initially, the rat must learn to respond to odor A when presented with the odor pair A–B. Then, in a separate phase of the experiment, the rat must learn to respond to odor C when presented with odor pair A–C, and during the same period must learn to respond to odor D when presented with odor pair D–E. In a counterbalanced design, rats received injections of scopolamine, methylscopolamine or saline after learning of A–B and before learning of A–C

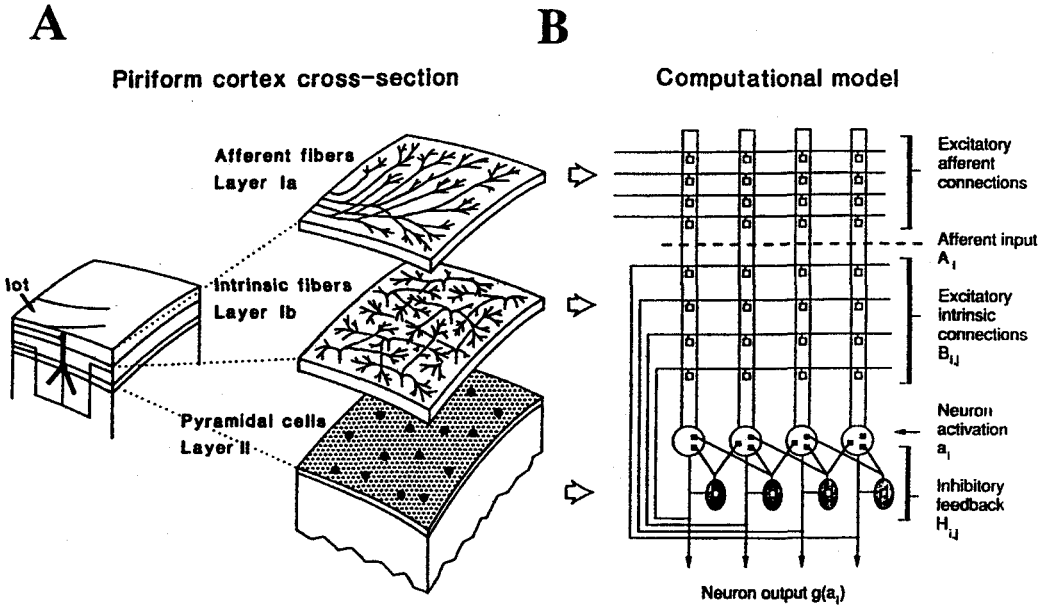

Figure 1 Overview of the anatomical structure of the piriform cortex compared with the basic components of computational models of associative memory function. **(A)** Left: a segment of piriform cortex shows the LOT entering along the surface and a pyramidal cell with its apical dendrite extending up through layer I. Right: the expanded diagram shows how afferent fibers from the LOT synapse on pyramidal cell distal dendrites in the superficial layer, layer Ia, whereas excitatory intrinsic fibers arising from other pyramidal cells within the cortex terminate on proximal dendrites in layer Ib. Pyramidal cell bodies are tightly packed in layer II. **(B)** The afferent and intrinsic connections correspond to the broadly distributed input and intrinsic connections of computational models of associative memory.

and D–E. This allowed analysis of how scopolamine influenced the learning of overlapping odor pairs (A–C) versus non-overlapping odor pairs (D–E).

This behavioral task was designed to test hypotheses arising from computational models of the piriform cortex (Hasselmo and Bower, 1992). The basic hypothesis is demonstrated in Figure 5. Figure 5A demonstrates the putative mechanisms for encoding the correct response to individual odor pairs. When presented with odor pair A–B, the response to odor A is rewarded. This association between the odor pair and the correct response can be encoded as strengthened synaptic connections between the population of neurons representing these two odors and the population of neurons activated during the response to odor A. The strengthening of synapses follows a Hebb rule, in which synapses are only strengthened in the presence of both pre- and post-synaptic activity. A direct association between activity evoked by sensory input and that evoked by motor responses is possible in the piriform cortex, as it has been shown that select populations of neurons in the piriform cortex fire during multiple different components of odor discrimination tasks, including odor sampling and response generation (Schoenbaum and Eichenbaum, 1995). Once this association has been encoded, the next time the odor pair is encountered, activity will spread along the previously strengthened connections, allowing activation of the response to odor A for correct retrieval.

This association works well for single odor pairs, but can run into difficulties of proactive interference for overlapping odor pairs. As illustrated in Figure 5B, if the rat has been trained to respond to odor A in the pair A–B, then it could

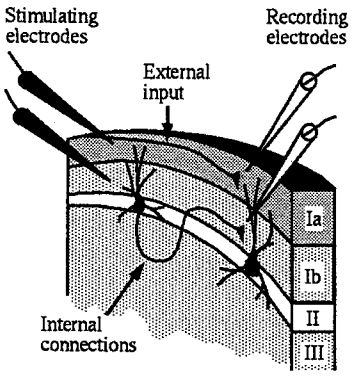

Figure 2 Schematic representation of brain slice preparation of piriform cortex. Stimulating electrodes can be placed either among afferent fibers from the LOT in layer Ia or among intrinsic and association fibers in layer Ib. Extracellular recording electrodes can be used to record synaptic potentials from either layer Ia or layer Ib. Intracellular or patch electrodes can be used to record from pyramidal cells in layer II.

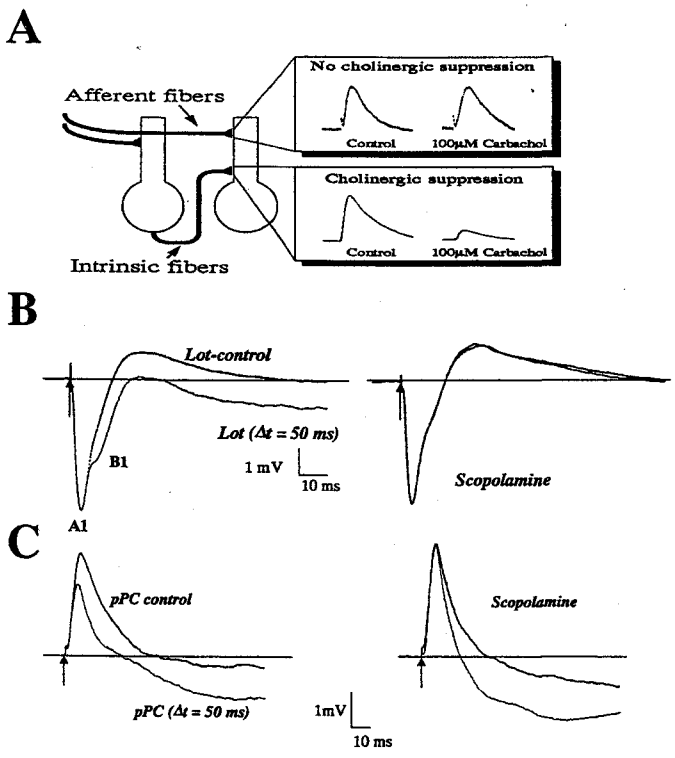

Figure 3 **(A)** Experimental data showing selective cholinergic suppression of excitatory intrinsic synaptic potentials in the piriform cortex. Stimulation of afferent fibers in layer Ia or intrinsic fibers in layer Ib elicits synaptic potentials recorded with intracellular electrodes in pyramidal cell bodies in layer II (Control). Perfusion of the slice chamber with the cholinergic agonist CCh causes a strong decrease in the magnitude of synaptic potentials elicited with layer Ib stimulation, while having a much weaker effect on synaptic potentials elicited with layer Ia stimulation. **(B)** Effect of stimulation of the HDB on the population EPSP in layer Ia of the piriform cortex in response to stimulation of the LOT recorded *in vivo*. Graph on the left side: responses to baseline pulse (baseline response) and test pulse 50 ms after HDB stimulation (test response, Δt = 50 ms). The population EPSP observed in layer Ia of the PC after stimulation of the LOT has a first negative peak (A1), followed by a second negative inflection (B1). A1 is generated by the monosynaptic EPSP in layer Ia and B1 is thought to reflect the disynaptic EPSP due to activation of the intrinsic fibers within the piriform cortex. At 50 ms after the tetanus in the HDB, component B1 is greatly enhanced. There is no effect on the monosynaptic component A1. Each trace is the average of 10 stimulations. The lines with arrows to the left of the potential indicate the measurements of the amplitude of the A1 and B1 components used for the analysis. Graph on the right side: responses to the baseline pulse and the test pulse 50 ms after HDB stimulation and 30 min after the injection of 0.5 mg/kg scopolamine. Scopolamine abolishes or greatly reduces the enhancement of component B1 after HDB stimulation. Each trace is the average of 10 stimulations. A and B are from the same animal. **(C)** Effect of stimulation of the HDB on the population EPSP in layer Ia in response to stimulation of layers II–III in the posterior piriform cortex recorded *in vivo*. Graph on the left side: responses to the baseline pulse (baseline response) and the test pulse 50 ms after HDB stimulation (Δt = 50 ms). In these experiments, we considered only the first peak of the response, which represents the monosynaptic population EPSP and could be reliably obtained at a short latency. The line with an arrow indicates the measurement of the peak of the response used in the analysis; the pointed lines show the measurement of the onset slope. After stimulation of the HDB, the first positive peak was reduced in most animals. Graph on the right side: Responses to the baseline pulse and the test pulse 50 ms after HDB stimulation and 30 min after the injection of 0.5 mg/kg scopolamine. Scopolamine abolished or greatly reduced the suppression of the first peak after HDB stimulation. Each trace is the average of 10 stimulations. A and B are from the same animal. From Linster *et al.* (Linster *et al.*, 1999).

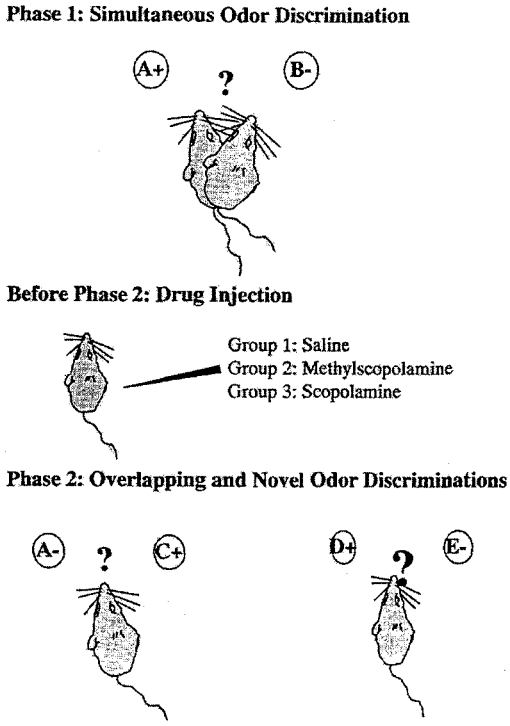

Figure 4 Schematic representation of the behavioral experiment. Phase 1: in phase 1, the rats learned a simultaneous odor discrimination task, in which two different odors were independently and simultaneously presented from both odor ports. Of the two odors, one odor was arbitrarily labeled the positive odor (A+B–). The rats indicated their choice with a nose poke to the odor port with the positive odor. Phase 1 ended when all the rats learned the A+B– discrimination to criterion (18 out of 20 consecutive trials correct). Phase 2: the animals were then tested on the two novel experimental odor pairs (overlapping and non-overlapping) under the influence of drugs. For four consecutive sessions, the rats were presented with 32 trials of A–C+ and 32 trials of D+E– intermixed in a pseudorandom order. At the beginning of each of the experimental sessions, they were presented with 16 'reminder' A+B– trials. These reminder trials only served as an opportunity for the experimenter to observe any attentional impairments and adjust the trial onset accordingly. The dependent measure was percentage of correct responses.

