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REVIEW | *Modulation of Dynamic Neural Networks: From Sensory Inputs to Motor Outputs*

Serotonergic modulation across sensory modalities

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Sizemore TR, Hurley LM, Dacks AM. Serotonergic modulation across sensory modalities. *J Neurophysiol* 123: 2406–2425, 2020. First published May 13, 2020; doi:10.1152/jn.00034.2020.—The serotonergic system has been widely studied across animal taxa and different functional networks. This modulatory system is therefore well positioned to compare the consequences of neuromodulation for sensory processing across species and modalities at multiple levels of sensory organization. Serotonergic neurons that innervate sensory networks often bidirectionally exchange information with these networks but also receive input representative of motor events or motivational state. This convergence of information supports serotonin's capacity for contextualizing sensory information according to the animal's physiological state and external events. At the level of sensory circuitry, serotonin can have variable effects due to differential projections across specific sensory subregions, as well as differential serotonin receptor type expression within those subregions. Functionally, this infrastructure may gate or filter sensory inputs to emphasize specific stimulus features or select among different streams of information. The near-ubiquitous presence of serotonin and other neuromodulators within sensory regions, coupled with their strong effects on stimulus representation, suggests that these signaling pathways should be considered integral components of sensory systems.

auditory system; comparative study; olfactory system; sensory processing; serotonin

NEUROMODULATION OF SENSORY PROCESSING

A fundamental concept explored by work in motor systems, such as the stomatogastric ganglion (STG) of decapod crustaceans, is that modulatory signaling chemicals represent a diverse tool set to alter network activity. Modulators can have immediate, or latent, effects on the biophysical or synaptic properties of a neuron across adjacent synapses and/or nonadjacent synapses, and these effects do not necessarily change the membrane potential (Bargmann 2012; Katz 1999; Marder 2012). The diverse effects of neuromodulation allow neural networks, even those with relatively few neurons, to produce a wide range of different functional outputs. These core principles from early work in STG and motor systems have emerged as essential features for every aspect of neural function, including sensory processing.

Sensory systems internalize and process information from the environment to form a neural representation of an animal's surroundings. However, all animals experience fluctuations in their ecology and internal state. To appropriately adjust behavior according to these fluctuations, neuromodulation endows the nervous system with the capacity to alter neural function at every level (synaptic, circuit, network, etc.) without necessarily adding new neurons. Neuromodulation supports effective sensory processing in a variable environment, allowing tuning of existing neural circuitry for flexible network output and consequently dynamic behavioral output. The goal of this review is to discuss fundamental features of neuromodulation of sensory processing by one neuromodulator, serotonin. Sensory neuromodulation by serotonergic neurons has been studied extensively in diverse taxa and different sensory systems and therefore offers an excellent opportunity to highlight common principles. Although we focus on the influence of serotonin on sensory processing, these common principles will hold true for other neuromodulatory systems that have comparable effects at cellular, circuit, and functional levels (McBurney-Lin et al. 2019; Schofield and Hurley 2018). It should be noted that this review is by no means exhaustive, and we have limited ourselves to the first few processing stages from the periphery in most cases. We provide numerous examples across taxa and sensory modalities that highlight several key aspects of the serotonergic system. These aspects include the anatomical and

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physiological characteristics of serotonergic neurons, serotonergic activity relative to context, and the pattern of serotonin receptor expression within sensory circuitry. Ultimately, these components of the serotonergic system enable serotonin to modulate the neuronal representation of sensory events.

SEROTONIN SOURCES ACROSS SENSORY SYSTEMS

Serotonin is an ancient and pervasive signaling molecule that acts in nearly every sensory system across diverse taxa (Gaspar and Lillesaar 2012; Hay-Schmidt 2000; Peroutka and Howell 1994). Concordantly, this single molecule has been implicated in a variety of broad state descriptors such as arousal, mood, and motivation (Cools et al. 2008; Luo et al. 2016; Miyazaki et al. 2012; Monti 2011). In general, there are two major sources of serotonin in mammals: gut derived and brain derived. The majority of the serotonin in the mammalian body is produced in the gut, chiefly by enterochromaffin cells, then absorbed by platelets and circulated throughout the periphery (reviewed in Bertrand and Bertrand 2010; Gershon 2013; Matthes and Bader 2018; Ni and Watts 2006). However, gut-derived serotonin does not appear to cross the blood-brain barrier (reviewed in Berger et al. 2009; El-Merahbi et al. 2015); therefore this review chiefly focuses on the consequences of brain-derived serotonin on sensory system operations across taxa.

