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A matter of focus: monoaminergic modulation of stimulus coding in mammalian sensory networks

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Although the presence of neuromodulators in mammalian sensory systems has been noted for some time, a groundswell of evidence has now begun to document the scope of these regulatory mechanisms in several sensory systems, highlighting the importance of neuromodulation in shaping feature extraction at all levels of neural processing. The emergence of more sophisticated models of sensory encoding and of the interaction between sensory and regulatory regions of the brain will challenge sensory neurobiologists to further incorporate a concept of sensory network function that is contingent on neuromodulatory and behavioral state.

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Abbreviations
5-HT 5-hydroxytryptamine (serotonin)
NE norepinephrine

Introduction

For sensory systems to guide behavior in adaptive ways, they must focus selectively on stimuli that are most likely to influence survival and reproduction. Coding and filtering of sensory signals are accomplished by the tuning of sensory receptors and by circuitry that uses classical neurotransmitters in ascending or descending pathways. Much evidence suggests that several intrinsic neuromodulatory systems further impose dynamic filters, whose properties are tied to environmental events or internal state, upon sensory circuits. Just as occurs in motor systems, endogenous neuromodulators transform sensory circuits into pluripotent networks, whose outputs can be fine-tuned to fit ever-changing behavioral circumstances.

A chemically diverse array of neuromodulators affect sensory circuit function. Here we limit our focus to two brainstem monoaminergic pathways and their respective neuromodulatory transmitters — norepinephrine (NE) and serotonin (5-hydroxytryptamine or 5-HT) — in the mature mammalian brain. Although other neuromodulatory substances have been shown to alter sensory processing, we focus on NE and 5HT because a great deal is known regarding the sources, effects on sensory processing, and mechanisms of action of these two molecules. In addition, aspects of the role of another important signalling molecule within sensory systems, acetylcholine, have recently been reviewed [1]. In mammals, both NE and 5-HT are synthesized and released by clusters of brainstem neurons that project broadly throughout cortical and subcortical sensory structures [2,3]. Although there have been many studies on the operation of NE and 5-HT in specific mammalian sensory systems, there has been less analysis of whether unifying principles of the neuromodulatory actions of these agents apply across systems.

Here, we address this issue by asking three fundamental questions. First, do these neuromodulators exert comparable effects on feature detection in different sensory pathways? Second, are the mechanisms underlying their neuromodulatory actions similar for different sensory modalities? Third, are there common principles of action by which these neuromodulatory systems regulate sensory-dependent behaviors? Overall, we find support in the literature for substantial similarities in the general ways in which NE and 5-HT function across diverse sensory networks.

NE, 5-HT and feature detection

The predominance of data suggests that, with several exceptions, NE and 5-HT do not transmit detailed information regarding sensory stimuli but rather alter the responses of sensory circuits to sensory-driven inputs [4,5]. In recent years, however, it has also become increasingly clear that NE and 5-HT do not simply regulate overall levels of activity in sensory pathways, but instead actively shape the response properties of sensory networks.

The transformative nature of the effects of NE and 5-HT on sensory responses is robust across cortical and subcortical structures [6–12,13••], is evident with the use of direct synaptic or naturalistic receptive field stimulation [8,11,12,14•,15,16], is apparent in both *in vitro* and *in vivo* preparations [8,15–19], and is prominent with either direct drug application or the activation of intrinsic NE- or 5-HT-containing efferent projection systems [6,7,14•,18,19]. Thus, regulating sensory neuron responsiveness and selectivity to synaptic input is a character-

istic and unifying feature of the effects of these neuromodulatory pathways across sensory modality.

Differences between the effects of NE and 5-HT have not been examined on a wide scale under identical experimental conditions. Although on their own NE might facilitate and 5-HT might suppress neural responses to other transmitters, there are many exceptions to these generalizations, and in some systems the nature of monoaminergic modulatory effects is dependent on neurotransmitter dose [10,11,15,19,20]. Below, we describe the effects of NE and 5-HT on specific aspects of stimulus coding (Table 1).