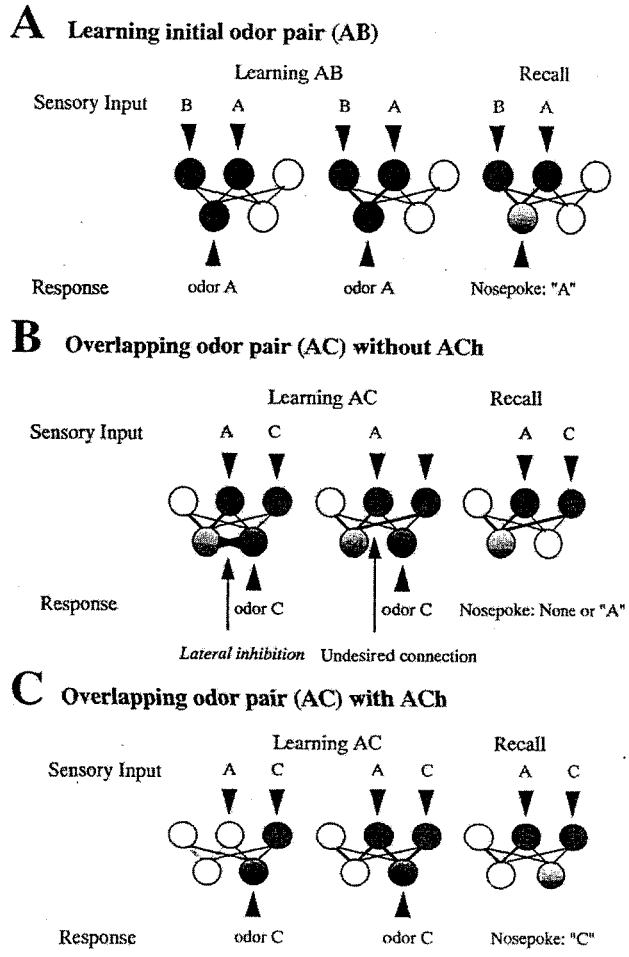

Figure 5 Overview of the potential role of cholinergic modulation learning of odor pairs in an example network. Each circle represents a population of neurons, with the thickness of lines representing the strength of synaptic connections between these populations. The shading of each neuron represents its activity level. **(A)** During initial learning of an odor pair response (Learning AB), the input of odors A and B (top row) is associated with the correct response to odor A (bottom row). This causes strengthening of connections from the input populations to the odor response population. During recall, activation of these sensory populations causes activity to spread across strengthened connections, activating the correct response (nosepoke to A). **(B)** Subsequent learning of an overlapping odor pair can suffer from proactive interference. In this case, during Learning of A–C+, sensory input activates populations A and C, and the correct response to odor C. However, activity spreads across previously modified connections to activate the population representing a nosepoke to A. This can result in strengthening of an 'undesired connection' and lateral inhibition, causing reduction of learning of the response to odor C. During recall, input of odors A and C then evokes no nosepoke or a response to odor A. This is analogous to what might happen under the influence of scopolamine. **(C)** With acetylcholine causing suppression of excitatory intrinsic transmission in the network, this prevents the spread of activity across previously modified synapses, allowing the response activity to only be influenced by the input of odor C. This allows accurate encoding of the new response to odors A and C, such that during recall the input of odors A and C results in nosepoke to C alone.

be more difficult to train the rat to respond to odor C in odor pair A–C. This problem of proactive interference arises because the presentation of odor A causes activity to spread along previously modified synapses to activate the previously learned response to odor A. This can result in incorrect responses, and undesired encoding of an association between odor C and the response to odor A. Thus, transmission across previously modified synapses interferes with the encoding of a new response.

Figure 5C shows how the selective cholinergic suppression of excitatory synaptic transmission can prevent this difficulty. Recall that acetylcholine does not suppress afferent input from the olfactory bulb. Thus, during encoding of odor pair A–C, acetylcholine does not block the sensory input activity. However, it does block the spread of activity along excitatory intrinsic connections within the cortex, preventing interference due to activation of the previous response to odor A. With this suppression of previous retrieval, the network can more effectively encode the new response to odor C. Thus, comparison of Figures 5B and 5C

shows the prediction for effects of scopolamine in this experiment. Scopolamine will block effects of acetylcholine on intrinsic synaptic transmission, enhancing the type of proactive interference illustrated in Figure 5B.

The results of the experiment support this hypothesis, as shown in Figure 6 (De Rosa and Hasselmo, 2000). Injections of scopolamine caused a stronger impairment of the ability to respond to odor C in the overlapping odor pair A–C, in comparison to its weaker impairment of the ability to respond to odor D in the non-overlapping odor pair D–E. Thus, scopolamine appears to enhance proactive interference, consistent with its blockade of the cholinergic suppression of excitatory synaptic transmission at intrinsic synapses in the piriform cortex. This model is further supported by experimental data showing that electrical stimulation of the olfactory cortex can modulate the activity of neurons in the HDB, thus providing a pathway for regulation of cholinergic activity (Linster and Hasselmo, 2000) (Figure 7). Similar effects have been obtained in an experiment performed in human subjects, in which scopolamine caused greater impairments in the encoding of overlapping versus non-overlapping word pairs (Kirchhoff *et al.*, 2000).

Cholinergic modulation of long-term potentiation

To prevent interference, the suppression of excitatory synaptic transmission should take place during the encoding of new information. This strict temporal correlation of suppressed transmission and modification can be obtained if the same modulator causes suppression of transmission and enhancement of synaptic modification. Experimental data support this role for acetylcholine. In addition to the suppression of transmission described above (Hasselmo and Bower, 1992; Linster *et al.*, 1999), acetylcholine causes enhancement of long-term potentiation in the piriform cortex (Hasselmo and Barkai, 1995; Patil *et al.*, 1998).

This was initially shown (Hasselmo and Barkai, 1995) by studying the effect of 5 Hz stimulation in two conditions: (i) during continuous infusion of the cholinergic agonist carbachol (CCh) and (ii) during perfusion of normal ACSF (artificial cerebrospinal fluid). A larger magnitude of long-term potentiation was obtained when the stimulation took place during cholinergic modulation. An example of data from this study is shown in Figure 8. This enhancement of long-term potentiation could result from a number of different effects of cholinergic modulation, including the depolarization of pyramidal cells and the suppression of spike frequency accommodation. Spike frequency accommodation occurs in piriform cortex pyramidal cells in response to long current injections. During the current injection, neurons initially fire spikes at a high frequency, which gradually decreases until spiking stops later in the

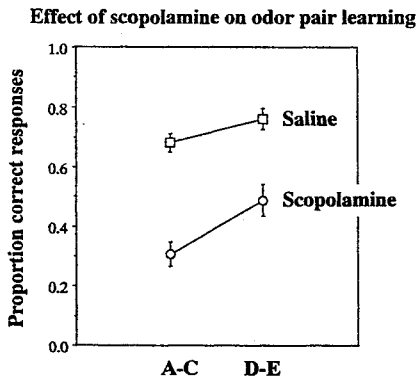

Figure 6 Experimental results from the study of scopolamine effects on behavior. The proportion of correct responses is shown for overlapping odor pairs A–C and non-overlapping pairs D–E in both control (saline) and scopolamine conditions. Note that scopolamine causes a greater decrease in performance for overlapping odor pairs A–C than for the non-overlapping odor pairs, supporting the hypothesis that blockade of acetylcholine enhances proactive interference due to spread of activity across previously modified synapses. From De Rosa and Hasselmo (De Rosa and Hasselmo, 2000).

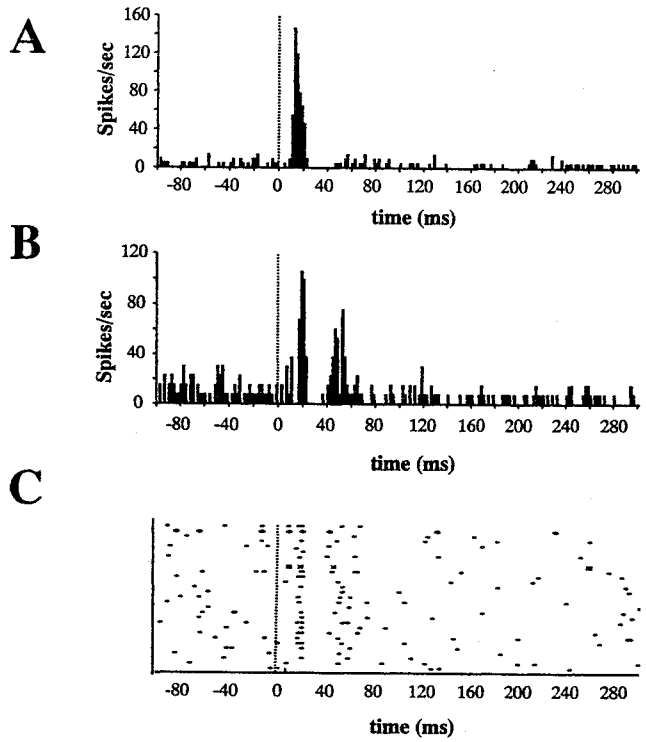

Figure 7 Effect of electrical stimulation of the PC on unit activity in the HDB. **(A)** Peristimulus time histogram of the effect of electrical stimulation (300 μA, 0.1 ms) of the PC on the spiking activity of an individual neuron recorded in the HDB. The neuron shown in this graph responded to the electrical stimulation with a single increase in spike rate. The histogram shows the summed numbers of action potentials (binsize = 2 ms) recorded during 100 successive sweeps. Stimulation occurred at time = 0 and is indicated by the dotted line. **(B)** The neuron shown in this graph responded with two periods of increased spiking to the electrical stimulation. **(C)** Dot raster showing the occurrence of action potentials during the 30 individual trials which were part of the summed histogram shown in B. Stimulation occurred at time = 0 and is indicated by the dotted line. From Linster and Hasselmo (Linster and Hasselmo, 2000).

injection due to activation of calcium-sensitive potassium currents. Cholinergic modulation suppresses the calcium-sensitive potassium current, allowing a more sustained spiking response to current injection. In computational models, this enhanced spiking response causes greater post-synaptic depolarization, which enhances the activation of NMDA receptors and the rate of Hebbian synaptic modification.

This enhancement of long-term potentiation would be particularly effective if it applied to dendrites on which there is a convergence of afferent input and active intrinsic synapses. This would enhance the accuracy of encoding of new afferent input. Experiments in our laboratory have demonstrated that cholinergic modulation enables associative long-term potentiation (Patil *et al.*, 1998) between the afferent fibers and the intrinsic association fibers (Figure 9A). In these experiments, a strong stimulation was presented to layer Ia of the piriform cortex (bursts of four pulses at 100 Hz at 200 ms intervals). This tetanic stimulation was accompanied by a weaker stimulation in layer Ib, given at

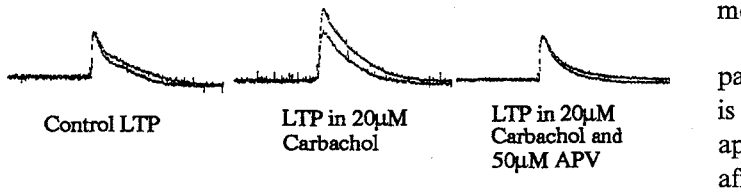

Figure 8 Cholinergic modulation of the long-term potentiation of intracellularly recorded EPSPs in the piriform cortex. Each pair of traces shows EPSPs recorded before and after 5 Hz stimulation in different conditions. Left: during perfusion of normal control solution, 5 Hz stimulation causes only a small increase in the magnitude of the potential. Middle: during perfusion of 20 μM CCh, the same stimulation paradigm elicits a much larger change in the size of the EPSP. Right: perfusion of 20 μM CCh with 50 μM APV blocks the induction of long-term potentiation by 5 Hz stimulation.

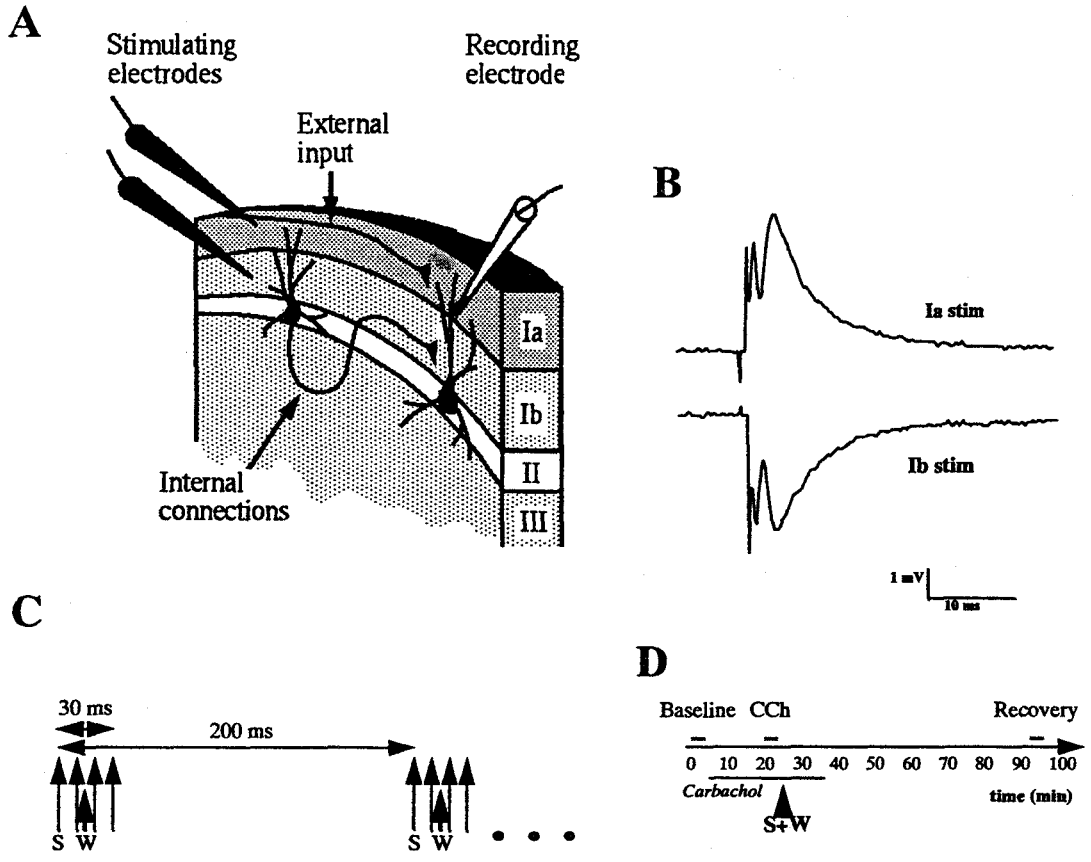

Figure 9 Schematic representation of the brain slice preparation of the piriform cortex and the experimental protocol. **(A)** Stimulating electrodes were placed among afferent fibers from the LOT in layer Ia and among association fibers in layer Ib under visual guidance. Extracellular recording electrodes were placed at the boundary of the two layers. **(B)** Potentials recorded in response to stimulation of layer Ia (afferent fibers) and layer Ib (association fibers) at the boundary of layers Ia and Ib. **(C)** Potentiation trains in layer Ia consisted of 10 sets of four pulses (100 Hz) (S) at 200 ms intervals. During pairing of strong (S) and weak (W) stimuli, weak test pulses in layer Ib were delivered at 200 ms intervals between the second and third pulses of the four pulse burst. In experiments using multiple pairings, three consecutive pairings of weak and strong stimuli were delivered at 5 min intervals. **(D)** Experimental protocol. Weak stimuli in layer Ib were delivered continuously throughout the experiment at 30 s intervals. Baseline responses to layer Ib test pulses were recorded at the beginning of the experiment. Approximately 20 min after the beginning of CCh application a single or three pairings of potentiation trains with weak stimuli were delivered (S+W). After washout, the response to test stimuli in ACSF was recorded for at least 60 min. For analysis, 10 consecutive trials were averaged 5 min after the beginning of the experiment (*Baseline*), 20 min after the beginning of CCh perfusion (*CCh*) and 40–45 min after the beginning of washout (*Recovery*). From Patil *et al.* (Patil *et al.*, 1998).

