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Neuromodulation of olfactory transformations

Christiane Linster[1] and Thomas A Cleland [2]

The olfactory bulb and piriform cortex are the best studied structures of the mammalian olfactory system and are heavily innervated by extrinsic neuromodulatory inputs. The state-dependent release of acetylcholine, norepinephrine, serotonin, and other neuromodulators into these olfactory structures alters a constellation of physiological parameters in neurons and synapses that together modify the computations performed on sensory signals. These modifications affect the specificity, detectability, discriminability, and other properties of odor representations and thereby govern perceptual performance. Whereas different neuromodulators have distinct cellular effects, and tend to be associated with nominally different functions, it also is clear that these purported functions overlap substantially, and that ad hoc hypotheses regarding the roles of particular neuromodulators may have reached the limits of their usefulness.

Addresses
[1] Computational Physiology Lab, Department of Neurobiology and Behavior, Cornell University, Ithaca, NY 14853, USA
[2] Computational Physiology Lab, Department of Psychology, Cornell University, Ithaca, NY 14853, USA

Corresponding author: Linster, Christiane (CL243@cornell.edu)

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Introduction

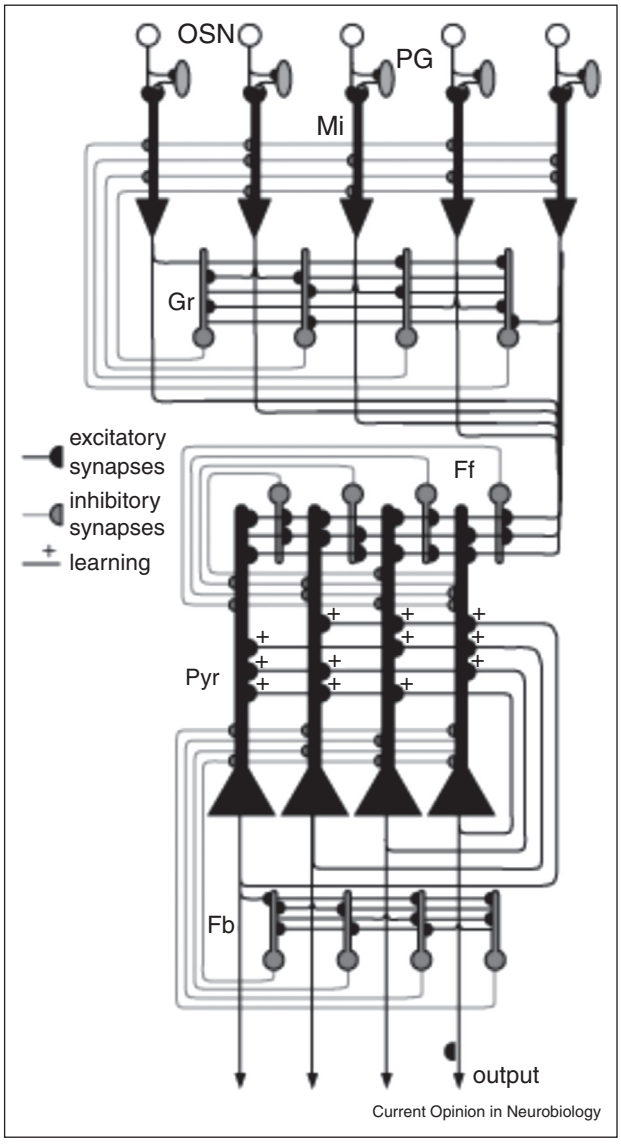
Neuromodulation can be defined as a neurochemical process that serves to modify (modulate) the computations performed by a neuron or network as a function of task demands or behavioral state. This modulation can be mediated by neurochemicals arising from extrinsic sources (including acetylcholine from basal forebrain nuclei, norepinephrine from the locus coeruleus, and other amines and peptides), as well as those released from neurons intrinsic to a local network (including ancillary effects of classical neurotransmitters mediated by metabotropic receptors as well as the release or co-release of aminergic or peptide neuromodulators). While the functional distinction between neurotransmitters and neuromodulators is imperfect, the latter are characterized by effects that are best understood as changes in neuronal or network state that alter responsivity to synaptic inputs.