Differential targeting of input pathways

Patterns of neuromodulatory fiber innervation suggest, and physiological experiments confirm, that NE and 5-HT can change the functional balance of different sources of input to single neurons, including ascending versus descending inputs or feedforward versus feedback signals, thereby reconfiguring the outputs of these sensory networks [6,7,12,13••,21–28]. Several examples are discussed in the following section on the mechanisms of neuromodulatory effects.

Signal-to-noise ratio

The signal-to-noise ratio is measured as stimulus-evoked spike train activity relative to spontaneous spike train activity over a defined period of time, and is interpreted as an index of the robustness of a neuron's response to sensory input. Both NE and 5-HT have been reported to alter the signal-to-noise ratio in several sensory systems [7,8,10,29–32]. For example, in visual cortex, norepinephrine can increase the signal-to-noise ratio by decreasing spontaneous activity and/or increasing evoked activity, whereas serotonin can decrease the signal-to-noise ratio by decreasing evoked activity proportionally more than spontaneous activity [32]. However, whether a neuromodulator increases or decreases the signal-to-noise ratio may vary even from cell to cell within a single preparation [9,19], and thus the significance of a change in this parameter may depend on the specific roles of individual neurons in the circuit under study.

Gating

The term 'gating' has been used in several ways in sensory neurobiology (see [33], in this issue), but here we use it to refer to an increase in responsiveness to otherwise subthreshold and perithreshold stimuli, with or without a corresponding increase in responsiveness to suprathreshold stimuli. Thus, gating represents an extension of the dynamic range of neural responsiveness to stimuli that were previously too weak to elicit a response. This phenomenon is a commonly reported effect of NE on neuronal responses to transmitter application, afferent pathway electrical stimulation, or more natural forms of receptive field stimulation [8,17,29,32], as exemplified by the norepinephrine-induced increase in the responses of olfactory mitral cells to perithreshold stimulation of the olfactory nerve [8].

Receptive field structure

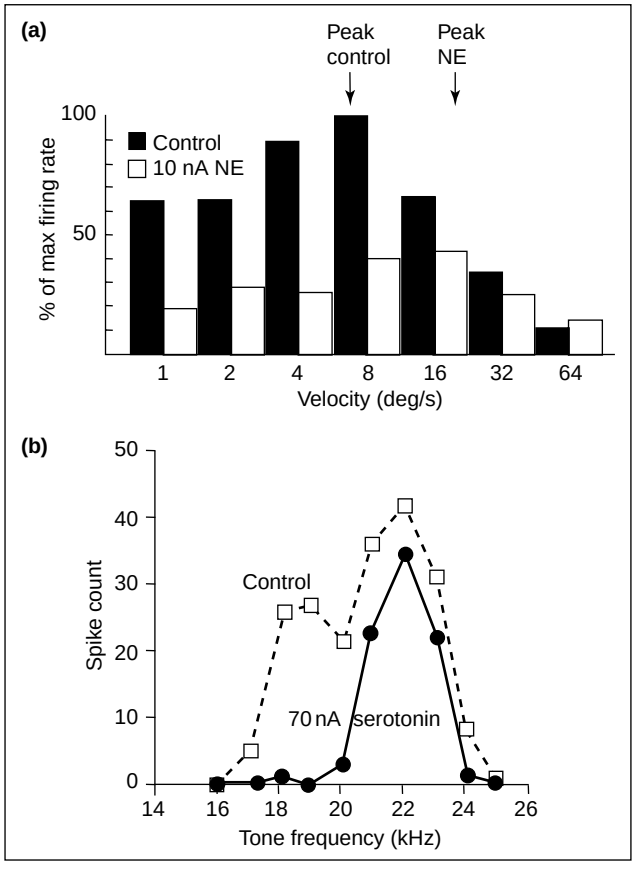
Because of their ability to modulate the efficacy of convergent excitation and inhibition, both NE and 5-HT can alter one of the most definitive characteristics of sensory neurons — the receptive field. In response to NE or 5-HT, receptive fields may be sharpened or blunted relative to the basal discharge of the cell, or they may be shifted in their borders because of selective effects of neuromodulators on portions of the receptive field [5,9,11,20,32].