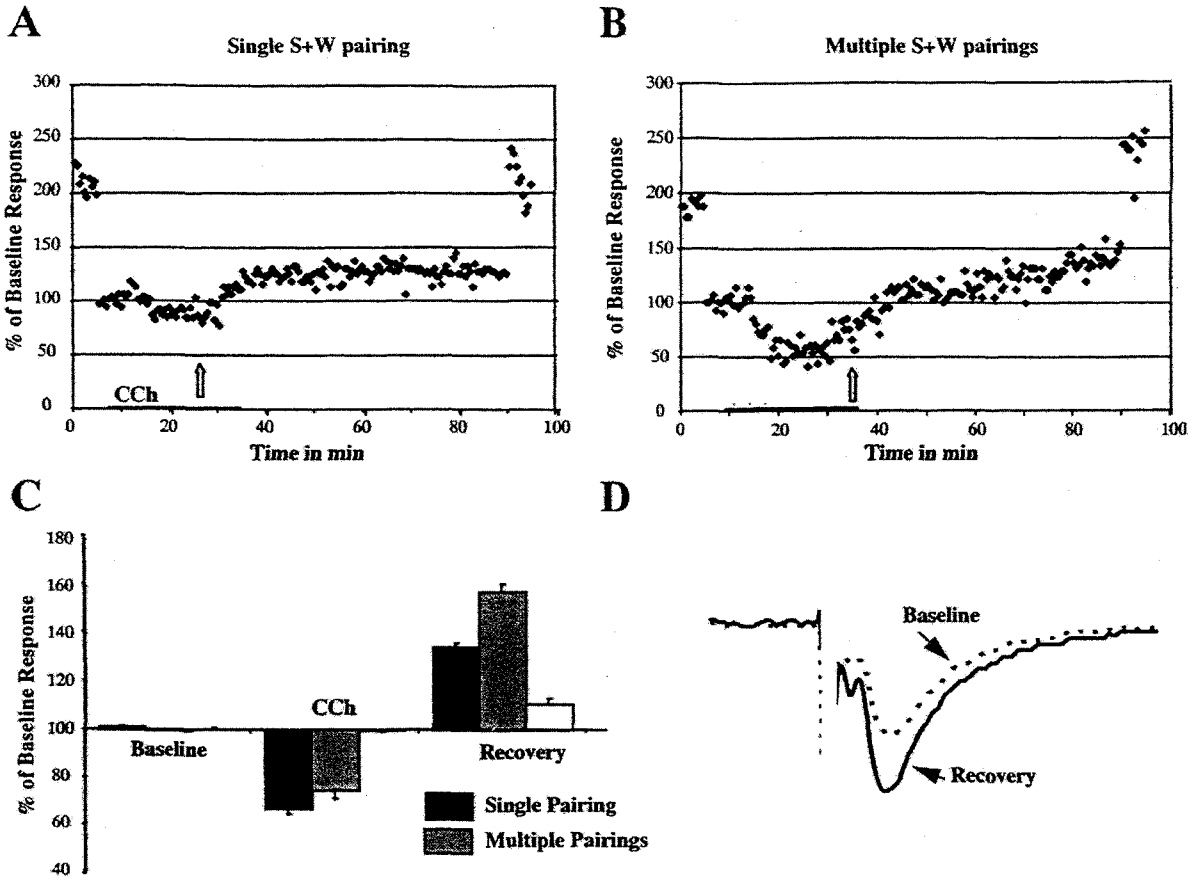

Figure 10 Summary of results at 50 μM CCh. **(A, B)** Time course of an experiment using a single pairing (A) and multiple pairings (B) of strong and weak stimuli. Onset slopes of potentials elicited by layer Ib test pulses are shown as a percentage of the baseline. At the beginning of the experiment, the maximal response to layer Ib stimulation was recorded. The stimulation strength was then adjusted to evoke ~50% of the maximal response. After bath application of CCh, the response amplitude to test stimuli decreased and stabilized after ~20–30 min. Pairing of strong and weak stimuli (arrow) resulted in an increase in the response to test stimuli in layer Ib. After washout, the response to test stimuli in layer Ib is significantly higher than the baseline recorded at the beginning of the experiment. At the end of the experiment, stimulation strength is adjusted to the maximal response strength recorded at the beginning of the experiment. **(C)** Average responses recorded in experiments using (i) single pairings in 50 μM CCh (n = 10); (ii) multiple pairings in 50 μM CCh (n = 10); and (iii) multiple pairings in 50 μM CCh and 10 μM scopolamine (n = 7). Onset slopes are given as a percentage of the baseline. Error bars indicate standard errors. CCh: average response 20–30 min after application of 50 μM CCh; Recovery: average response recorded 40–45 min after the beginning of washout. **(D)** Potentials in response to layer Ib stimulation. Each trace is an average of five recorded potentials. The response was recorded in ACSF before application of potentiating stimulus (dashed line) and 60 min after beginning of washout (solid line). From Patil *et al.* (Patil *et al.*, 1998).

5 Hz between the second and third pulse of the four pulse burst in layer Ia (Figure 9B). Under both normal saline or CCh, neither the tetanus in layer Ia nor the weak stimulation alone produced changes in the population excitatory post-synaptic potential (EPSP) observed in response to stimulation of layer Ib. However, under bath application of 50 μM CCh, the pairing of the weak stimulation in layer Ib with the tetanic stimulation in layer Ia produced a significant increase of the population EPSP in response to layer Ib stimulation (Figure 10).

In previous work, this enhancement of associative long-term potentiation was obtained with selective blockade of inhibitory synaptic transmission (Kanter and Haberly, 1993). Cholinergic modulation could provide this same effect through modulation of inhibitory synaptic potentials. Recordings from piriform cortex pyramidal cells have

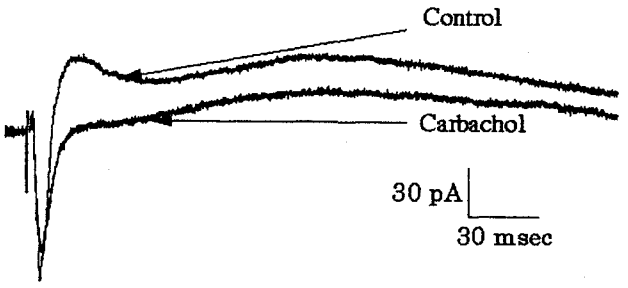

Figure 11 Effect of cholinergic modulation on inhibitory post-synaptic potentials evoked by layer Ib stimulation recorded in voltage clamp mode. Stimulation of layer Ib when the cell was held at –60 mV elicited a fast excitatory post-synaptic current followed by fast and slow inhibitory post-synaptic currents (IPSCs) (Control). Perfusion of the slice chamber with CCh (50 μM) suppressed both IPSC components (Carbachol). From Patil and Hasselmo (Patil and Hasselmo, 1999).

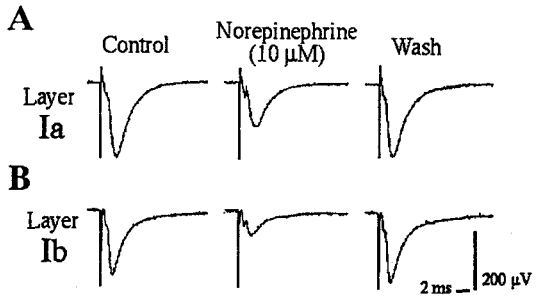

Figure 12 Suppression of synaptic potentials by norepinephrine recorded in a brain slice preparation of the olfactory cortex. **(A)** Evoked synaptic potentials in layer Ia recorded before (Control), during (Norepinephrine) and after (Washout) perfusion with 10 μM norepinephrine. **(B)** Evoked synaptic potentials in layer Ib recorded before (Control), during (Norepinephrine) and after (Washout) perfusion with 10 μM norepinephrine. Norepinephrine has a greater effect on intrinsic synaptic potentials. From Hasselmo *et al.* (Hasselmo *et al.*, 1997).

demonstrated cholinergic modulation of inhibitory synaptic potentials, as illustrated in Figure 11 (Patil and Hasselmo, 1999). In these experiments, perfusion of the cholinergic agonist CCh caused suppression of inhibitory synaptic potentials recorded with sharp electrode techniques as well as inhibitory synaptic currents recorded with whole cell patch clamp (Patil and Hasselmo, 1999). This modulation of inhibitory transmission appears to be stronger for transmission in layer Ib than for that in layer Ia.

Noradrenergic modulation in the piriform cortex

Noradrenergic modulation appears to have some effects similar to those of acetylcholine, providing a similar enhancement of the network response to external afferent input relative to intrinsic transmission. In particular, noradrenergic modulation causes selective suppression of excitatory intrinsic synaptic transmission, as shown in Figure 12 (Hasselmo *et al.*, 1997).

Network simulations demonstrate that the noradrenergic suppression of transmission could result in an enhancement of response to afferent input relative to internal activity. This can be referred to as enhanced signal-to-noise ratio—an effect that has been studied in a number of other cortical regions (Sara, 1985; Servan-Schreiber *et al.*, 1990). Simulations of the piriform cortex illustrate how modulation of synaptic transmission influences the response to afferent input, as shown in Figure 13. Thus, the net effects of norepinephrine may result in enhanced encoding of sensory input. This could provide cellular mechanisms for the important role of norepinephrine observed in early olfactory learning [reviewed by Sullivan *et al.* (Sullivan *et al.*, 1992)].

Summary

In summary, the piriform cortex provides an excellent structure for analysis of neuromodulatory effects on cortical

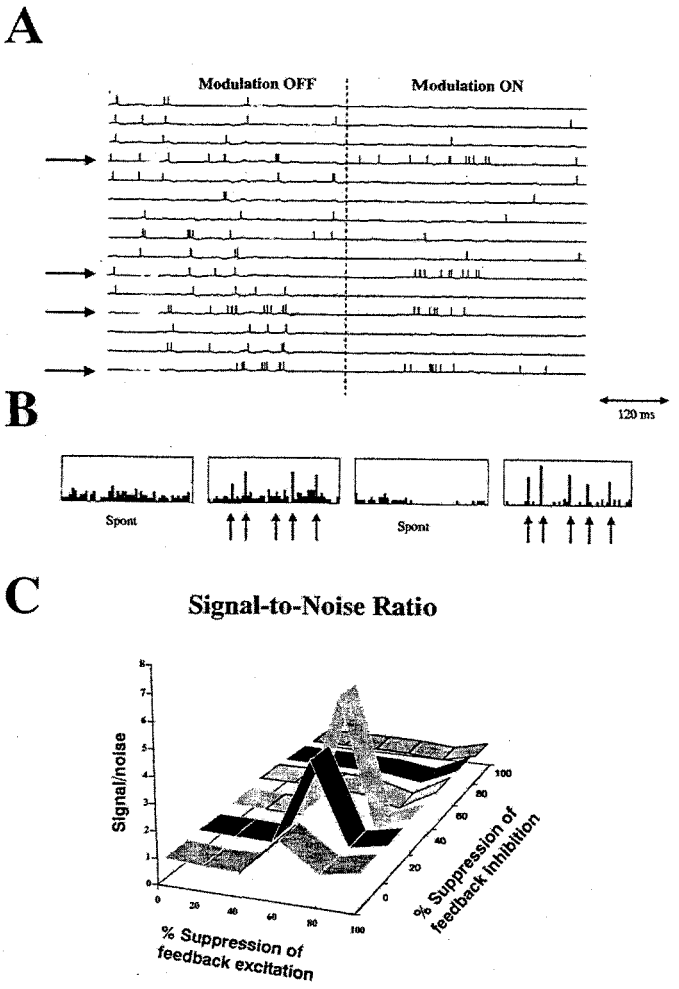

Figure 13 Effect of noradrenergic suppression of feedback excitation and feedback inhibition on pyramidal cell response to afferent input. **(A)** Membrane potentials and action potentials of 16 pyramidal cells are shown. Pyramidal cells receiving afferent input are indicated (horizontal arrows). Stimulus onset and offset are indicated by vertical arrows. Background activity and response to afferent input are shown in the absence (Modulation OFF) and in the presence (Modulation ON) of 60% suppression of feedback excitation and 40% suppression of feedback inhibition. **(B)** Average activities of 50 pyramidal cells in network during 120 ms background activity (Spont) and in response to input. Pyramidal cells receiving input are indicated by arrows. **(C)** The signal-to-noise ratio as a function of feedback excitation and inhibition in the spiking network model. For each point in parameter space, 50 networks were constructed and presented with random input patterns. The signal-to-noise ratio was computed as the number of spikes generated by neurons receiving input divided by the total number of spikes during the time of input presentation (120 ms). Suppression of feedback excitation and feedback inhibition is varied from 0 to 100% in 20% steps. The maximal signal-to-noise ratio occurred when feedback excitation was suppressed by 60% and feedback inhibition was suppressed by 40%. From Hasselmo *et al.* (Hasselmo *et al.*, 1997).

processing, allowing analysis of selective effects on excitatory and inhibitory synaptic transmission, and computational modeling of these effects in the framework of associative memory function. This allows explanation of some existing behavioral data on cholinergic and noradren-

ergic modulation, and generation of further hypotheses to guide additional behavioral experiments.