Olfactory networks (Figure 1) are constructed to extract and recognize pertinent signals from unpredictable, chemically noisy environments, and must be able to adapt flexibly to changes in the sensory environment as well as to internal state variables such as hunger or alarm. These adaptive transformations are often regulated by neuromodulatory inputs, a wide variety of which innervate the olfactory system. Consequently, the olfactory system has served as an important model system for understanding the functional roles and computational mechanisms of neuromodulation, particularly in mammals. One of its advantages in this role is that there has been somewhat less of a tendency to associate individual neuromodulators with broad behavioral states such as attention or arousal. While these relationships may have merit, their presumption also can introduce bias into experimental design and interpretation. In contrast, the construction of multiscale models of neuromodulation can elucidate the relationships between cellular and synaptic effects and the resulting systems-level transformations of (sensory) input, providing rich insights into the complexity and contingencies of neural circuit function. We here review some examples of the neuromodulatory regulation of specific functional computations hypothesized for olfactory circuitry in adult rodents.

Olfactory processing and neuromodulation

Chemical signals are transduced by primary olfactory sensory neurons (OSNs) in the nasal cavities, which project directly to the central nervous system to form discrete neuropilar glomeruli within the olfactory bulb (OB). Within these glomeruli, OSN axonal arbors interact with mitral and tufted cells (principal neurons) along with several local interneuron species that together form glomerular microcircuits (reviewed in [1,2]). Computational studies of experimental data have shown that these glomerular circuits can enhance signal-to-noise ratios, regulate contrast among odor stimuli, decorrelate odor signals, and generate concentration-tolerant representations of olfactory stimuli in principal neuron populations—particularly the mitral cells (reviewed in [3,4]). A second layer of computation is then performed in the deep OB, mediated by additional interneuron populations of which granule cells are the most prominent (reviewed in [2]). Notably, these deep bulbar circuits are thought to exert their functional effects on mitral cells via the regulation of spike timing, presumably tuned to the readout properties of postsynaptic targets [5,6,7••]. These secondary olfactory target structures include,