Table 1

Selected examples of NE and 5HT-evoked changes in the response properties of sensory neurons.

Response properties	Modality	Neuromodulator	Preparation	References
Signal:noise	Somatosensory	5HT	Rat cortex	[30]
	Visual	NE, 5HT	Rat cortex	[32]
	Olfactory	NE	Rat olfactory bulb	[8]
	Auditory	NE, 5HT	Bat inferior colliculus Cochlear nucleus	[10,31]
Gating	Somatosensory	NE	Rat cortex	[80]
	Visual	NE	Rat cortex	[32]
	Olfactory	NE	Rat olfactory bulb	[8,17]
Selected inputs	Somatosensory	5HT	Rat cortex	[28]
	Visual	5HT	Hamster superior colliculus Rat cortex	[6,24]
	Olfactory	NE, 5HT	Rat cortex Gerbil olfactory bulb	[7,23]
	Auditory	5HT	Bat, rat brainstem	[22,25]
Receptive field	Somatosensory	NE	Rat cortex	[81]
	Visual	NE, 5HT	Rat, cat cortex	[20,32]
	Auditory	NE, 5HT	Guinea pig cortex Bat inferior colliculus	[9,11]

Figure 1



Examples of neuromodulator-evoked changes in receptive fields in two different sensory modalities. **(a)** In addition to suppressing the firing rate of a neuron in visual cortical area 17, norepinephrine (NE) changes the range of stimulus velocities evoking the largest response. Adapted with permission from [19]. **(b)** In the inferior colliculus, an auditory midbrain nucleus, serotonin (5-HT) changes the range of tone frequencies capable of eliciting a response from this neuron. Adapted with permission from [10].

However, within this wide range of possibilities, most effects of NE and 5-HT represent some type of refinement of sensory receptive fields: there are relatively few reports of receptive field expansion. Figure 1 illustrates parallel neuromodulator-induced changes in receptive field dimensions for visual and auditory neurons.

Distributed coding of sensory signals

Through changes at the single-cell level, NE and 5-HT alter population codes, that is, information encoded in the magnitude or pattern of the discharges of ensembles of neurons. Such changes have been identified both by recording simultaneously from ensembles of sensory neurons and through modeling studies [12,34,35]. For example, NE can induce changes in the relationship of the firing patterns of single neurons to sensory stimuli, indicating a reorganization of the functional ensemble that encodes sensory information [12]. Although noradrenergic and serotonergic modulation of population codes is a fairly recent conceptual advance, investigation of this phenomenon will help to bridge the gap between the effects of monoamines on neural codes and sensory-related behaviors.

Temporal dynamics of responses

Sensory stimulus features may be represented by the temporal properties of neuronal responses [36,37,38•]. Consequently, the timing of neural signals has an important role in sensory-guided percepts such as surface texture or the position of an object's edge [39], movement velocity across a sensory field [40] or stimulus frequency [38•]. Recent data indicate that NE and 5-HT can alter such temporal components of sensory neuron responses [14•,31], as when activation of NE afferents to the piriform cortex alters the temporal organization of cortical responses to olfactory stimulation [14].

Mechanisms underlying NE and 5-HT effects

Many of the effects of NE and 5-HT on feature extraction by sensory circuits arise through a nested array of mechanisms that are evident at both the cellular and the circuit level of organization (Figure 2). These are the same mechanisms that have been so well documented in reconfiguring the outputs of motor and other brain circuits [41–43,44•]. Within a given sensory circuit, several different mechanisms may interact to influence signal processing.