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REVIEW Communicated by P. Read Montague

Computational Models of Neuromodulation

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Computational modeling of neural substrates provides an excellent theoretical framework for the understanding of the computational roles of neuromodulation. In this review, we illustrate, with a large number of modeling studies, the specific computations performed by neuromodulation in the context of various neural models of invertebrate and vertebrate preparations. We base our characterization of neuromodulations on their computational and functional roles rather than on anatomical or chemical criteria. We review the main framework in which neuromodulation has been studied theoretically (central pattern generation and oscillations, sensory processing, memory and information integration). Finally, we present a detailed mathematical overview of how neuromodulation has been implemented at the single cell and network levels in modeling studies. Overall, neuromodulation is found to increase and control computational complexity.

1 Introduction

Organisms, from invertebrates to mammals, exhibit diverse behaviors when coping with their environments. Correspondingly, the nervous systems of these organisms can differ significantly in their organization and cellular components. Despite such cross-species variability, computational models of nervous systems have shown that complex computations can emerge from the interaction of relatively simple circuits of neurons. A typical connectionist model, for example, involves a transfer function computing the output of the neuron given the sum of its inputs and a synaptic learning rule determining how the strength of synaptic connections is updated. With this type of simple model, a variety of behavioral functions have been modeled, providing insights into how complex phenomena, such as perception, memory, and motor control, can be explained in terms of simple neural mechanisms. Simple models, however, often fail to capture important aspects of neural processing such as neuromodulation (Cooper, Bloom, &

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Roth, 1991; Harris-Warrick & Marder, 1991; Hasselmo, 1995; Kaczmarek & Levitan, 1987).

In addition to the classic excitatory and inhibitory neurotransmission, such as those mediated by glutamate or GABA, a large number of biophysical processes serve to modify the response of a neuron to a given input signal or to alter the input signals before their arrival. These modulatory effects often involve substances such as acetylcholine (ACh), norepinephrine (NE), histamine, serotonin (5-HT), dopamine (DA), and a variety of neuropeptides. Although these substances are known to act at different types of receptors, originate from different structures, and have different spatial distributions and time courses of action, they have at least one of the following three functional effects: modulation of intrinsic neural properties (such as input-output function, or threshold), modulation of afferent properties (such as strengthening some neural inputs rather than others), or modulation of efferent properties (such as presynaptic modulation of release). At the behavioral level, such modulations can profoundly affect the function of the nervous tissue involved.

Much is now known about the detailed action of neuromodulatory substances and their agonists and antagonists at the level of small circuits, single neurons, single synapses, or single channels. On the other hand, psychopharmacologists have examined the effects of many drugs that affect various neuromodulatory systems on behaviors such as perception, learning and memory, and motor control. Because of the wider use of modeling techniques and growing interest in systems neuroscience, the computational role of neuromodulation in information processing is receiving increased attention in both the modeling and experimental communities. As we will suggest, the study of neuromodulation may help bridge the gap between elementary neural principles and behavior.

Computational models provide a formal framework in which the function of a neuron or a group of neurons can be expressed rigorously. In general, neural dynamics is represented as a set of equations with variables and parameters. Variables are determined by both the level of description of the model (concentration, membrane potential, firing rate, etc.) and the function under study. Parameters are potential neuromodulatory factors. They are diffuse (nonspecific to each neuron) and are assumed to change more slowly than variables, so that keeping them constant (or very slowly varying) will not perturb the function of the network. In this formalism, neuromodulation appears as a means of changing the way the function is achieved, without changing the function itself. However, not all parameters have a biological meaning. Some are abstract place holders used to make up for the lack of knowledge about the details of a particular phenomenon (the learning rate, for example), others ensure the ad hoc goodness of fit ("tuning") of the model to certain experimental data that are not the primary targets of the model ("time constants" of synaptic alpha functions for example). Moreover, not all the parameters that have putative biological correlates have

identified neuromodulatory roles in situ. For example, some chemical time constants might characterize complex biophysical mechanisms that are normally severely constrained ("regulated"), and consequently have no neuromodulatory function. Furthermore, not all neuromodulatory phenomena can be represented by simple parameter changes.

The purpose of this article is to highlight, through a targeted review of the modeling literature, some of the basic computational roles assigned to neuromodulation and present their possible neural implementation. Due to the diversity and ubiquity of neuromodulatory phenomena, we will not provide a comprehensive review of all neuromodulatory systems in terms of their anatomical loci, detailed biochemical pathways, and individual physiological effects. Nor will we attempt to define it; rather, we will review neuromodulation according to the computational framework provided by a chosen set of modeling studies. Our intent is not to be exhaustive. Many models not mentioned here have discussed how specific neuromodulations can be implemented and how they affect particular aspects of the neural system they consider. We include here a selection of studies that have dealt explicitly with neuromodulation and will help readers understand a specific computational role of neuromodulation.

In the first section, we characterize neuromodulation on the basis of its spatial origin (extrinsic or intrinsic), its functional coupling with neural computation (tuning versus regulation), and its time course. We then review in more detail the computational role of neuromodulation in three important classes of models that address issues pertaining to oscillations and synchrony in small and large networks, sensory processing, and memory function. Finally, in the appendix, we give a detailed mathematical account of the way neuromodulation has been implemented in the various modeling frameworks reviewed.

2 Characterizing Neuromodulation

Neuromodulations can be described by their spatial and temporal characteristics, and in the computational framework chosen here, they can also be characterized by their level of coupling with the specific neural computations under consideration.

2.1 Extrinsic and Intrinsic Neuromodulation. A first class of neuromodulatory signals may originate from an area extrinsic to the neural substrate whose computation is under study, so that lesioning the neuromodulatory center does not usually perturb the function itself, but only modifies its quality. The computational functions of such extrinsic neuromodulation are expected to be somewhat global, because they usually influence many functionally different sites simultaneously. A second class consists of neuromodulations that originate in the relevant substrate itself or in a distant site but are controlled locally within the substrate. In such systems, neuromod-

ulation is an integral part of the computation. Cotransmission (Brezina, Orekhova, & Weiss, 1996; Chan-Palay & Palay, 1984; Kupfermann, 1991; Marder, Christie, & Kilman, 1995), presynaptic receptions (Marder, 1996; Starke, Gothert, & Kilbinger, 1989), glial modulation (Hansson & Ronnback, 1994), and volume transmission (Fuxe & Agnati, 1991; Ridet, Rajaofetra, Teilhac, Geffard, & Privat, 1993) are examples of such phenomena. The functions of such intrinsic modulations are more specific to the substrate under consideration (Katz & Frost, 1996).

2.1.1 Extrinsic Neuromodulation. In many models, the origin of the modulation is known but does not depend in general on the computation of the substrate being modulated. Rather, it depends on the parallel activity of functionally distinct systems, extrinsic to the substrate. Such is the case of most neuromodulatory centers releasing specific neuroactive substances that modify the cellular and synaptic properties of their targets. Most of the actions of dopamine (Cooper, 1991) and norepinephrine (van Dongen, 1981) enter in this category. Here, we illustrate this point with a recent model of sequence learning in hippocampal region CA3 showing that computations may crucially depend on the extrinsic modulation by GABAergic and cholinergic inputs from the septum (Wallenstein & Hasselmo, 1997b).

In this large multicompartmental model, CA3 interneurons receive external periodic (4–10 Hz) inhibitory GABAergic signals from the septum (itself not modeled), while pyramidal cell and interneuron excitability is increased by steadily lowering their leak potassium conductance, simulating the cholinergic influences of the septum. In this modulatory regime, interneurons spontaneously fire gamma (30–100 Hz) bursts of action potentials at the theta (4–10 Hz) frequency externally imposed by the septum (Wallenstein & Hasselmo, 1997a). This pattern of firing in turn entrains the pyramidal cell network at theta frequency, yielding an overall network behavior compatible with much in vivo and in vitro experimental data. The emerging theta-gamma pattern of interneuronal GABAergic activation results in a periodic activation of $GABA_B$ receptors on pyramidal cells: $GABA_B$ activation is greatest at the start of each theta cycle and decreases smoothly until the end of each cycle. Because $GABA_B$ receptors primarily control synaptic activation at intrinsic (CA3 recurrent collaterals) rather than extrinsic (sensory) pyramidal inputs, their net effect is to modify periodically the balance between internal and external information processing. Sensory inputs dominate at early phases of the theta cycle; intrinsic inputs dominate at later phases. This pattern of modulation is shown to be crucial to the computations of CA3 in that it allows for the development of place fields and for the learning and recall of sequence information modeled as a path learned by a rat running on a linear track. Without $GABA_B$ modulation, the network still functions, but it is qualitatively impaired, yielding place fields that do not develop and making significant errors during the recall of learned sequences.

In this example, extrinsic neuromodulation acts as a separate clocking device whose net effect is to improve the nature of information processing in the CA3 region of the hippocampus. Both the timing of the modulatory signal (theta frequency) and its pharmacological consequences ($GABA_B$ receptor activation) are important and generate testable predictions as to what might happen if either is modified. Other models have viewed extrinsic modulation as a signal influencing synaptic mechanisms. Such is the case of the reward signal entering the weight modification rule, between the ventral tegmental area (VTA) and cortex (Montague, Dayan, & Sejnowski, 1996), discussed in the following sections, or the direct change of synaptic efficacy triggered by an external center (Linster & Gervais, 1996; Linster & Masson, 1996; Raymond, Baxter, Buonomano, & Byrne, 1992).

2.1.2 Intrinsic Neuromodulation. In some interesting instances, it is not possible to isolate the neuromodulatory phenomenon from the system it modulates. In such cases, neuromodulation is intrinsic to the network whose computation is under study. Unfortunately, to our knowledge, there are no direct modeling studies of such phenomena. Some experimental evidence for intrinsic neuromodulation is reviewed elsewhere (Katz & Frost 1996). We briefly mention two examples.

In the stomatogastric ganglion (STG) of the lobster, an afferent axon (SNAX1) has been characterized as both a participant in the rhythmicity of the gastric mill network and as a conveyor of modulatory information (Nusbaum, Weimann, Golowasch, & Marder, 1992). SNAX1 receives (inhibitory) synaptic inputs from the STG and is capable of initiating action potentials (intrinsically, within the STG and not near the cell body, a few centimeters away), which generate excitatory postsynaptic potentials (EPSPs) on the STG elements, therefore participating in the generation of the rhythm. However, because SNAX1 is also electrically coupled with key neurons of the central pattern generator, its level of depolarization (whether or not action potentials are present) modulates the activity of the network.

Similarly, in the tritonia, dorsal swim interneuron DSI (a serotonergic central pattern generator (CPG) neuron), is known to enhance synaptic transmission presynaptically at synapses made by a key CPG neuron (Katz & Frost, 1995b; Katz & Frost, 1996; Katz, Getting, & Frost, 1994). DSI elicits both a fast, neurotransmitter-like EPSP, and a slow neuromodulatory-like EPSP (Katz & Frost, 1995a), both pharmacologically separable. DSI therefore modulates the oscillatory pattern it is contributing to.

It is, of course, possible to envision dual extrinsic and intrinsic neuromodulations, whereby the former would express state or stimulus dependency and the latter would be activity dependent. In the computational framework of modeling studies, extrinsic neuromodulations can be easily implemented by choosing appropriate sets of parameters (tuning), whereas intrinsic neuromodulations require that the neuromodulatory mechanisms be regulated by the computations under consideration.

2.2 Regulation and Tuning. Choosing a computational framework to study neuromodulation inherently places it within a larger continuum.

2.2.1 Regulation. At one extreme, when neuromodulation is tightly coupled with neural computations, it becomes regulatory, an integral part of the computations. Such is the case of second messenger systems described in a Markovian kinetics formalism (Destexhe, Mainen, & Sejnowski, 1994b) or of activity-dependent regulation of maximal conductances (LeMasson, Marder, & Abbott, 1993), which we briefly discuss next.

Using a single-compartment model of the lateral pyloric neuron of the stomastogastric ganglion of the crab (Buchholtz, Golowasch, Epstein, & Marder, 1992), LeMasson et al. (1993) elegantly illustrate how neurons can maintain a given firing behavior in the face of perturbations such as changes in extracellular K^+ concentrations or sudden shifts in certain membrane current maximal conductances. This is achieved by making the intrinsic properties of the neuron (maximal conductances) dependent on the intracellular calcium concentration, and hence indirectly on previous activity. This feedback regulation ensures that conductances are stable and that the firing pattern of the cell (silent, bursting, or tonically firing) is preserved. The authors propose that this regulation, because it happens on a relatively slow timescale, could correspond physiologically to calcium regulation of channel synthesis, insertion, or degradation. Interestingly, in this particular model, the same mechanism that regulates the firing pattern in the face of certain perturbations may also change it in the face of other perturbations, such as external patterns of stimulation, therefore increasing the complexity of the input-output relationship of the cell.