Figure 1



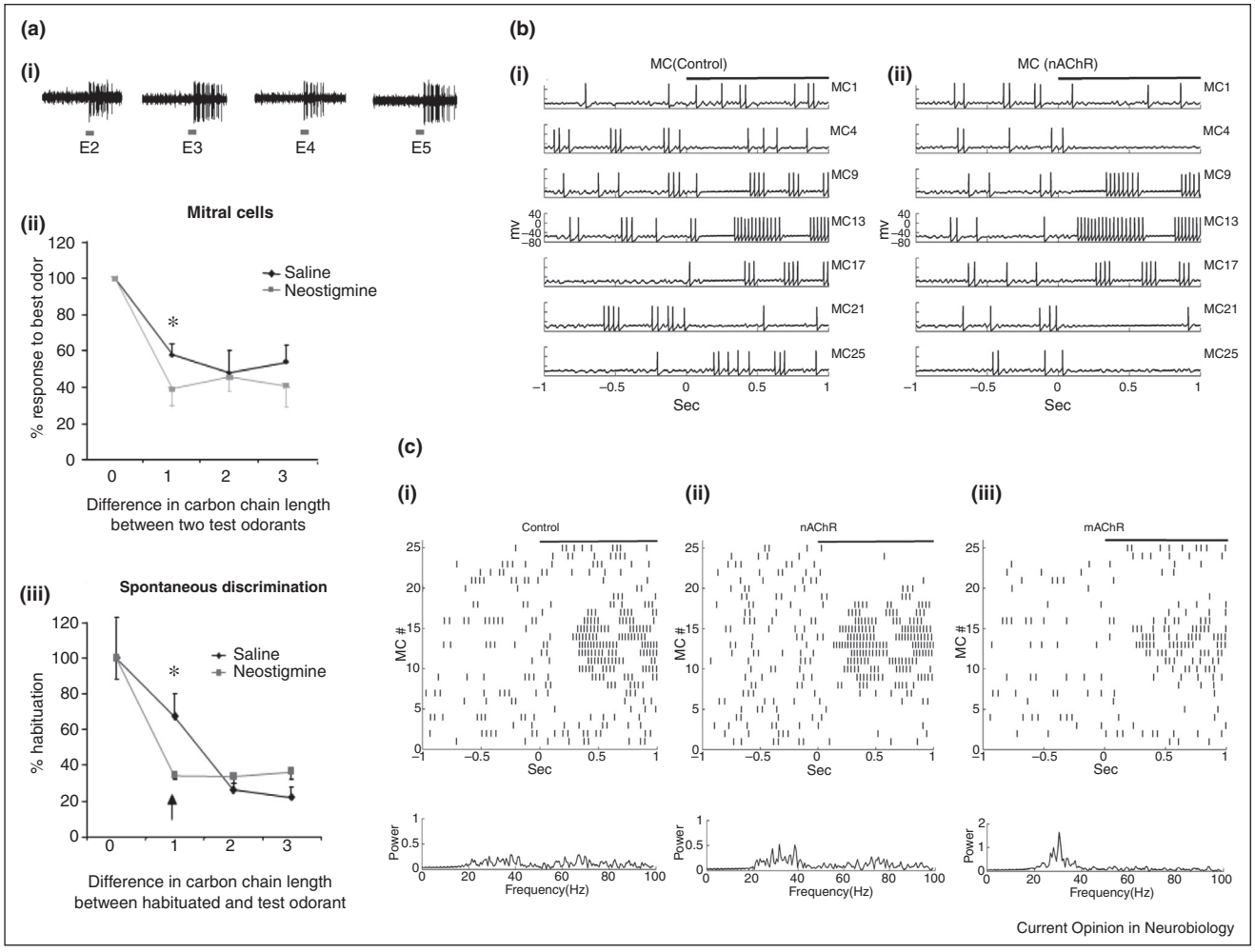
Simplified network structure of the olfactory bulb (*above*) and piriform cortex (*below*). Olfactory sensory neuron subpopulations (OSN) expressing the same receptor converge to one specific glomerular column (five of which are depicted), in which they connect to mitral cells (Mi), a subclass of periglomerular/superficial short-axon cells (PG), and external tufted cells (not depicted). Mitral cells (and tufted cells, not shown) are the principal neurons of the OB; their activity is regulated by these glomerular-layer interneurons as well as by granule cell interneurons (Gr) within the deep OB. Granule cells connect to mitral cells via reciprocal dendrodendritic synapses; the mitral-to-granule cell synapses are excitatory, and the granule-to-mitral synapses are inhibitory. In the piriform cortex, mitral cell axons synapse onto piriform pyramidal cells (Pyr) and onto a class of feedforward inhibitory interneurons (Ff) that project their axons onto the apical dendrites of Pyr cells, modulating the excitatory input coming from the OB [46]. Pyr cells project axons out of the piriform cortex (bottom), but also project axon collaterals that synapse onto a second class of feedback inhibitory interneurons (Fb; [46]) as well as directly onto other Pyr neurons, thereby creating a dense intrinsic associative network. It is this intrinsic excitatory network that is suppressed by cholinergic neuromodulation so as to favor the afferent input arising from OB mitral cells [43].

among others, the anterior olfactory nucleus, piriform cortex, olfactory tubercle, anterior hippocampal continuation, indusium griseum, and tenia tecta (reviewed in [8]), among which the piriform cortex is the best studied. Owing largely to its intrinsic excitatory interconnections, piriform cortex has been proposed to function as an associative memory system capable of recognizing incomplete sensory input patterns [9]. More recently, piriform cortex has been implicated as important for the learning of odor–context associations [10••], and for the extraction of odor quality information from complex mixtures [11]. Finally, both short-term and long-term synaptic plasticity have been demonstrated in the piriform cortex and are thought to be involved in specific types of olfactory learning (reviewed in [12]).