First, neurons within a circuit may differentially express receptors for NE and 5-HT, in effect allowing these agents to 'target' particular pre- or postsynaptic elements of sensory circuits. Second, the receptor subtypes activated by NE and 5-HT and their expression by individual neurons may also vary. The effects of NE are mediated by two main families of metabotropic receptors, α and β [45]. Similarly, 5-HT receptors are found in seven main families (5HT1 to 5HT7), all of which are metabotropic except the ionotropic 5HT3 receptors [46].

Third, different subtypes of NE and 5-HT receptors are ultimately coupled to a range of ion channel, and other, effector molecules. Because differences in the complements of ion channels gives rise to vastly different membrane properties among discrete populations of cells in the same neural network [47,48], the observed actions of a given neuromodulator are expected to vary markedly across individual neurons. In this section, we briefly detail examples of each of these three levels of neuromodulatory action and how they interact to influence feature detection.

Targeting of individual circuit elements

In almost every sensory circuit examined, NE and 5-HT affect different neurons in different ways (Figure 2a). For example, in sensory cortices NE frequently has divergent

Figure 2

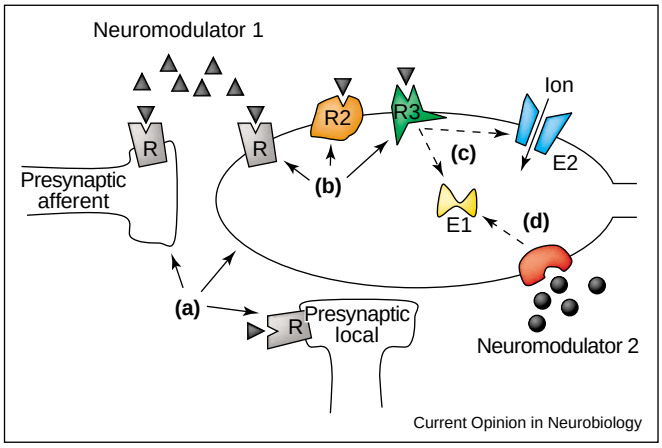


Diagram illustrating a diversity of mechanisms through which neuromodulators may act on neural circuits. **(a)** Neuromodulators may function through receptors (R) located on presynaptic versus postsynaptic neurons that are either on afferent pathways or that mediate local feedback. **(b)** Neuromodulators may function through different receptor types (R1, R2, etc) that act through **(c)** divergent effector systems (E1, E2, etc). **(d)** Multiple neuromodulators such as NE and 5-HT may also act on the same target neurons, as discussed in the Conclusions.

effects on neurons found in different layers, changing the coding of features such as the signal-to-noise ratio or the flow of afferent information [7,19]. In the olfactory bulb, an NE-mediated decrease in the recurrent inhibition from granule cells to mitral cells, a major output cell type, has been proposed to underlie a gating effect of NE on perithreshold stimuli [8,17].

Receptor identity

When combined with localization to pre- or postsynaptic neurons, receptor identity is crucial in determining the effect of a given neuromodulator (Figure 2b). For example, in the superficial layers of the superior colliculus, 5-HT causes a greater suppression of responses to inputs from the retina than of responses to cortical inputs, shifting the balance between ascending and descending inputs to neurons in these layers. This shift results from a decrease in retinotectal transmission mediated by 5HT1B receptors that are selectively expressed by optic afferents, although postsynaptic 5HT1A receptors may also mediate a decline in responsiveness [6].

Effector systems

The modulation of ion channel effectors by NE- and 5-HT-activated signaling cascades, coupled with the resultant changes in membrane potential, is an important determinant of neuromodulatory effects (Figure 2c). For example, NE-induced blockade of a calcium-activated potassium conductance in neocortex, hippocampus and thalamus [49–51] prolongs evoked excitatory discharge. It has been suggested that this effect, in conjunction with a membrane hyperpolarizing action of NE, can enhance the signal-to-noise ratio of threshold level excitatory synaptic responses [29,52].