2.2.2 Tuning. At the other extreme, when neuromodulation is entirely decoupled from the network under study, its actual implementation becomes a matter of parameter tuning. Such is the case of the choice of particular parameter sets that yield different bursting modes in invertebrate pattern generators (Epstein & Marder, 1990) or different cell frequency adaptation characteristics in piriform cortex (Barkai & Hasselmo, 1994), as we discuss next.

In slices, piriform cortex pyramidal cells can generally be classified into strongly adapting or weakly adapting cells, depending on their response to long constant depolarizing current pulses (Barkai & Hasselmo, 1994). This difference in firing frequency adaptation may influence the computations at hand. Carbachol, a muscarinic receptor agonist, has been found to decrease the spike frequency adaptation of pyramidal cells and, in effect, switches strongly adapting cells into weakly adapting ones. On the basis of the experimental finding that carbachol primarily modulates two membrane potassium currents, IK (AHP) and IK (M) (Madison, Lancaster, & Nicoll, 1987), Barkai and Hasselmo used a compartmental model and found that different values of the maximal conductances of these two cur-

embrane resistance, would reproduce
viors identified experimentally. These
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ıolinergic modulation. The computa-
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e onset of a trigger signal. Correct re-

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the delivery of the reward, regardless

of the delay introduced. This firing behavior is in marked contrast to some of their neural targets, such as the striatum or prefrontal cortex, whose neural activity may be tonically increased during the whole delay period (Goldman-Rakic, Lidow, Smiley, & Williams, 1992). Moreover, the increase of VTA activity after reward appears to be present only during learning, and not once the animal has acquired the task. These data suggest that the transient actions of DA after reward delivery may be specifically involved in learning. The precise duration of the postsynaptic effects of the release of dopamine in the prefrontal cortex during such a task is not known, but it might be as short as 100–200 ms (Jay, Glowinski, & Thierry, 1995). Insofar as one considers that the performance of the delayed response task is a slow process (lasting up to 4 sec), a 150-ms phasic involvement of the dopaminergic system appears as a fast modulatory process influencing a slow sequence of neural computations.

In a model of VTA activity, Montague et al. (1996) propose a way in which DA neuron may transiently affect learning. Their model suggests that DA signals $\delta(t)$ carry a composite information about external reward $r(t)$, and internal fluctuations between present $V(t)$ and immediately past $V(t-1)$ sensory cortical signals. This DA signal is used to modulate the rate of change of the synaptic weights, which link cortical signals $x(t)$ to dopaminergic neurons. Mathematically, this modulation is expressed as a transient change of learning rate, which tends to reduce the amount of excitation forwarded to the dopaminergic neurons, as learning develops, compatible with experimental data (Schultz et al., 1993), and following the general idea of temporal difference learning (Sutton & Barto, 1990):

$$\Delta w_i^\tau = \eta x_i \delta(t) \text{ if } t = \tau. \ 0 \text{ if not.}$$

with

$$\delta(t) = r(t) + V(t) - V(t-1)$$

and

$$V_i(t) = x_i w_i^\tau(t), V(t) = \sum_i V_i(t).$$

Interestingly, this model chooses to label weights explicitly with space (i, origin of cortical activity) and time (τ, relative to the start of each trial). In this paradigm, each weight codes for the occurrence of a particular cortical signal, at a particular time within the experiment.

The spatial diffusion of the DA signal is expressed by the fact that the same $\delta(t)$ affects all synaptic weights equally (it is not indexed by i) and by the fact that it is built on the basis of the sum of all cortical inputs, rather than specialized cortical inputs only (V rather than V_i).

During the initial stages of learning, when weights are uniformly distributed, DA activity closely follows the temporal patterns of reward. During learning, if the time of reward is fixed (such as in the instructed spatial task; Schultz et al., 1993), the weights that code for the particular time (τ_r) of the reward will be strengthened, so that $\delta(\tau_r)$ eventually vanishes. If the

time of reward is variable, as in a delayed spatial task, the activity of DA neurons will become small, but nonzero, around the mean of the times when reward was delivered. After learning, in both cases, DA activity becomes particularly significant when the initial target sensory cue is presented. DA neurons therefore learn to respond to the target sensory cue predictive of the reward rather than to the reward itself.

In this model, the timing characteristics of the modulation are crucial. Its short duration is directly related to the precision with which the prediction of reward is made. Phasic modulation is also important in other modeling studied involving $GABA_B$ receptors (Wallenstein & Hasselmo, 1997b) and in other experimental systems involving norepinephrine and locus coeruleus response to attentional signals and novelty (Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994; Rajkowski, Kubiak, & Aston-Jones, 1994; Sara, Vankov, & Herve, 1994).

3 Computational Aspects of Neuromodulation

3.1 Modulation of Oscillation and Synchrony. Neural computation is dynamic and modular and requires that functionally distinct structures communicate in a coordinated fashion. Experimental and theoretical evidence suggests that the generation and synchronization of oscillatory activity may be used to this effect (Gray, 1994). Invertebrate studies have been crucial in furthering our understanding of how both intrinsic membrane properties and synaptic interactions may contribute to the creation and modulation of rhythmic firing (Calabrese & De Schutter, 1992; Harris-Warrick & Marder, 1991). Vertebrate studies of the cortex have built on these results and have proposed ways in which oscillations may synchronize across functionally distinct structures (Gray, 1994). In this context, the neuromodulation of the generation and synchronization of oscillations is bound to play an important computational role.

3.1.1 Central Pattern Generators: Creating and Modulating Rhythmicity. A long tradition of experimental work in invertebrates has led to a detailed knowledge of the effects of various substances on the behavior of individual neurons and small networks of neurons (see for reviews, Calabrese & De Schutter, 1992; Marder, 1996; Marder & Selverston, 1992). Most of these effects can be modeled by changes in the maximal conductance of one or more membrane currents. In these systems, attention is given to neurons whose putative function is to provide, through their rhythmic firing, timing signals necessary for one or several rhythmic motor behaviors (Pearson, 1993), such as chewing in the crustaceans or hormone release during egg-laying behavior in Aplysia. These cells are often referred to as conditional bursters because of their ability to fire rhythmically, either intrinsically or under the influence of a small network of connected cells. Two examples can be found in the pyloric network of the crustacean stomatogastric ganglion and in the Aplysia bursting neuron R15.

In the STG of the lobster, various modulatory substances such as dopamine, pilocarpine, serotonin, or proctolin can elicit rhythmic burst firing. The mechanisms involved, even though they result in similar bursting behaviors, are by no means simple and depend on the particular substance applied. For example, tetrodoxin (TTX) may block the effects of serotonin and octopamine but have no effects on the bursting evoked by dopamine and pilocarpine. One possibility is that each of these neuromodulatory effects is mediated by a particular change in the mix of membrane conductances of the cells (Harris-Warrick & Flamm, 1987), which may be studied theoretically using the Hodgkin-Huxley (HH) formalism (Hodgkin & Huxley, 1952; Rinzel & Lee, 1987).

Epstein and Marder (1990) provide a model for the conditional bursting of the anterior burster (AB) neuron of the lobster STG and investigate the effects of the change of a selected set of maximal conductance on the oscillatory properties of the model. They are able to show that two different mixes of fast sodium, leakage, and voltage-dependent calcium maximal conductances were able to model the bursting behaviors of the AB neuron under various neuromodulatory conditions and show why TTX has a different effect on two of these oscillatory modes. Kepler, Marder, and Abbott (1990) showed that, in addition to being intrinsically modulated, the frequency of the modeled AB cell might also depend on the state of follower neurons, provided that both neurons are coupled via gap junctions. Unfortunately, the effects of isolated membrane conductances are often not accessible experimentally. To study the putative effect of pharmacological agents (expressed as continuous maximal conductance changes) on the oscillatory properties of this cell, researchers may then use different modeling techniques, such as exhaustive parameter searches (Bhalla & Bower, 1993; Foster, Ungar, & Schwaber, 1993) or dynamical systems theory (Guckenheimer, Gueron, & Harris-Warrick, 1993; Guckenheimer, Harris-Warrick, Peck, & Willms, 1997). Further experimental and theoretical studies focused on other STG neurons (Golowasch, Buchholtz, Epstein, & Marder, 1992). These models essentially consider neuromodulation to be extrinsic to the oscillatory circuit, and implement it using parameter tuning. Interestingly, further work has attempted to show how maximal conductances may also be changed by intrinsic phenomena. LeMasson et al. (1993), for example, show how intracellular calcium concentrations can be used to implement the activity-dependent modulation of certain maximal conductances (Turrigiano, Abbott, & Marder, 1994). Their model shows that depending on the nature of the perturbations imposed onto the cells, this modulation can be regulatory (maintaining the behavior of the cells when extracellular $[K^+]$ is modified) or truly modulatory, by enriching the behavioral repertoire of the cell in response to external patterns of stimulations.

Most modeling studies of the extrinsic effects of neuromodulatory substances have addressed the problem at the level of maximal conductances by tuning them to different values. Very few have actually modeled the

explicit effect of these substances on the conductances (Brezina et al., 1996; Butera, Clark, Canavier, Baxter, & Byrne, 1995). A different line of research in Aplysia, however, has achieved this.

Burster neuron R15 in Aplysia has been studied in much detail, and its electrophysiological and biochemical properties have been investigated intensively (reviewed in Adams & Benson, 1985; Lechner, Baxter, Clark, & Byrne, 1996). Numerous mathematical models have been developed to explain the cellular basis of single-cell oscillatory activity and bursting. Some models went further and studied the extrinsic modulation of oscillatory dynamics by substances such as DA and 5-HT (Bertram, 1993, 1994; Butera et al., 1995), while others focused on the role of intrinsic modulation by calcium-dependent processes in conditioning (Gingrich & Byrne, 1987; Raymond et al., 1992).

A first series of studies used a simplified HH framework to model the effect of 5-HT as modifications in the conductance of a subthreshold K^+ current (Bertram, 1993, 1994). As for the models of the AB neuron, these models show that changes in maximal conductance can modify the firing properties of R15 from silent to bursting and beating and that the sensitivity of the cell to synaptic inputs is increased. In a separate study Butera et al. (1995) show that even though the apparent effects of DA and 5-HT on the firing properties of R15 are similar, its subsequent responses to depolarizing inputs differ. Effects of 5-HT and DA were implemented as a change in the conductance of two opposing currents: an anomalous delayed rectifier current and a slow inward Ca^{2+} current. Unlike the models mentioned above, this change is directly related to the concentration of extrinsic neuromodulators (see the appendix). Their dynamics are such that both 5-HT and DA can hyperpolarize the cell into silence. However, the subsequent response to a brief depolarizing current pulse elicits a burst of spikes if the cell was silenced with 5-HT and occasional single spikes if it was inhibited by DA, as observed experimentally. Because they make the concentration of these neuromodulatory substances explicit, the authors are able to show that although the effects of 5-HT and DA can be modeled as changes in maximal conductances, they cannot be understood without taking into account the indirect effects of other currents and second messenger systems (such as Ca^{2+} or cAMP). In turn, these indirect effects lead to further modeling that shows their functional importance.

Indeed, the roles of intracellular cAMP and Ca^{2+} are known to be important in activity-dependent neuromodulation in the context of associative classical conditioning in aplysia (reviewed in Abrams & Kandel, 1988; Byrne, 1987). In a study using detailed representations of membrane parameters, Gingrich and Byrne have shown that intrinsic regulation of cAMP by Ca^{2+} in an aplysia single sensory neuron can simulate the neural analogues of nonassociative learning and classical conditioning (Gingrich & Byrne, 1987). A subsequent study showed that a circuit of six neuron-like elements (including central pattern generators), some of which have synapses mod-

ifiable according to an activity-dependent neuromodulation learning rule, can account for simple features of operant conditioning as well (Raymond et al., 1992).

3.1.2 Modulation of Rhythmicity in the Cortex: Toward Information Processing. Current research in the vertebrate cortex has indicated the functional importance of oscillation and synchronization (Gray, 1994; Singer, 1993). Experimental and theoretical evidence suggest their role in odor coding in the olfactory bulb, in feature integration in the visual cortex, in synaptic plasticity in hippocampus, in attentive behaviors in somatomotor cortex (Gray, 1994), and in the gating of sensory information during awake and sleep states in the thalamocortical circuit (McCormick, 1992). Unfortunately, the computational role of neuromodulation in the generation and synchronization of these rhythms has rarely been studied from a modeling point of view. However, an interesting line of research in the thalamocortical loop is setting the stage for modeling work in other systems.