Neuromodulatory effects in the OB and piriform cortex have been studied both electrophysiologically and behaviorally [13,14•]. Classical neuromodulatory inputs to the OB include acetylcholine from the horizontal limb of the diagonal band of Broca, norepinephrine from the locus coeruleus, and serotonin from the raphe nucleus. Unlike other sensory structures, the OB does not receive extrinsic dopaminergic inputs from the ventral tegmental area (VTA), but it does contain intrinsic dopaminergic neurons. Piriform cortex receives neuromodulatory input from the same sources as does the OB, as well as extrinsic dopaminergic inputs from the VTA. The cellular effects of these modulators in the OB have been relatively well characterized, as have those of acetylcholine and norepinephrine in the piriform cortex [5,15] (Table 1). Computational modeling has been used to understand how combinations of these distinct cellular effects interact so as to produce the functional consequences of neuromodulation observed at the systems and behavioral levels (e.g., [16••]; Table 2). These functional neuromodulatory effects traditionally have been clustered into ad hoc categories such as the following:

(a) *Contrast enhancement and decorrelation* of odor representations within the olfactory bulb are considered to be critical operations in odor processing, particularly because the primary representations of multiple distinct odors overlap heavily. That is, all but the most strongly dissimilar pairs of odorants activate substantial numbers of primary receptors in common, and it is thought that reducing the extent of this overlap (at the level of bulbar output) enhances an animal's capacity to discriminate between those odors. The first instantiation of olfactory contrast enhancement has been proposed to be mediated by glomerular-layer circuitry, within which inhibitory interneurons suppress medium-affinity odorant responses in mitral cells while enhancing higher-affinity responses, thereby sharpening representations via a high-dimensional variant of Mexican-hat surround suppression ([17]; reviewed in [3]). In

Figure 2



Contrast enhancement in odor representations. **(a)** Electrophysiological and behavioral results. $\mathbf{a_i}$ depicts extracellular recordings from mitral cells in the rat OB *in vivo* in response to a series of four aliphatic ester odorants with increasing carbon chain lengths. $\mathbf{a_{ii}}$ illustrates how population responses of mitral cells to the odorants in this series overlap less after increasing the acetylcholine concentration in the OB (via the administration of neostigmine, an acetylcholinesterase inhibitor). $\mathbf{a_{iii}}$. Pairs of odorants that differ in structure by a single carbon also are rendered less perceptually similar to each other after neostigmine administration. Figures adapted with permission from [18]. **(b and c)** Computational modeling results. **(b)** Simulated mitral cell (MC) responses to odorants under control conditions ($\mathbf{b_i}$) and after induction of nicotinic cholinergic neuromodulation (nAChR; $\mathbf{b_{ii}}$). Seven mitral cell timeseries are depicted from a larger simulated population embedded within an OB network. The horizontal bar depicts stimulation with a simulated odorant that activates each depicted cell to a different degree. When cholinergic neuromodulation was activated in the model, weakly responsive mitral cells were inhibited, sharpening the representation (contrast enhancement) and improving its signal to noise ratio. Figure adapted with permission from [16••]. **(c)** Raster plots of mitral cell spiking responses to odorants under control conditions ($\mathbf{c_i}$), under nicotinic cholinergic neuromodulation ($\mathbf{c_{ii}}$) and under muscarinic cholinergic receptor neuromodulation ($\mathbf{c_{iii}}$). Traces under the raster plots depict the power spectra of mitral cell population activities during odor stimulation under these three conditions, demonstrating that muscarinic activation, in particular, potentiates coherent membrane potential oscillations and sharpens spike timing constraints within the dynamical OB network, reflecting greater spike synchronization among activated mitral cells.
Figure adapted with permission from [16••].

subsequent behavioral and electrophysiological studies, the neuromodulation of this process has been most strongly ascribed to the activation of OB cholinergic receptors (Figure 2a,b; [5,18,19]). Activation of cholinergic receptors on PG cells enhances local inhibition, while activation of similar receptors on mitral cells increases their excitability. At the same time, cholinergic receptor activation modulates granule cell responses by suppressing a post-spike afterhyperpolarizing current to reveal an afterdepolarization current ([20]; modeled by [21,22]; Figure 2c). This prolonged window of granule cell depolarization increases and extends their synaptic inhibition of mitral cells, potentiating network oscillatory dynamics and regulating the timing of mitral cell action potentials. Together, these

processes contribute to a relatively sparse and temporally synchronized representation at the output of the OB that is well tuned for driving cortical pyramidal cells strongly [23] and for inducing plasticity in piriform cortex. Notably, at the same time that acetylcholine release modulates OB odor processing, it also activates synaptic plasticity in the piriform cortex by enabling Hebbian learning and reducing afterhyperpolarization currents in piriform pyramidal cells [24,25].