Combined effects

Alone, each of the above levels of neuromodulatory action could have a significant impact on sensory circuitry. Together, they combine to orchestrate fundamental shifts in the outputs of these circuits and thus confer great flexibility on their feature detection properties. For instance, in heterogeneous populations of inhibitory cortical interneurons, an experimental focus has been on suppression of neuronal activity mediated by 5HT1A receptors and facilitation of neuronal activity mediated by 5HT2 and 5HT3 receptors [13••,28,53,54].

In visual cortex, 5-HT hyperpolarizes a specific type of interneuron by acting on 5HT1A receptors and increasing potassium current [13••]. At the same time, 5-HT depolarizes a subset of a second type of interneuron by activating the ionotropic 5HT3 receptor, which carries a nonspecific cation current. Given the different projection and firing patterns of these and other subgroups of interneurons, it has been proposed that 5-HT functionally reconfigures cortical sensory circuits in a way that regulates horizontal (intercolumnar) versus vertical (intracolumnar) communication between pyramidal neurons [13••,28,55]. Such multilevel interactions are likely to be the rule for NE and 5-HT actions in sensory networks.

Impact of neuromodulatory systems on behavior and perception

A converging range of studies suggests that noradrenergic projections from locus coeruleus and serotonergic projections from raphe nuclei regulate signal processing in sensory circuits according to behavioral state. Anatomical studies have shown that both NE and 5-HT projections arise from relatively few neurons that provide input via extensive axonal collateralization to several sensory

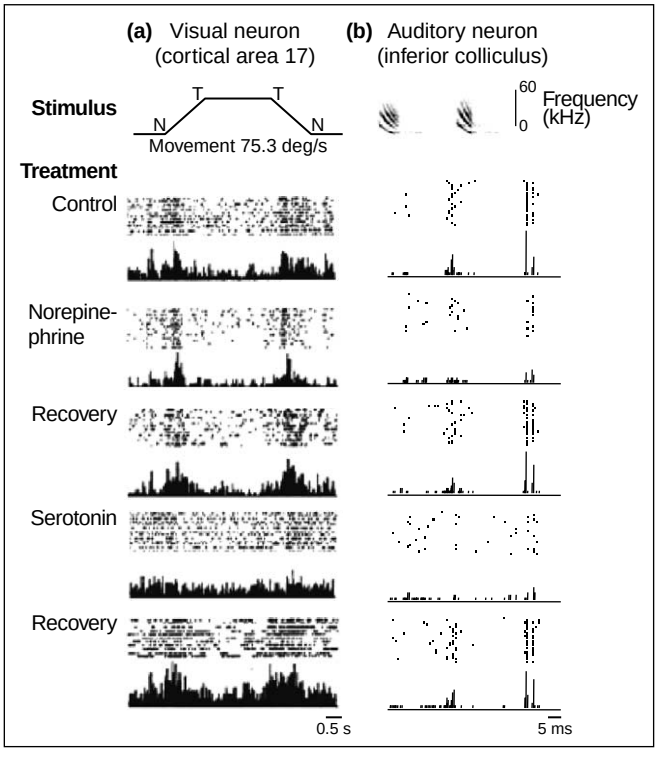
neuronal circuits throughout the neuraxis [2,22,44•,56–59]. The increased discharge of locus coeruleus and dorsal raphe neurons that parallels transitions between sleep, waking and arousal, combined with transient changes in discharge in response to sensory stimuli, suggests that these pathways alter the levels of NE and 5-HT in sensory terminal fields according to behavioral state or in response to external events [41,44•,60]. Alterations in synaptic transmission and cortical neuron responsiveness do in fact occur with arousal or during behavioral tasks that require sustained attention or vigilance [61–65,66••]. Moreover, the manipulation of neuromodulator efflux can alter neural activity during sensory attention tasks [67,68].

As discussed above, more recent work suggests that, because of the ability of NE and 5-HT to change neuronal responsiveness to sensory stimuli, sensory neurons can encode information more precisely or selectively from the sensory surround. In doing so, neuromodulators may shape sensory circuits to subserve specific behavioral functions, just as NE, and to some extent 5-HT, does within the olfactory bulb and piriform cortex to promote olfactory associative learning [69,70•]. For a given sensory system, however, the exact subsets of NE and 5-HT actions that give rise to increases in performance remain to be elucidated.