In the past decade, tremendous breakthroughs have been achieved in the understanding of synchronized oscillations in the thalamocortical circuit (see de Carvalho, 1994; McCormick, 1992, for reviews). Their neuromodulation has been studied in vitro and in vivo, and their cellular mechanisms explored both experimentally and theoretically through computer simulations. The functional significance of the neuromodulation of this system is summarized next. In slow-wave sleep, with low cholinergic, serotonergic, noradrenergic, and histaminergic modulation, the thalamocortical system presents slow, spontaneous basal intrinsic and circuit oscillations (delta waves and spindle waves). During this state, cholinergic inhibition of thalamic interneurons is absent, resulting in massive inhibition of incoming sensory information, which is consequently only poorly transmitted to the cortex. The increase of cholinergic activation (but decrease of noradrenergic, serotonergic, and histaminergic activation) characteristic of rapid eye movement (REM) sleep results in an abolition of oscillatory activity and an increase of endogenous (without sensory inputs) phasic activity (pontogeniculate-occipital [PGO] waves), thought to be at the origin of the pseudosensorial perceptions experienced during dream states. Finally, the tonic activation of all neuromodulatory systems (including cholinergic, noradrenergic, serotonergic, and histaminergic) results in complex patterns of activity and sets the stage for awake attentive cognitive processing. The precise nature of the sensory processing in the thalamus and its modulation by neuromodulatory centers are limited by the lack of understanding of the nature of the sensory codes themselves. However, understanding how oscillations are generated and how they propagate in a synchronized manner across the thalamic networks might help shed some light on the computations achieved by this structure.

A line of experimental and theoretical work shows that the behavioral-dependent rhythmic firing patterns of thalamocortical (TC) relay cells de-

pend on only a small number of membrane currents (McCormick & Huguenard, 1992) and a functionally intact group of inhibitory thalamic reticular (RE) cells. RE cells are capable of oscillating on their own in vivo, and a crucial role for their neuromodulations by NE or 5-HT has been proposed on experimental (McCormick & Wang, 1991) and theoretical (Destexhe, Contreras, Sejnowski, & Steriade, 1994a) grounds. By deactivating a potassium leak current, this extrinsic neuromodulation is able to depolarize RE cells so that GABAergic inhibitory postsynaptic potentials (IPSPs) received from other RE cells deinactivate the low-threshold Ca membrane current I_T. This current triggers a rebound burst at the single-cell level, which generates network oscillations in the frequency range of spindle waves (Destexhe et al., 1994a). Through their influence on intracellular levels of G-protein (a second messenger), NE or 5-HT has the potential of switching a silent network of RE cells between quiescent and oscillatory states.

Interestingly, the inclusion of TC cells in this network has prompted the study of a form of intrinsic activity-dependent neuromodulation (Destexhe, Bal, McCormick, & Sejnowski, 1996). In a model of synchronized oscillations and propagating waves in thalamic slices Destexhe et al. (1996) show how the activity-dependent modulation (which they term *upregulation*) of a mixed cationic current I_h in TC cells contributes to the waning phase of the characteristic waning and waxing pattern of spindle oscillations. Whereas neuromodulation is often expressed as a change in maximal conductances, previous work on the STG has indicated how serotonin-mediated shifts in the voltage dependence of the activation curve of I_h could also contribute to the pattern of oscillations of an intrinsically oscillating cell (Golowasch et al., 1992; Harris-Warrick, Coniglio, Levini, Gueron, & Guckenheimer, 1995). In the STG model, shifts were artificially introduced and their effects studied. In this model, however, a different formalism is proposed and introduces an activity-dependent shift of the activation of the I_h current:

$$I_h = \bar{G}([O] + K[O_L])(V - E_{rev}) \text{ with}$$

$$C \xleftrightarrow{\alpha(V)/\beta(V)} O$$

$$P_u + 2Ca^{2+} \longleftrightarrow P_b$$

$$O + P_b \longleftrightarrow O_L,$$

where C, O, and O_L are closed and opened forms of the h channel and P_u and P_b are unbound and bound forms of a slow intracellular regulating factor, which could be cAMP. The kinetics are such that the transition from O_L to a closed state is very improbable, leading effectively to a locking of the O_L fraction of the channels into the open state. This effect is responsible for a bounded shift of the activation curve of I_h toward depolarized values, as the intracellular calcium concentration is increased during bursting activity. Moreover, because K is chosen greater than 1, the binding of calcium

also triggers an increase in conductance. Both effects have been observed experimentally (Hagiwara & Irisawa, 1989).

Because of the dependence of I_h kinetics on Ca, deactivation of I_h occurs only during low-frequency firing when Ca does not accumulate. During bursts, the accumulation of calcium shifts the activation curve of I_h toward more depolarized states and keeps I_h active. During a burst, therefore, O_L (and consequently I_h) increases, leading to a progressive afterdepolarization (ADP). The ADP eventually counteracts the I_T-mediated rebound bursts, and the spindle oscillatory episodes are terminated. The subsequent slow return of I_h to its basal value results in an 8–10 sec refractory period during which further oscillations cannot be initiated. Evoked or spontaneous activity may ultimately restart the spindle episode, after a total waning phase of 15–25 sec, including the refractory period.

In addition to contributing to the waning phase of spindle oscillation, the modulation of I_h also enables the synchronization of several independent colliding spindle waves into a single propagating wave (but see Contreras, Destexhe, Sejnowski, & Steriade, 1997, for in vivo data). Other forms of I_h modulations have been proposed elsewhere in the thalamus (Wallenstein, 1996) and in the STG of the lobster (Golowasch et al., 1992; Harris-Warrick et al., 1995).

In the piriform cortex and olfactory bulb, oscillatory dynamics are modulated by noradrenergic and cholinergic afferents (Biedenbach, 1966; Bressler & Freeman, 1980). Liljenstroem and Hasselmo (1995) investigate the effects of cholinergic modulation on piriform cortex oscillatory dynamics. These include cholinergic suppression of neuronal adaptation, cholinergic suppression of intrinsic fiber synaptic transmission, and cholinergic enhancement of interneuron activity. Their model provides a basis for understanding the involvement of acetylcholine modulation in cortical EEG oscillations (Wilson & Bower, 1992). They demonstrate that the suppression of neuronal adaptation could explain the appearance of evoked gamma oscillations after potentials. They also find that such suppression of adaptation, when coupled with the other cholinergic effects mentioned above, was particularly effective in switching the network into spontaneous theta oscillations. These results are related to others in the hippocampus (Traub, Miles, & Buzsaki, 1992; Traub, Whittington, Colling, Buzsaki, & Jefferys, 1996; Wang & Buzsaki, 1996) that do not involve neuromodulation explicitly. The putative functional significance of neuronal adaptation, and its consequence on rhythmicity, is made apparent in later studies on learning and memory in the hippocampus and will be discussed separately.

3.2 Modulation of the Processing of Sensory Signals: Filtering and Signal-to-Noise Ratio. Processing of sensory information often relies on preprocessing functions like filtering, contrast enhancement, and noise reduction. Many of these functions can be modulated, enabling the sensory

system to respond differently to various components of complex incoming sensory streams.

In the visual domain, one example of such a function is the temporal transformation that some lateral geniculate nucleus (LGN) cells perform on their retinal input (Mukherjee & Kaplan, 1995). The experimental data show that the temporal response of these cells is variable and is related to their ability to burst. Such cells can behave as either relays, responding at the same frequency as their retinal inputs by firing tonically (in alert/awake state), or as bandpass filters, responding optimally at frequencies of 2–8 Hz by firing in a bursting mode (in sleep states), presumably failing to transmit sensory information accurately. In a biophysical model, Mukherjee and Kaplan (1995) show that LGN cell responses can vary from low-pass, with no apparent bursting properties, to bandpass, with frequent burst discharges, depending on the value of their resting membrane potential, and provided that the low-threshold calcium T current is kept active. The authors propose that the LGN acts as a temporal filter, which can be dynamically tuned by attentional signals from the brainstem and the visual cortex, through their modulatory effects on LGN cells' resting membrane potential. In a separate connectionist model, Jackson, Marrocco, and Posner (1994) model such modulatory signals by the putative effects of NE release, expressed as a combination of self-feedback excitation and lateral inhibition. The computational role of such modulation is to achieve contrast enhancement, such that small initial differences in the incoming signal are amplified, and consequently direct attention.

In their model of the olfactory bulb, Linster and Gervais (1996) showed that the modulation of two families of interneurons might sensitively improve odorant signal detection. On the one hand, the modulation (increase) of lateral inhibition mediated by the periglomerular interneurons may result in the sparsification of the mitral activation patterns of complex odors, which otherwise would involve a large, undifferentiated population of mitral cells. On the other hand, under conditions when mitral cell responses are close to noise levels, a global modulation (decrease) of the inhibition mediated by glomerular interneurons may result in an enhancement of their responses. In an extension of this model, Linster and Hasselmo (1997) show that such modulation of inhibition could depend on the global activity of the mitral cells. They introduce a modulator neuron (a putative NE or ACh cell) that receives inputs from all mitral cells and that feeds back on periglomerular cells while simultaneously modulating the connection strength between granule cells and mitral cells. The modulation of inhibition in the glomerular layer ensures a constant average number of active mitral cells, irrespective of the complexity of the input patterns, while modulation of granule cells inhibition ensures a constant average mitral cells spiking probability. Together, these modulations decrease the overlap between pairs of output patterns, making discrimination between overlapping input patterns easier and more reliable.

Addressing similar questions in a model of olfactory processing in the honeybee, Linster and Masson (1996) showed that modulation of inhibition in the antennal lobe may serve for feature extraction of complex and fluctuating chemical signals. This modulation is expressed through the synaptic strength of inhibitory synapses, the biological basis of which has yet to be investigated experimentally. Changes of the balance between excitation and inhibition during the presentation of a stimulus allow the network to act as a short-term memory, displaying the neural activity patterns elicited by the stimulus even after its offset, compatible with experimental data (Sun, Fonta, & Masson, 1993). Expanding on this idea, Linster and Smith (1997) constructed a model of reinforcement learning in the honeybee olfactory system. In this model, modulation of lateral inhibition is introduced via an external modulatory neuron that receives reinforcement signals. This neuron makes plastic synapses onto the circuit under consideration. The authors show that such extrinsic modulation accounts for various behavioral phenomena, such as blocking, unblocking, and overshadowing.

Sensory processing may also involve computations aimed at separating a sensory signal from the background noise. When seen at a system level, the modulation of the signal-to-noise ratio appears as a powerful computational tool by selectively enhancing a signal in a specific pathway, while leaving it undifferentiated with noise in others. A line of modeling work has shown that the cellular mechanisms involved in the known effects of catecholamines on signal detection performance (Clark, Geffen, & Geffen, 1987a, 1987b) may be modeled by a modulation of the slope (gain) of the sigmoid function of a network of leaky-integrator neurons (Servan-Schreiber, Printz, & Cohen, 1990). Changes of this gain at the level of an individual neuron do not affect its signal-detecting capabilities, while increases of this gain in a feedforward chain of neurons augment the signal-to-noise ratio of the whole chain. The model accounts for experimental observations pertaining to the cellular effects of norepinephrine, which show that NE-mediated blockade of Iahp may result in the selective diminution of weak EPSPs and the increase of the depolarization associated with trains of EPSPs, thereby increasing signal- to-noise ratio (Madison & Nicoll, 1986). The model is then used in a backpropagation network to model the improvement in signal detection measured experimentally in human subjects performing a continuous performance task. In this task, subjects are submitted to pharmacological challenges that release catecholamines from synaptic terminals or prevent their reuptake. In an extension of this model, Cohen and Servan-Schreiber (1992) simulate several schizophrenic deficits in selective attention and language processing assessed by tasks such as the Stroop task, the continuous performance test, and a lexical disambiguation task. They successfully show that even though these tasks are seemingly different, the deficits exhibited by schizophrenics can be understood as a general disturbance of the internal representation of contextual information. Such disturbances are implemented as a decrease in the gain of the sigmoid func-

tion of modeled prefrontal cortex units, simulating the possible functional effects of the loss of dopaminergic modulation observed in schizophrenic patients. This theoretical work has been followed by experimental work that confirmed and refined the hypothesis advanced (Cohen, Braver, & O'Reilly, 1996).

In a separate experimental and theoretical study in piriform cortex, Hasselmo and coworkers show that noradrenergic enhancement of the signal-to-noise ratio may also be due to a modulation of synaptic transmission rather than a modulation of input-output function, as was first proposed by Servan-Schreiber et al. (1990). They found that NE, like ACh, may suppress excitatory neurotransmission at intrinsic (collateral) fibers and may also depress feedback inhibition. In a model of piriform cortex, they show that these two effects can act synergistically to increase signal-to-noise ratio (Hasselmo, Linster, Patil, Ma, & Cekic, 1997).

Finally, another interesting body of research has pointed to the role of noise itself as a means of modifying the signal-to-noise ratio (Bulsara, Jacobs, Zhou, Moss, & Kiss, 1991; Levin & Miller, 1996; Longtin, 1993; Longtin, Bulsara, Pierson, & Moss, 1994; McNamara & Wiesenfeld, 1989). To our knowledge, no explicit links to neuromodulation have yet been made.

3.3 Modulation of Memory Function. A large class of memory models is based on the assumption that memories are stored as patterns of synaptic strengths mediating the spread of activation in a network. Learning is achieved according to a synaptic modification rule (or equation) that relates synaptic strength and presynaptic and postsynaptic activities (Brown, Kairiss, & Keenan, 1990; Hasselmo, 1995; Zador, Koch, & Brown, 1990). In this framework, memory function is defined by the synaptic learning rule and the dynamics of individual neurons.