While it is usually considered separately, this form of stimulus decorrelation is closely related to signal-to-noise regulation and background suppression processes (described below). For example, norepinephrine release in the OB not only lowers odor detection thresholds, possibly by modulating neural signal-to-noise ratios, but also simultaneously enhances discrimination between very similar odors at low concentrations [26].

(b) *Signal-to-noise ratio regulation and signal/background segmentation* are tightly linked functions in which a relevant signal is identified and enhanced at the expense of a behaviorally irrelevant background. Embedded in this problem, of course, is how to distinguish signal from background. Moreover, the signal/background distinction depends on behavioral context; for example, a food odor may be signal against a background of less-interesting odors, but swiftly become background in the presence of a recognized predator odor. Consequently, the enhancement and suppression of stimulus components must rely on flexible and plastic functions governed by behavioral state and situational context. Theoretically, these functions can be mediated in the olfactory bulb by enhancing or suppressing the firing rates of responsive neuron classes as well as by synchronizing or desynchronizing responsive neurons, in coordination with piriform cortical operations that generate attractor-type memories for the relevant stimuli of interest. When integrated, such a network can strengthen and regulate the representations of previously learned stimuli at the expense of other sources of afferent activation. That said, neurophysiological work to date on signal to noise regulation in the OB largely has studied a simpler variant that enhances weak afferent signals without reference to previously learned stimuli.

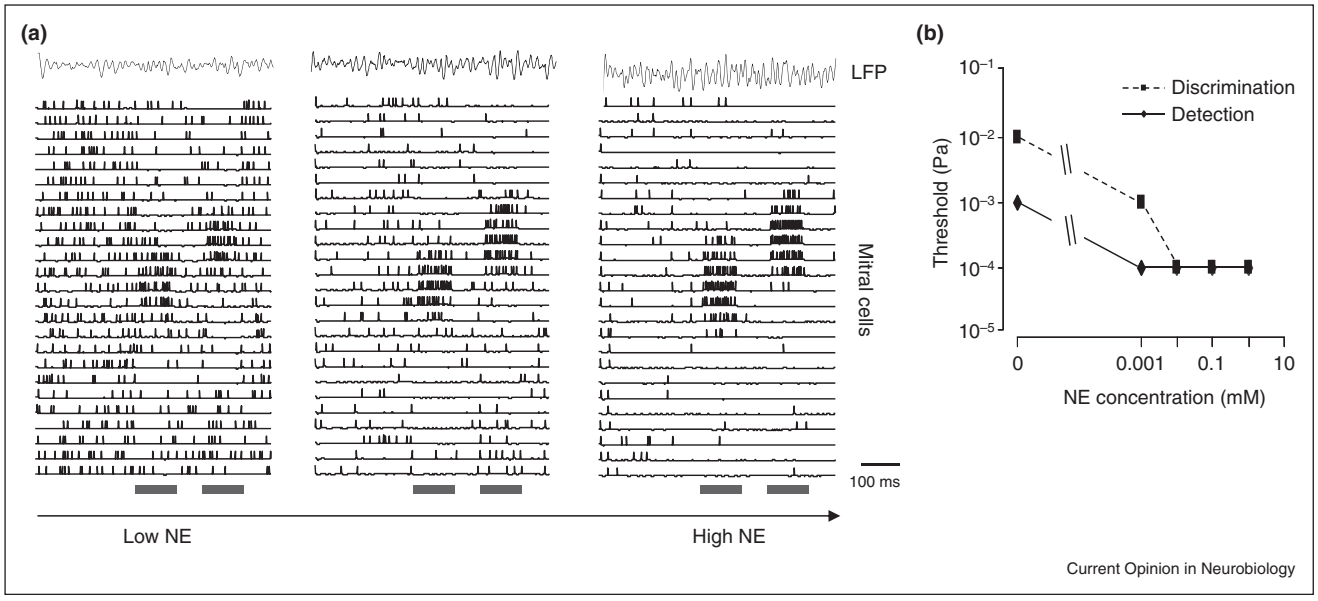
Signal-to-noise ratios in the olfactory bulb can be regulated as early as the convergent axonal arbors of primary olfactory sensory neurons [27], which form the bulk of the glomerular neuropil within the OB. Specifically, afferent olfactory input can modulated by noradrenergic, serotonergic, and cholinergic receptor activation [28•,29•,30]. These modulators are thought to act on a subclass of periglomerular interneurons that deliver presynaptic inhibition onto these afferent arbors, suppressing weaker activity and thus enhancing the signal-to-noise ratio. This modulation of interneuron activity and mitral cell excitability in the glomerular layer is complemented by concerted effects in the deeper OB layer. Increases in mitral and granule cell excitability effected by norepinephrine or acetylcholine can enhance the synchronization of responding mitral cells and thereby further enhance the signal while suppressing background activity (Figure 3; [31]). In these simulations, the known cellular effects of noradrenergic modulation in mitral and granule cells were implemented in a network model, and together effected a suppression of spontaneous activity due to increased inhibition accompanied by increased activation of specifically odor-responsive neurons owing to enhanced excitability [31]. The results of these simulations predict the significant reductions in odor detection and discrimination thresholds that have been observed in rats with norepinephrine infused into the OB [26,32].