There are ~26,000 neurons in the mouse and rat brain that produce serotonin (Table 1), but the majority of these serotoninergic neurons (~17,000 neurons) are collectively referred to as the raphe nuclei (Ishimura et al. 1988; Steinbusch 1981; Steinbusch and Nieuwenhuys 1981; Vertes and Crane 1997). The raphe nuclei can be further divided into several subpopulations, such as the dorsal raphe nucleus (DRN). In mice, the DRN constitutes the majority of serotonergic neurons in the brain (~9,000 serotonergic neurons; Ishimura et al. 1988; Ren et al. 2018; also see Hornung 2010). These DRN neurons, together with neurons from the median raphe nucleus (MRN), innervate and modulate every sensory processing center (Azmitia and Segal 1978; Doty 1983; Hurley et al. 2004; Jacob and Nienborg 2018; Jacobs and Azmitia 1992; McLean and Shipley 1987; Muzerelle et al. 2016; Takeuchi et al. 1982; Törk 1990).

Invertebrate brains contain far fewer neurons than vertebrate brains. For instance, the central nervous system of *Caenorhabditis elegans* has 302 neurons and *Drosophila* has ~135,000 neurons relative to ~70 million neurons estimated in mice (Bates et al. 2019; Chiang et al. 2011; Cook et al. 2019; Emmons 2015; Herculano-Houzel et al. 2006; Kohl and Jefferis 2011; Meinertzhagen 2018; Schlegel et al. 2017; White et al. 1986; Zheng et al. 2018). Despite having orders of magnitude fewer neurons, invertebrate sensory systems must accomplish the same fundamental neural computations as those of vertebrates. This notion extends to invertebrate serotonergic modulatory networks, where there are typically far fewer serotonergic neurons (Table 1) but many of the mechanisms for how serotonin modulates sensory processing are conserved. The *Drosophila* central brain, for instance, contains only ~90 serotonergic neurons (Vallés and White 1988), and only 2 widely projecting neurons (the "CSDns") provide synaptic serotonin to the primary olfactory center, the antennal lobe (Dacks et al. 2006a; Roy et al. 2007). Despite having only 2 serotonergic neurons, compared with >100 neurons that innervate the vertebrate olfactory bulb from the DRN (Ren et al. 2018) and MRN (Muzerelle et al. 2016), serotonin modulates similar aspects of olfactory encoding in these taxa (see below). Thus, because vertebrate and invertebrate sensory systems must solve similar problems, comparing across taxa can reveal fundamental motifs of neuromodulation of sensory processing.

Although much of this review details the consequences of synaptic release of serotonin, serotonergic neurons, like other modulatory neurons, do not have to form a synapse with a given cell to modulate the cell's activity (Eid et al. 2013; Fuxe et al. 2015). Serotonergic neurons have long been noted to use volume or bulk transmission as a means to release serotonin over large distances (sometimes >100 μm) and extended epochs (on the order of seconds) (Agnati et al. 1995; Beaudet and Descarries 1981; Bunin and Wightman 1998, 1999; Chazal and Ralston 1987; Gaudry 2018; Hornung 2010). For instance, in the cat auditory cortex most of the serotonergic boutons lack conventional synapses (DeFelipe et al. 1991). This principle extends across taxa, such as in the visual system of the house fly, *Calliphora*. Here, serotonergic processes are separated from other neurons by glia, lack synaptic specializations, and are dense core vesicle rich (a hallmark of bulk transmission) (Nässel et al. 1985). In addition, blood-borne serotonin contributes to sensory processing. For instance, blood-borne serotonin activates nociceptors (Sommer 2004; Viguier et al. 2013), is implicated in enhanced olfactory gain control (Suzuki et al. 2020; Zhang and Gaudry 2016), and potentially activates insect peripheral sensory structures. The CSDns in *Drosophila* do not directly synapse onto the olfactory sensory neurons (Coates et al. 2017), yet these neurons express the excitatory 5-HT2B receptor (Sizemore and Dacks 2016). In experiments where the olfactory sensory neuron somata were removed for performing antennal nerve shock, bath application of serotonin did not directly affect activity measured at the axon terminals of these neurons (Dacks et al. 2009). Therefore, the 5-HT2B receptor may localize to olfactory afferent soma in the antennae where serotonin in the hemolymph can act on them. Indeed, there are serotonergic fibers in the periphery (Vallés and White 1988), and the antennal hearts of many insects constantly circulate hemolymph into these olfactory appendages (Miller 1950; Pass 2000; Zhukovskaya and Polyanovsky 2017). Endocrine release of serotonin could coordinate the activity of olfactory afferents according to the animal's current needs or directly modulate the gain of olfactory afferents. Alternatively, these mechanisms may operate as redundancies for the similar effects of presynaptic serotonin on afferents in other sensory systems (see below). Overall, bulk transmission of serotonin, whether endocrine or paracrine, can modulate sensory processing over a relatively large distance and over potentially slower timescales.