Conclusions

In light of the complexity and specificity of the effects of NE and 5-HT across sensory circuits, rather than formulate a blanket hypothesis for neuromodulator function in sensory systems, we prefer to summarize this review in terms that may spur inquiry. A unifying principle of the actions of NE and 5-HT in sensory networks is that they are much more nuanced and selective than a simple gain control mechanism would be. Indeed, these agents both modulate specific receptive field properties of individual sensory neurons and alter population representations of sensory stimuli. These generalities also apply to additional neuromodulators that we have not reviewed here, including acetylcholine (for example, [1,71•]). Many findings further relate the release of NE and 5-HT in sensory networks to attentional state. Despite this evidence, however, relatively few data link these potentially

Figure 3



Norepinephrine (NE) and serotonin (5-HT) act on overlapping neural targets in two different sensory systems. Shown is a comparison of the effects of NE and 5-HT on single neurons in visual cortical area 17 **(a)** and the auditory midbrain nucleus, the inferior colliculus **(b)**. The response of the visual neuron to a moving visual stimulus and the response of the auditory neuron to a recorded set of species-specific vocalizations (frequency modulated sweeps) are shown as raster plots and peristimulus time histograms, respectively. For the visual stimulus, 'N' indicates a nasal location and 'T' indicates a temporal location. Both types of stimuli are comparable in that they trigger waves of receptor activation along their respective sensory surfaces: the spatial map of the retina and the tonotopic map of the cochlea. Whereas NE sharpens the evoked response of the visual neuron, it reduces the peak response of the auditory neuron. By contrast, 5-HT has a similar effect in both neurons in that it suppresses responsiveness but increases background activity, thereby causing a decrease in the signal-to-noise ratio. Panel (a) is adapted with permission from [31]; panel (b) is unpublished (L Hurley, unpublished).

state-dependent neuromodulatory effects to specific behaviors, with some notable exceptions [27,72,73]. For example, a recent modeling study suggests that acetylcholine increases the discriminability of similar odorants within the olfactory bulb, in parallel with behavioral observations [71•]. Such studies underscore a clear need for further research in vertebrates, although this line of inquiry has long been a part of invertebrate studies [74,75].

Another area that is largely unexplored is the potential for interactions among multiple neuromodulatory substances at the level of target neurons. Neurons containing NE and 5-HT colocalize with numerous peptides and other neuroactive substances that, on release, could influence synaptic transmission in sensory circuits either alone or in combination with the monoaminergic neuromodulators [76,77]. Such interactions are likely to be essential to shaping the response of a sensory system under different behavioral contingencies.

Furthermore, it is well-established that NE- and 5-HT-containing fibers target the same structures in sensory networks, and that the output of noradrenergic locus coeruleus and serotonergic dorsal raphe neurons fluctuates across the sleep–wake cycle. The potential interplay between these two monoamines in cells in co-innervated terminal fields has, however, received relatively little experimental attention [32,53]. Studies exploring the physiological outcome of simultaneous application of NE and 5-HT may help to define the potential impact of dynamically fluctuating levels of these monoamines on sensory circuit function and could contribute to identifying differences or synergies in the roles of NE and 5-HT in sensory processing (Figure 2, mechanism d, and Figure 3).

Determining additional mechanisms, such as circulating hormone levels and circadian rhythms, that influence the expression of monoaminergic receptors and the levels of NE and 5-HT in terminal fields will also be integral to elucidating the functions of NE and 5-HT in intact sensory systems [78,79]. The expectation is that these types of inquiry, as well as the continuation of work on the physiological effects and mechanisms of NE and 5-HT action, will not only form a more complete narrative on the functions of neuromodulators in sensory systems, but also forge strong links between this work and general models of neuromodulator function and dysfunction in the brain.

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