Together, neuromodulation of the two OB processing layers can enhance and amplify odor-activated patterns in the OB for delivery to piriform cortex (Figures 2 and 3). In the piriform cortex, odor/background segmentation is further enhanced by the rapid suppression of active synapses, which suppresses background activity and further enhances signal [33]. Additionally, serotonergic neuromodulation in piriform cortex can reduce spontaneous activity, which also can be construed as enhancing the signal-to-noise ratio [34•].

(c) *Short term nonassociative memory*. Short term nonassociative olfactory memory is often assessed in tests measuring animals' behavioral habituation to odorants [35]. Habituation is demonstrated by measuring progressively reduced levels of investigation to a repeatedly presented odorant, and is considered to represent a learned disinterest in odors that, over multiple encounters, have no apparent behavioral relevance. Both norepinephrine and estrogen within the OB have been shown to regulate the persistence of a nonassociative habituation memory [36,37].

A distinct form of short term nonassociative memory, operating on a shorter timescale and mediated in the piriform cortex rather than the olfactory bulb [38], is mediated by presynaptic metabotropic glutamate receptors expressed on mitral cell axonal arbors within piriform cortex (reviewed in [12]). The specificity of these odor memory traces has been shown to depend on muscarinic cholinergic receptors in the piriform cortex [39]. Notably, cholinergic activation in PC is thought to be coupled with cholinergic activation in the OB, such that this modulation of cortical memory specificity is functionally linked to OB decorrelation and the suppression of proactive interference within piriform cortex.