HETEROGENEITY IN SEROTONERGIC NETWORKS

Animals constantly integrate information from different sensory modalities under different internal physiological states and ecological contexts. The nervous system therefore must be able to independently modulate computations performed by sensory networks, so that information pertinent to the animal's current state evokes the appropriate behavior. The serotonergic system has the capacity to influence sensory processing within

Table 1. *Serotonergic neuron/perikarya estimates across taxa*

Order	Species	Serotonergic Neuron Estimates	Method	Reference
Anaspidea	*Aplysia californica*	120†	α	(Ono and McCaman 1984)
Arthrotardigrada	*Batillipes pennaki*	10†	α	(Schulze et al. 2014)
	Actinarctus doryphorus ocellatus	5†		
Blattodea	*Periplaneta americana*	125*	α	(Bishop and O'Shea 1983; Klemm et al. 1984)
Calanoida	*Calanus finmarchicus*	24†	α	(Hartline and Christie 2010)
Decapoda	*Homarus americanus*	100†	α	(Beltz and Kravitz 1983)
	Hyas araneus (zoea 1)	55*§	α	(Harzsch and Dawirs 1995)
	Hyas araneus (zoea 2)	110*§		
Diptera	*Calliphora erythrocephalus*	182‡§	α and β	(Cantera and Nässel 1987; Nässel 1988)
	Calliphora erythrocephalus (larvae)	97†	α and β	(Cantera and Nässel 1987)
	Drosophila melanogaster	106†	α	(Vallés and White 1988)
	Drosophila melanogaster (larvae)	84†		
Haplotaxida	*Allonais paraguayensis*	2‡	α	(Zattara and Bely 2015)
	Amphichaeta sp.	2‡		
	Chaetogaster sp.	0‡		
	Dero digitata	4‡		
	Dero furcata	6‡		
	Monopylephorus rubroniveus	2‡		
	Nais stolci	8‡		
	Paranais litoralis	10‡		
	Pristina aequiseta	2‡		
	Pristina leidyi	2‡		
	Stylaria lacustris	4‡		
	Tubifex	6‡		
Hemiptera	*Rhodnius prolixus*	150†	α	(Lange et al. 1988)
	Triatoma infestans	286‡§	α	(Settembrini and Villar 2004)
Hirudinida	*Hirudo medicinalis*	214†	γ	(Lent et al. 1991)
Hymenoptera	*Apis mellifera*	75‡	α	(Schürmann and Klemm 1984)
Isopoda	*Armadillidium vulgare*	80†	α	(Thompson et al. 1994b)
	Asellus meridianus	80†		
	Ligia oceanica	80†		
	Oniscus asellus	60†		
Ixodida	*Amblyomma americanum*	69†	α	(Hummel et al. 2007)
	Dermacentor albipictus	76†		
Lepidoptera	*Helicoverpa armigera* (larvae)	60†	α	(Tang et al. 2019)
	Manduca sexta	60‡	α	(Homberg and Hildebrand 1989a, 1989b)
Odonata	*Epitheca sp.* (nymph)	32§	α	(Longley and Longley 1986)
	Pachydiplax longipennis (nymph)	32§		
Opisthopora	*Lumbricus terrestris*	1,729†	α	(Spörhase-Eichmann et al. 1987a, 1987b)
Petromyzontiformes	*Petromyzon marinus*	1,225	α	(Antri et al. 2006)
Primates	*Homo sapiens*	250,000	α	(Baker et al. 1990; Baker et al. 1991)
Rhabditida	*Caenorhabditis elegans*	16†	α and δ	(Desai et al. 1988; Duerr et al. 1999; Horvitz et al. 1982; Loer and Kenyon 1993; Sze et al. 2000)
Rodentia	*Mus musculus*	25,824	β	(Ishimura et al. 1988)
	Rattus norvegicus	25,861	α	(Vertes and Crane 1997)
Xiphosura	*Limulus polyphemus*	158†	α	(Battelle et al. 1999)