3.3.1 Modulation of the Synaptic Learning Rule. In their model of the response of dopamine neurons to reward and conditioned stimuli (Schultz et al., 1993), Montague, Dayan, and Sejnowski (1996) propose a learning rule in which the postsynaptic activity is augmented by an external reward signal of neuromodulatory origin. In addition, plasticity is made sensitive to temporal differences (Sutton & Barto, 1990) in the postsynaptic activity, rather than to the postsynaptic activity itself. This formulation of the Hebbian learning rule makes time explicit in that some synapses represent early events and others represent later ones. The authors show that after learning a delayed matching-to-sample task, dopaminergic neurons act as a temporal predictor of reward, compatible with experimental data. In this context, dopamine centers have the role of computing and sending diffuse modulatory error signals to the cortex, and hence influence its computation of action in the time domain. The same approach has been used elsewhere (Montague, Dayan, Person, & Sejnowski, 1995) to show how an identified interneuron in the honeybee brain, VUMmx1, could predict reward values

of spatial location during foraging. In this model, VUMmx1 cells influence flight in a manner that accounts for the previous learning of the landscape and its rewarding regions. A similar implementation of VUMmx1 modulation can be found elsewhere (Linster & Smith, 1997).

One of the problems with most learning-rule-based neural models of memory function is the fact that learning and recall may interfere in undesirable ways. Unless care is taken to prevent this, the presentation of a new pattern during learning may elicit an erroneous response from the network. This spurious activity perturbs (if not prevents) learning. In a series of experimental and theoretical studies, Hasselmo and coworkers have shown how selective cholinergic modulation of some synapses, but not others, might provide an elegant solution to this problem.

Experimental data from field recordings in the piriform cortex suggest that cholinergic, noradrenergic, and GABAergic modulation might selectively suppress intrinsic but not afferent excitatory synaptic transmission in the piriform cortex (Hasselmo & Bower, 1992; Hasselmo et al., 1997; Tang & Hasselmo, 1994). In a mathematical model of associative memory, Hasselmo (1993) shows that this selective suppression may prevent previously learned patterns from interfering with the storage of new patterns, especially when previous and new patterns are coded by overlapping populations of neurons (Hasselmo, 1993). This modulation is expressed as a decrease in glutamate release in the activation rule, coupled with a rescaling of the learning rate in the learning rule. In further experimental and theoretical studies, Barkai and Hasselmo (1994) present a detailed biophysical model of a single pyramidal cell in piriform cortex. They show that in addition to its effects on synaptic transmission observed with field potentials, intracellular recordings show that cholinergic modulation of single cells also results in the suppression of neuronal adaptation and in marked depolarization from resting potential. Their single-cell model shows these effects as changes in the maximal conductance of two potassium currents. These results lead to a detailed model of autoassociative memory in the piriform cortex, including 240 pyramidal cells as well as feedforward and feedback interneurons (Barkai et al., 1994). Results from intracellular recordings (suppression of neuronal adaptation and depolarization) and field recordings (suppression of intrinsic synaptic transmission) are included in the model. During learning, the overall effects of cholinergic modulation are to enhance pyramidal cell activity, increasing learning performance. After learning, cholinergic modulation is suppressed and sets the stage for recall. ACh therefore ensures that learning and recall do not interfere and controls the computations of the network.

3.3.2 Modulation of Neural Dynamics. In a large associative network of Fitzhugh-Nagumo-like cells, Abbott (1990) shows that a simple modulation (of putative neuromodulatory origin) of the dynamics of the slow variable (see the appendix) may switch the network from implementing a nonselective short-term latching memory to behaving as a long-term associative

memory. This change in mode of operation of the network increases its computational capabilities without changing its learning rule or architecture. Repetitive firing can also be the result of intrinsic cellular properties such as cholinergically or serotonergically induced afterdepolarization. Models of associative memory based on this phenomenon have shown that repetitive firing can be temporally organized into nested theta and gamma oscillations in order to learn and maintain several memory items active in a short-term memory buffer (Jensen, Idiart, & Lisman, 1996; Lisman & Idiart, 1995).

Building on their work in the piriform cortex, Hasselmo and Schnell (1994) show that the dynamics of learning and recall in the hippocampus can also be regulated by overall network activity. In their model of hippocampal layers CA1 and CA3, the total activity of CA1 pyramidal cells feeds back to the cholinergic system (presumably in the septum) and regulates cholinergic neuromodulation. This model involves a closed and autonomous system that has a clear function and in which neuromodulation is regulated by its target. The septum modulates the function of the hippocampus, which in return regulates the septum in a diffuse, activity-dependent manner. These ideas have been incorporated in a model of corticohippocampal classical eye-blink conditioning (Gluck & Myers, 1993) as a septally driven modification of the learning rate of the hippocampus autoassociative module (Myers et al., 1996). In this model, septal neuromodulation controls the relative amount of time spent by the hippocampus in learning new stimuli and the time necessary to transfer information to neocortical regions.

Finally, in a model of hierarchical associative memory, Cartling (1996) shows that different levels of coupling between activity and excitability may change the dynamics of memory recall. In a Hopfield-like architecture, activity may be chaotic (memories fail to be retrieved), oscillatory (memories are retrieved cyclically, one after the other), or tonic (only one memory item is eventually retrieved) as the coupling is decreased. Neuromodulation is implemented as a change in the shape of the sigmoid transfer function linking membrane potential to firing rate. This change is regulated by overall network activity and depends on intracellular calcium concentrations. However, while some experimental and theoretical work shows that a decrease of cholinergic modulation is associated with stable network dynamics (Hasselmo & Schnell, 1994), this model assumes that an increase of cholinergic modulation yields stable states.

3.4 Neuromodulation for Input Selection and Information Integration. In complex neural networks, information flows along many divergent routes. Much experimental and theoretical work has assigned to neuromodulation the role of selecting the input to particular neural systems, thereby controlling the flow of information. Neuromodulation can act as a routing mechanism and control whether synaptic inputs will activate a particular circuit. The general flow of information between functionally distinct circuits is therefore determined by their modulatory state. Neuromodulation

can also act within a circuit to control what subsets of the available information will be processed.

At the single-cell level, the combined actions of different neuromodulatory systems on cellular or synaptic mechanisms may determine whether the cell will be responsive to a given pattern of synaptic stimulation, therefore enabling or disabling processing.

In Aplysia, for example, while both DA and 5-HT silence the bursting neuron R15, only the serotonergic modulation will allow brief depolarization to elicit a sustained bursting response. A modeling study of this system has proposed that the underlying mechanism is rooted in the modulation by DA and 5-HT of two distinct currents (Butera et al., 1995). The authors show that DA prevents input signals from eliciting R15 firing, while 5-HT enhances its response, effectively amplifying synaptic inputs. Together these two neuromodulatory systems control when input signals to R15 may be forwarded to later processing stages.

Similarly, at the network level in the vertebrate, experimental and theoretical evidence suggest that ACh levels, together with other neuromodulatory systems, may control the flow of sensory information through the thalamus to the cortex (see sections 3.1.2 and 3.2).

Modeling studies in piriform cortex and hippocampus show that neuromodulation within a circuit may control the nature of the information processed. In a series of experimental and modeling studies (see section 3.2), it was shown that selective cholinergic (Hasselmo & Bower, 1992), noradrenergic (Hasselmo et al., 1997), or GABAergic (Tang & Hasselmo, 1994) suppression of intrinsic (recurrent) but not extrinsic (sensory) inputs promotes learning, while the absence of such suppression allows for memory recall. In this system, the selection of the information that is processed therefore depends on a rich class of neuromodulatory conditions, itself related to the behavioral state of the animal.

Finally, modulation of signal-to-noise ratio (see section 3.2) can also be considered as a form of input selection. By selectively enhancing certain neural inputs (the signal) and decreasing others (the noise), the system makes a de facto selection, which may change with neuromodulatory and behavioral conditions. This observation is at the basis of several models of selective attention involving the noradrenergic locus coeruleus (Aston-Jones et al., 1994; Rajkowski et al., 1994; Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1995) and of the DA-mediated control of cognitive processing in the prefrontal cortex and its relation to schizophrenia (Cohen et al., 1996).

4 Conclusion: Neuromodulation Increases and Controls Complexity

Our review has shown that neuromodulation may play a significant computational role in a large spectrum of systems, from invertebrate central pattern generators to vertebrate cortical memory networks. In all cases, neuromodulation appears to be a powerful tool destined to increase and/or control the

computational complexity of a given network, without necessarily increasing the structural or dynamical complexity of the network itself. Spatially diffuse and slow neuromodulations of current conductances may trigger drastic changes of rhythmic patterns in central pattern generators, as well as in the thalamus, probably changing the nature of the downstream computations and increasing the complexity of the computations achieved by the whole circuit. Spatially selective and phasic neuromodulatory controls of specific neuronal input pathways help complex recurrent memory networks function properly.

Our review has also revealed two major limitations to the study of neuromodulation. Overcoming them requires the design of new theoretical and experimental tools, which undoubtedly will be beneficial.

The first stems from the observation that most modeling studies reviewed consider neuromodulation as an enhancing addition to a basic model. Often it is reduced to ad hoc parameter variations. We believe, however, that such an approach will no longer suffice as efforts are made to make computational models more biologically plausible in both their design and their function. Neuromodulation should be an integral part of the models. Only then will comprehensive theories of neuromodulation emerge and new neural computational principles may be discovered.

Second, in actual biological systems, neuromodulation has multiple simultaneous or sequential (cascade) effects on neural information processing. However, their experimental study almost always consists of individual modulations, keeping others constant. Moreover, in most cases, neuromodulation is present or absent and is rarely studied as a continuous phenomenon. It is not generally known whether the effects of different kinds of neuromodulation are truly independent, and if not, how they interact, nor is it known whether various levels of a single neuromodulation may yield drastically different neural behaviors. If some models propose interesting ways in which various modulatory phenomena might coexist, most of the models reviewed here still assume that multiple neuromodulatory effects are independent. As first proposed elsewhere (Harris-Warrick & Marder, 1991; Marder, Hooper, & Eisen, 1987), it is likely that accounting for the simultaneous effects of several neuroactive substances on a single network may increase its computational complexity in relevant and interesting ways, giving further insight into its function in the larger context of behavior.

Overall, computational and experimental models of neuromodulation appear to be powerful tools for the understanding of the computation of single cells as well as large neural networks.

Appendix: The Mathematical Tools

Uppercase letters are constants unless otherwise noted; lowercase letters are variables. The appendix is organized by levels of modeling, from more detailed to more abstract.

A.1 Markovian Chemical Kinetics Models.

$$i = \bar{G} s_1^o, \ldots, s_i^o, \ldots, (\mathrm{v} - E)$$

$$S_i \underset{R_{ji}}{\overset{R_{ij}}{\rightleftarrows}} S_j \quad \text{with} \quad \frac{ds_i}{dt} = \sum_j R_{ji} s_j - s_i \sum_j R_{ij}.$$

R are rate constants, and s are concentrations (fraction of channels in state S). s_k^o is an open state.

At the most elementary level of modeling, neuronal processes can be described as chemical reactions, provided that their kinetics are quantitatively determined. In this framework, neuromodulatory phenomena are not distinguishable from others.

Destexhe et al. (1994a) expresses intracellular phenomena, membrane mechanisms, synaptic transmission, and neuromodulation with a single set of kinetic equations. In the model proposed, the neuromodulation by second messenger G-protein gated K+ channel ($GABA_B$, 5HT, M2 (ACh), $\alpha 2$ (NE), D2 (DA), histamine, opioid, and somatostatin receptors) is expressed by the appropriate formulation of rate constants of the type $R_{ij} = R_{ij}(\mathrm{v}) = A_{ij} e^{-\frac{\mathrm{v}}{B_{ij}}}$ for voltage-dependent gating and $R_{ij} = [L]\bar{R}_{ij}$ for ligand-activated gating.

Using a simplified formulation of this model, Destexhe et al. (1994a) model the putative role of NE and 5-HT in modulating rhythmic activity in thalamic reticular cells. G-protein activation is taken as a consequence of both NE and 5-HT neuromodulation. It is implemented as a modulating factor to the activation dynamics of a leak potassium current according to $g_{Kleak} = \bar{G}_{Kleak} \cdot m$, with $\frac{dm}{dt} = K[S]m - K'(1 - m)$, [S] representing the concentration of second messenger present in the cell.

A.2 Hodgkin-Huxley Models. For a multicompartment model (x indexes compartments):

$$C\frac{d\mathrm{v}}{dt} = \sum i + \frac{E_{leak} - \mathrm{v}}{R} + \sum_x \frac{\mathrm{v}_x - \mathrm{v}}{R_a} + i_{syn} + I_{inject}$$

$$i = \bar{G} m^A n^B (\mathrm{v} - E) \quad \text{with} \quad \frac{dm}{dt} = \frac{L_\infty^m(\mathrm{v}) - m}{\tau_m(\mathrm{v})} \quad \text{and} \quad \frac{dn}{dt} = \frac{L_\infty^n(\mathrm{v}) - n}{\tau_n(\mathrm{v})}.$$

m and n are activation and inactivation variables, respectively. Eventual synaptic potentials are modeled by:

$$i_{syn} = g_{syn}(\mathrm{v} - E_{syn}) \text{ with } g_{syn} = W\bar{G}_{syn}\frac{\tau_1}{\tau_2 - \tau_1}\left(-e^{\frac{t}{\tau_1}} - -e^{\frac{t}{\tau_2}}\right),$$

where W is the synaptic weight.

In the Hodgkin-Huxley formalism, neuromodulation is often expressed as a change in the maximal conductance of some particular membrane currents. At this level of modeling, it also may be implemented as a variation of the dynamics of some currents, variations in intracellular concentrations of some substances, and variation in synaptic transmission.