Figure 3

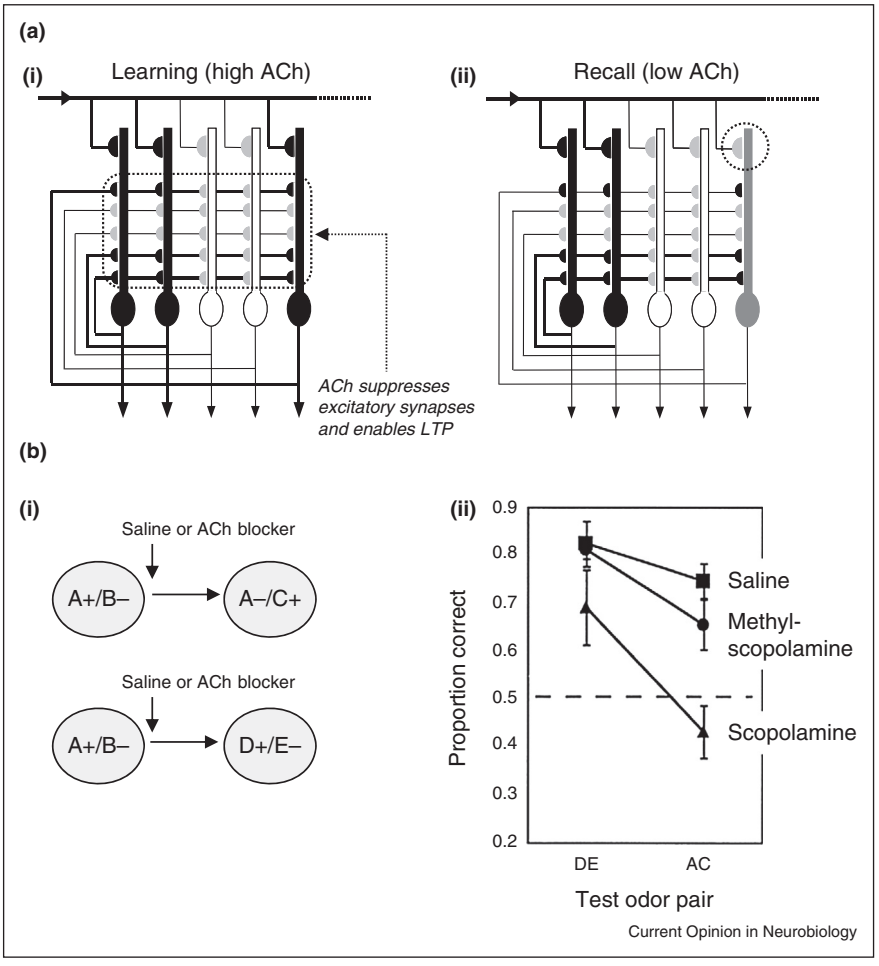


Signal-to-noise ratio regulation. **(a)** Simulation results showing strong signal-to-noise ratio modulation by activation of alpha-1 noradrenergic receptors in the OB. Each panel depicts the membrane potential and action potentials of mitral cells in a computational model of the OB, with increasing concentrations of simulated norepinephrine (NE; left to right). Two moderately similar odors were simulated (indicated by horizontal bars). The upper trace shows the simulated local field potential (LFP), which demonstrates an increase in the power of field potential oscillations at higher NE concentrations. With increasing NE modulation, spontaneous activity was reduced and odor responses were strengthened, resulting in an increased signal-to-noise ratio. Figure adapted with permission from [31]. **(b)** Behavioral results. Rats first were presented with either an odorant (discrimination) or an unscented odor pot (detection) over four successive 1-minute habituation trials with 5-minute intertrial intervals. They then were presented with a test odorant that was moderately similar to the habituation odorant (discrimination), but which of course was entirely novel to the rats habituated to the unscented pot (detection). Detection thresholds were measured as the lowest odor concentration at which rats significantly dishabituated from the blank, and discrimination thresholds were measured as the lowest odor concentration at which rats significantly dishabituated from the similar habituation odor. Rats were infused locally into the OBs with control saline or one of a range of NE concentrations. The graph depicts detection and discrimination thresholds as a function of OB norepinephrine concentration. The declining detection and discrimination thresholds as NE concentration increases suggest an increase in the perceptual signal to noise ratio. Figure adapted with permission from [26].

(d) *Cortical learning, associative memory and proactive interference*. The neuromodulation of piriform cortical dynamics by acetylcholine has long been thought necessary for the formation of associative odor memories in the piriform cortex [40]. In piriform cortex, odor learning is regulated by acetylcholine via its facilitation of long-term potentiation between pyramidal cells, its reduction of afterhyperpolarization currents in pyramidal cells, and its modulation of neural excitability (reviewed in [41,42]). Briefly, piriform cortex has been suggested to function as an associative memory device, receiving sensory inputs from the olfactory bulb and storing this information in the dense association fiber network among pyramidal cells (Figure 4a). On the basis of data from brain slices, Hasselmo and colleagues [43] suggested that cholinergic neuromodulation facilitates learning in this network by enhancing pyramidal cell excitability and intrinsic synaptic plasticity while simultaneously suppressing intrinsic (but not afferent) synaptic efficacy.