Method(s) used in each reference: α, immunohistochemistry; β, peroxidase-antiperoxidase fluorescence; γ, glyoxylic acid-induced histochemistry; δ, formaldehyde-induced fluorescence. The following symbols indicate where certain numerical estimates correspond to: †central nervous system; ‡central brain; *central brain without optic lobes; §ventral nerve cord/spine.

a wide swath of behavioral contexts in a complex and even stimulus-specific manner. Individual DRN neurons are incredibly diverse in terms of efferent projections, nonserotonin transmitter content, intrinsic biophysical properties, sources of input, and transcriptional profiles (reviewed in Okaty et al. 2019). Together, these heterogeneous features of serotonergic neurons enable serotonin to have a nonuniform and complex influence on sensory processing.

Anatomical Heterogeneity of Serotonergic Neurons

Serotonergic neurons have heterogeneous anatomical projections, which can reflect multiple functional domains within specific sensory systems. For instance, serotonergic neurons do not project uniformly throughout the insect visual system but rather differentially innervate distinct layers within individual visual neuropils (Hamanaka et al. 2012; Homberg and Hildebrand 1989b; Nässel et al. 1987; Paulk et al. 2008; Schürmann and Klemm 1984; Vallés and White 1988). Additionally, in the moth *Manduca* antennal lobe, the CSDns do not innervate the regions occupied by olfactory afferents (Lizbinski et al. 2016; Sun et al. 1993). This suggests that *Manduca* CSDns do not directly act on olfactory afferents. In vertebrates, the olfactory bulb is innervated by serotonergic processes from both the MRN and DRN, but these processes are most dense in distinct synaptic layers (Gracia-Llanes et al. 2010; McLean and Shipley 1987; Muzerelle et al. 2016; Suzuki et al. 2015). Here, processes from the MRN are most dense in the region occupied mostly by periglomerular cells (a subclass of local interneu-

ron), whereas processes from the DRN are densest in regions occupied by mitral/tufted cells (output neurons) and granule cells (another subclass of interneuron) (Muzerelle et al. 2016). Similarly, the density of serotonergic innervation varies both within and between rodent auditory nuclei, as is the case for nuclei in the superior olivary complex and the inferior colliculus (Hurley and Thompson 2001; Keesom et al. 2018; Thompson et al. 1994a). Within the *Drosophila* antennal lobe, the CSDns innervate glomeruli to varying degrees (Coates et al. 2017; Singh et al. 2013) and differentially connect with the various principal antennal lobe neuron types from animal to animal (Coates et al. 2017). Together, these examples illustrate the heterogeneous nature of serotonergic innervation of sensory networks. This heterogeneity allows distinct targeting of processing layers or stimulus-specific subcircuits.

Cotransmission and Serotonergic Neurons

In addition to different projection fields, recent technological innovations have revealed the molecular and anatomical diversity of subsets of serotonergic neurons within the vertebrate nuclei (Calizo et al. 2011; Fernandez et al. 2016; Huang et al. 2019; Ren et al. 2019; Spaethling et al. 2014; Templin et al. 2012). For instance, subpopulations of serotonergic DRN neurons with distinct trajectories coexpress either glutamate or GABA (Huang et al. 2019; Liu et al. 2014; Ren et al. 2018; Sengupta et al. 2017). Similarly, serotonergic DRN neurons can express several neuropeptides and nitric oxide synthase (Fu et al. 2010; Huang et al. 2019; Sengupta et al. 2017). In *Drosophila*, the CSDns polysynaptically evoke excitation via acetylcholine (Zhang and Gaudry 2016), although they may not synthesize acetylcholine, as an intersectional approach suggests that the CSDns may not express choline acetyltransferase (ChAT; Fig. 1*A*). Regardless, serotonergic neurons often use these cotransmitters to impact sensory systems in different ways. For example, when DRN projections to the olfactory bulb are activated, DRN-derived serotonin and glutamate differentially act on both output neuron subtypes (mitral and tufted cells). In this instance, glutamate directly enhances the odor-evoked responses in both output neuron subtypes, whereas serotonin enhances decorrelation of only mitral cell odor responses (Kapoor et al. 2016). Moreover, this enhancement is increased by pharmacologically blocking serotonin