When the actual pharmacology of the channels is known, it is possible to express the conductances as functions of other intracellular quantities, including concentrations of neuromodulatory substances. For example, Butera et al. (1995) propose a scheme of interaction between dopamine and serotonin that yields expressions for conductances of the type:

$$\bar{G} = \bar{G}_1 \left(\frac{K}{[Ca]_i + K} \right) \times \left(\frac{K_{DA}}{[DA] + K_{DA}} \right) \times \left(1 + \frac{K'}{1 + e^{-\frac{[cAMP]-K''}{D''}}} \right)$$

$$\bar{G} = \bar{G}_1 \left(\frac{\mathrm{v} - E}{1 + e^{\frac{ZF(\mathrm{v}-E')}{RT}}} \right) \times \left(1 + \frac{K'}{1 + e^{-\frac{[cAMP]-K''}{D'}}} \right)$$

$$\frac{d[cAMP]}{dt} = K \left(1 + K' \frac{[5\mathrm{HT}]}{[5\mathrm{HT}] + K''} \right) + C \frac{[cAMP]}{[cAMP] + K'''} .$$

In some cases it is possible to obtain only an experimental curve quantitatively measuring the influence of a modulatory substance on given conductances. Bertram (1993) models two serotonin-sensitive conductances using a fit to their experimental values. The fit chosen takes the form:

$$\bar{G} = \bar{G}(s) = A + \frac{B}{1 + e^{-C(Ds-F)}} \text{ with } s \in [0, 1],$$

where s represents the concentration of serotonin applied. A similar formulation is used to describe the influence of two neuromodulatory substances (small cardioactive peptides, and myomodulins) on several currents in invertebrate neuromuscular circuits (Brezina et al., 1996).

In other cases, maximal conductances can be made dynamically dependent on intracellular quantities such as calcium (LeMasson et al., 1993) with

$$\tau \frac{d\bar{G}}{dt} = f([Ca]) - \bar{G} \text{ and } f([Ca]) = \frac{G_{\max}}{1 + e^{\pm \frac{[Ca]-C_T}{\Delta}}} .$$

Barkai et al. (1994) and Barkai and Hasselmo (1994) have access only to a qualitative experimental description of the effects of two potassium conductances on the firing adaptation of cortical cells. They therefore model these effects by choosing two parameter sets that yield adapting or weakly adapting model cells:

$$(\bar{G}, R) \in \{(\bar{G}_1, R_1), (\bar{G}_2, R_2)\}.$$

In a different system Epstein and Marder (1990) consider intermediate values, extrapolated linearly from the experimental ones following:

$$\bar{G} = \bar{G}(\alpha) = \alpha\bar{G}_1 + (1-\alpha)\bar{G}_2,$$

where α is a dimensionless parameter.

When values for maximal conductances are not accessible experimentally, a theoretical search might be fruitful. In some cases, the set of conductances under neuromodulatory influence is known or hypothesized, and the dynamics of the network are under investigation. Dynamical systems theory (Guckenheimer et al., 1993) maps conductances values to possible network dynamics. The study of their stability leads them to experimental predictions about conductance values and their effects. In other cases, the dynamics of the network is known, but the set of conductances under neuromodulatory influences is unknown. Exhaustive search (Bhalla & Bower, 1993; Foster et al., 1993) allows for a systematic exploration of the parameter space constituted by all the maximal conductances hypothesized to be functional. Some regions of this space yield the dynamics under study. The location and shape of these regions predict what conductances are likely to be important (i.e., under neuromodulatory control) and what their possible values are.

Neuromodulation can also be expressed as a change in the dynamics (rather than maximal conductance) of some particular membrane currents. Such is the case of a variation in an inactivation time constant (Mukherjee & Kaplan, 1995) such as,

$$\tau_n(\mathrm{v}) = \bar{T}_n\bar{\tau}_n(\mathrm{v}) \qquad \text{with } \bar{T}_n \in \left[\bar{T}_n^{\min}, \bar{T}_n^{\max}\right],$$

or of a variation in the voltage dependence of the steady-state activation curve $L_\infty^m(\mathrm{v})$, as for I_h (Destexhe et al., 1996; Golowasch et al., 1992).

Neuromodulation can also be expressed through changes in the intracellular concentration of some substances such as cAMP (Raymond et al., 1992) rather than as changes in maximal conductance of some membrane current.

Finally, neuromodulation can be expressed at the level of synaptic transmission. Such is the case for the presynaptic modulation of synaptic transmission by the activation of $GABA_B$ receptors (Wallenstein & Hasselmo, 1997b).

In this model, the concentration of $[GABA]_o$ in the synaptic cleft is first calculated as a function of the number of local active inhibitory synapses (n_{pre}) and a local diffusion term leading to:

$$\frac{d[GABA]_o}{dt} = C.n_{pre} - D.[GABA]_o,$$

where C and D are constants. At any point in time, $[GABA]_o$ is then used to decrease synaptic currents, with $i_{syn} = i_{syn} - A.[GABA]_o$ where A is a constant.

Other models have viewed modulation as signal influencing synaptic mechanisms. Such is the case of the reward signal entering the weight modification rule, between VTA and cortex (Montague et al., 1996), or the direct change of synaptic efficacy triggered by an external center (Linster & Hasselmo, 1997; Linster & Smith, 1997; Raymond et al., 1992).

A.3 Fitzhugh-Nagumo Models.

$$C\frac{dv}{dt} - f(v) - w + I_{inject}$$

$$\tau\frac{dw}{dt} = v - Dw$$

v is the fast (voltage-like, C small) variable; w is the slow (recovery-like) variable.

In this simplified framework (as for BonHoeffer-van der Pol or Morris-Lecar systems), individual concentrations and current conductance are not accessible, and fast Hodgkin-Huxley-type timescales are relaxed to pseudo-steady-state values. Neuronal behavior is assessed macroscopically through overall activity.

In a model of associative learning, Abbott (1990) proposes that neuromodulation may serve as a mechanism for initiating and terminating learning. Using the following formulation for the slow variable,

$$\tau\frac{dw}{dt} = av - (1-a)w$$

he shows that depending on the value of a and the strength of the external inputs (I_{inject}), single cells may settle in regions of hyperpolarization, depolarization, oscillations, or bistability. At the network level, for values of a yielding oscillation, the network behaves like an associative memory (phase-locked oscillations, patterned according to synaptic coupling). For values of a yielding bistability, a putative consequence of neuromodulation, the network behaves like a nonselective latching short-term memory, maintaining the activity elicited initially by the input pattern, and allowing Hebbian plasticity to take place.

Interesting approaches to neuromodulation have also focused on the role of noise. Longtin (1993) uses stochastic resonance theory to show that the introduction of noise can have modulatory effects on the signal-to-noise ratio of a neuronal system, measured on the basis of the transfer of the oscillatory inputs to the output. The formulation used to illustrate this point introduces noise in v and a periodic forcing on w:

$$C\frac{dv}{dt} = v(v-A)(1-v) - w + I_{inject} + \xi(t)$$

$$\tau\frac{dw}{dt} = v - Dw - [B + R\sin(\omega t)],$$

where $\xi(t)$ is a white noise (gaussian distributed) function, and $B+R\sin(\omega t)$ is a subthreshold oscillatory forcing. Experimental evidence has recently been found in support of the role of noise in improving information processing (Levin & Miller, 1996).

In this framework, neuromodulation can also be expressed as a change of electrical coupling between two cells, as in the STG (Kepler et al., 1990). It can be expressed as a shared current following:

$$I_{inject} = W(\mathrm{v}_f - \mathrm{v}) \text{ and } f(\mathrm{v}) = G\mathrm{v} - (G+\alpha)\bar{V}$$

$$C_f \frac{d\mathrm{v}_f}{dt} = -G_f(\mathrm{v}_f - \bar{V}_f) + W(\mathrm{v} - \mathrm{v}_f).$$

We also should mention attempts at modeling NE-mediated decrease in K^+ current effects on the oscillatory behavior of a small thalamo-cortical model (Wallenstein, 1993). The effects were modeled by current injection in a Bonhoeffer–van der Pol modeling framework.

A.4 Leaky Integrator Models.

$$\tau \frac{d\mathrm{v}}{dt} = -\mathrm{v} + \sum_i W_i S(\mathrm{v}_i) + I_{inject}$$

where $S(\,)$ is usually nonlinear (the sigmoid function), and v is the average membrane potential.

This representation allows for qualitative descriptions of the overall effects of average pools of neurons on behavior. Neuromodulation can be expressed by a change in firing threshold or a significant modification of synaptic weights (Linster & Masson, 1996) with:

$$\mathrm{v} \le \theta_{\min} \Rightarrow S(\mathrm{v}) = 0 \quad \text{and} \quad \mathrm{v} \ge \theta_{\max} \Rightarrow S(\mathrm{v}) = 1$$

$$\theta_{\min} \le \mathrm{v} \le \theta_{\max} \Rightarrow S(\mathrm{v}) = \alpha\mathrm{v}.$$

Neuromodulation can also be expressed by introducing a multiplicative factor to the upper and lower bounds of the sigmoid function or by decreasing weights by a fraction (Liljenstrom & Hasselmo, 1995):

$$(\theta_{\min}, \theta_{\max}) \Rightarrow (\beta\theta_{\min}, \beta\theta_{\max}) \quad \text{or} \quad W \Rightarrow \frac{W}{\gamma}.$$

It can also be expressed as a dependence of the sigmoid function on other quantities such as the intracellular calcium concentration. Cartling (1996) models neuromodulation as a change in neuronal adaptability (coupling between activity and excitability). It is expressed as a multiplicative factor (a) to the intracellular Ca concentration (c) with activity-dependent second-order dynamics:

$$S(\mathrm{v}) = S(\mathrm{v}, c) = MAX(\tanh(A\mathrm{v} - ac - \theta), 0)$$

$$\text{with} \quad \frac{dc}{dt} = \frac{K}{K' + c} S(\mathrm{v}, c) + \frac{K'' - c}{T},$$

where c is the intracellular calcium concentration and a is the adaptability.

Neuromodulation is measured by a, which depends on the total activity of the network:

$$a = A_{\max}(1-n) \quad \text{with} \quad \frac{dn}{dt} = C(1-n)\sum_i \alpha_i v_i.$$

α_i is the size of the population having v_i as state variable.

A.5 Connectionist Models.

$$o = \sum_i W_i S(o_i).$$

In case of modifiable synapses:

$$\frac{dw}{dt} = \eta x(t) y(t),$$

where $x(t)$ represents the presynaptic activity, and $y(t)$ represents the postsynaptic activity. $S(\,)$ is analogous to the sigmoid function of leaky integrator models.

Neuromodulation in connectionist models has been expressed in two general ways. The first expresses neuromodulation in the sigmoid function, the second in the dynamics of the synaptic weights.

Neuromodulation can be implemented as a modification of the slope (gain) of the sigmoid function (Cohen & Servan-Schreiber, 1992; Servan-Schreiber et al., 1990) in a small network (chain) of connectionist elements, following:

$$S(o) = \frac{1}{1+e^{-(Go+B)}} \text{ with } G \in [G_{\min}, G_{\max}].$$

Other modifications to the sigmoid function can be made to express other neuromodulatory properties, such as suppression of neuronal adaptation (Liljenstrom & Hasselmo, 1995). Using a nonmodulated sigmoid function,

$$S(o_i) = CQ_i\left(1 - e^{-\frac{o_i+1}{Q_i}}\right),$$

activity-dependent neuromodulation is expressed as:

$$S(o_i) = CQ_i\left(1 - e^{-\frac{o_i+1}{Q_i}}\right) \times e^{-\alpha\langle S(o_i)\rangle^2_{t-T}},$$

where T is a fixed time window and t is time.

A second modeling approach consists of introducing neuromodulatory effects to the learning rule. Montague et al. (1996) modeled the activity of

dopamine cells in the VTA by augmenting the postsynaptic activity with an external reward signal:

$$S(o) = o$$

$$\Delta w = \eta x(t)(r(t) + y(t)),$$

where $r(t)$ is the external reward signal.

Hasselmo (1993) selectively modifies the learning rate of certain synapses to include the effects of ACh with

$$\frac{dw}{dt} = \eta(1 - c)x(t)y(t) \qquad \text{with } c \in [0, 1],$$

where c measures the amount of cholinergic suppression. Myers et al. (1996) adopt a similar approach in their model of cholinergic influence on cortico-hippocampal interaction during eye-blink conditioning.

Both sigmoid and synaptic modulation can coexist and have been modeled by Hasselmo and Schnell (1994). The synaptic modulation is expressed using:

$$W_i = (1 - cC_{W_i})w_i \text{ and } \frac{dw_i}{dt} = \eta(1 + cC_\eta - C_\eta)x(t)y(t)$$

and replacing θ with $(1 - cT_{\max})\theta$ in the normal ramplike sigmoid function:

$$o \leq \theta \Rightarrow S(o) = 0$$

$$o \geq \theta \Rightarrow S(o) = o - \theta.$$

Finally we should mention the modeling of morphological changes in Alzheimer"s disease (Horn, Ruppin, Usher, & Herrmann, 1993) expressing modulation of activity by random synaptic deletion, and appropriate compensation with:

$$o = c\sum_{i \in \Delta} W_i S(o_i) \text{ with } |\Delta| = (1 - d)N \text{ and } \qquad S(o) = Step(o - T).$$

c is the compensation factor, d is the deletion factor, and $c = 1 + \frac{dk}{1-d}$ with $k \in [0, 1]$.

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