In associative memory networks, prior learning about odors can interfere with the processing and/or learning of new olfactory information. One of the important effects of signal decorrelation in the olfactory bulb, as described above (Figure 2), is to limit such interference by reducing the overlap among different odor representations. Cortical cholinergic modulation has further been proposed to prevent specifically *proactive* interference—the process by which previously learned odor information interferes with the acquisition of new odor information [44]. At the cellular level, acetylcholine release in the piriform cortex suppresses excitatory synaptic transmission across the associative network interlinking pyramidal neurons (Figure 4a). As this intrinsic associative network has been proposed to underlie a pattern-completion process that contributes to the recall of previously learned odor representations, the cholinergic suppression of intrinsic cortical synapses results in a bias towards the new afferent information being delivered onto piriform pyramidal neurons by

Figure 4



Cortical associative memory function and proactive interference. **(a)** Piriform cortical pyramidal neurons receive sensory inputs from OB mitral cells and interact with each other in a dense network of intrinsic excitatory connections (additional inhibitory connections are shown in Figure 1). **a_i**. During learning, when acetylcholine (ACh) levels are high, the intrinsic synapses between pyramidal neurons co-activated by odors (black) are systematically strengthened. Darker intrinsic synapses represent strengthened connections, whereas darker afferent synapses from the OB (top) represent higher levels of sensory input. The responsive pyramidal neurons are then linked in an associative network from which non-coactivated pyramidal neurons (white) are excluded. **a_{ii}**. During recall (low ACh), these previously strengthened connections (darker synapses) can reactivate the complete learned stimulus when stimulated with only a partial afferent input (the circled afferent synaptic input is absent). The grey cell depicts a neuron that is not receiving afferent input but is nevertheless activated via intrinsic excitatory synapses. **(b)** Cholinergic suppression of pro-active interference. **b_i**. Rats were trained to be rewarded for odor A (A+) but not B (B−). After injection with either saline, methylscopolamine (muscarinic antagonist that does not cross the blood–brain barrier) or scopolamine (muscarinic antagonist that does cross the blood–brain barrier and therefore affects the central nervous system), the rats were trained either on an overlapping (A−/C+) or non-overlapping (D+/E−) odor pair. **b_{ii}**. Rats injected with scopolamine were significantly impaired in learning the overlapping (AC) odor pair but not the non-overlapping odor pair (DE). These results were interpreted as blocking the normal cholinergic suppression of proactive interference, which normally prevents previously learned information from interfering with new learning.
Figure adapted with permission from [44]).

OB mitral cells [41]. Indeed, behavioral data have shown that the global blockade of cholinergic receptors significantly increases proactive interference in odor learning in rats [44]. Specifically, rats were first trained to discriminate a rewarded odor A+ rom an unrewarded odor B−. They then were injected with the muscarinic cholinergic receptor blocker scopolamine, a related blocker (methylscopolamine) that does not cross the blood-brain barrier and hence blocked muscarinic receptors only in the periphery, or a saline control. They then were trained again on a discrimination task (Figure 4bi), either with two new, perceptually dissimilar odors (rewarded odor D+ and unrewarded odor E−) or with one new odor and one previously learned odor for which the previously learned information had to be disregarded (rewarded odor C+ and unrewarded odor A−). When muscarinic receptors in the central

nervous system were blocked by scopolamine, rats were significantly impaired in the acquisition of the overlapping odor pair AC, but not the novel odor pair DE (Figure 4bii). That is, cholinergic neuromodulation suppressed proactive interference between related odor discriminations. From a theoretical standpoint, this is due to the active suppression of synapses encoding the previously stored memory, enabling the more efficient acquisition of new information [45].

Synthesis

Neuromodulators regulate olfactory networks and modify their computational transformations at multiple processing stages. Whereas the individual cellular effects of different neuromodulators clearly differ, some of their observed functional effects on network processing appear similar or closely integrated. Nevertheless, the functional effects of different modulators tend to be labeled differently, partially for historical reasons, even when their concrete effects are difficult to distinguish. Moreover, the different modulators often are loosely associated with particular behavioral states such as attention, arousal, or stress. While these ad hoc labels have facilitated our understanding of how concerted cellular effects can produce coordinated changes in system operations, it is likely that they now are clouding our assessment of the singular and combinatorial effects of neuromodulation on olfactory system function. An unbiased reconsideration of the concerted systematic effects of neuromodulators, alone or in combination, is likely to be better able to differentiate among their respective effects and identify their coordinated capacities. Coordinated experimental and computational modeling work, together with a careful redefinition of key terms and concepts, will be required in order to construct this systematic framework of olfactory system computations.

Conflict of interest statement

Nothing declared.

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