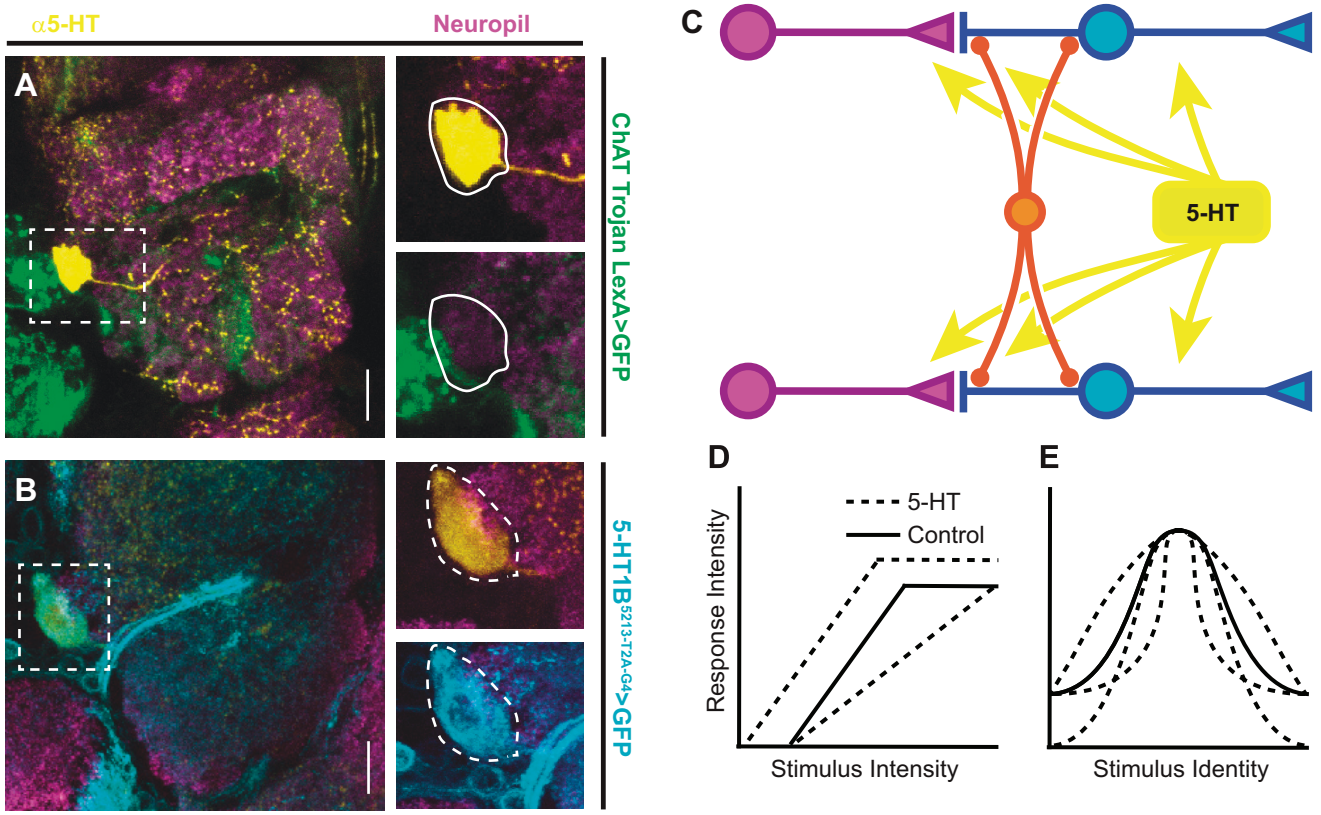

Fig. 1. Serotonergic modulation of sensory processing. *A*: intersectional immunohistochemistry using a rabbit polyclonal antibody against serotonin (5-HT, yellow; 1:5,000 dilution; ImmunoStar no. 20080) reveals that serotonergic *Drosophila* CSDns do not colabel with green fluorescent protein (GFP) expression with a protein-trap transgenic LexA driver for choline acetyltransferase (ChAT, green; BDSC_60319). Neuropil (magenta) delineated with a rat monoclonal antibody against N-cadherin (1:50 dilution; DSHB no. DN-Ex#8). No antibody was used to increase GFP signal. *B*: intersectional immunohistochemistry reveals that *Drosophila* CSDns express the 5-HT1B receptor subtype. Here, a protein-trap transgenic GAL4 driver for the 5-HT1B receptor subtype driving the expression of GFP (cyan; the 5-HT1B transgenics were a kind gift from Dr. Herman Dierick, Baylor College of Medicine) colabels with a goat polyclonal antibody against serotonin (yellow; 1:5,000 dilution; ImmunoStar no. 20079). Neuropil (magenta) delineated with a mouse monoclonal antibody against Bruchpilot (1:50 dilution; DSHB no. nc82). A rabbit polyclonal GFP antibody was used to increase GFP signal (1:1,000 dilution; ThermoFisher no. A-11122). *C*: schematic illustrating general network targets of 5-HT (yellow) highlighted in this review including sensory afferents (purple), local interneurons (orange), in particular presynaptic inhibition, and output neurons (blue). *D*: 5-HT can alter stimulus intensity coding by shifting the slope of the input-output relationship, modulating response strength, or offsetting the threshold for activation. *E*: 5-HT can also alter the encoding of stimulus identity by altering tuning breadth or by decreasing spontaneous activity to increase the signal-to-noise ratio. For both *A* and *B*, the same immunohistochemistry techniques described in Sizemore and Dacks (2016) were used to collect data. Scale bars, 10 μm.

receptors and nearly abolished when glutamate receptors are similarly blocked (Kapoor et al. 2016). Although serotonin may be acting through polysynaptic interactions in this particular case (Brill et al. 2016; Hardy et al. 2005; Liu et al. 2012), the overall consequence is that cotransmission allows raphe neurons to affect their targets on different timescales through ionotropic and metabotropic receptors, respectively. This allows raphe neurons to both quickly alter a given downstream target's neuronal activity and also leave that target's activity altered for extended epochs.

Molecular Heterogeneity of Serotonergic Neurons

In addition to the anatomical and transmitter diversity of serotonergic neurons highlighted above, neurons within the DRN are highly molecularly diverse. For instance, different neurons within the DRN have different electrical properties due to differential ion channel expression levels (Calizo et al. 2011; Templin et al. 2012). This suggests that two given DRN neurons receiving identical synaptic input can still differentially modulate the same sensory network. To the best of our knowledge, ion channel expression profiles of serotonergic neurons have not been compared in invertebrates. However, the intrinsic properties and region-specific synaptic inputs for the CSDns enable a single serotonergic neuron to perform multiple operations across different regions of a given sensory domain (Zhang et al. 2019). Altogether, these heterogeneous features of individual and groups of serotonergic neurons support serotonin's capacity for nuanced modulation of sensory processing.

THE CONTEXT FOR SEROTONIN RELEASE

Understanding how serotonin affects sensory processing has been, and remains, a fruitful and career-long endeavor of many investigators. Perhaps just as critical is to understand the circumstances in which serotonin exerts these effects. Serotonin release depends on both sensory and nonsensory input, and thus corresponds to many aspects of external events, self-generated behavioral patterns, and internal state.

Serotonergic Interactions with Sensory Systems Are Bidirectional

In addition to modulating sensory circuitry, serotonergic neurons often receive input from sensory systems, allowing their influence to be tempered based on the sensory input that the animal is experiencing. This may allow sensory networks to adapt to varying stimulus regimes. For example, serotonin-evoked changes in the signal-to-noise ratio might allow for stable stimulus representation in the face of heterogeneous environmental background (Hurley and Pollak 1999; Waterhouse et al. 1986, 1990). Sensory input to serotonergic neurons could also provide an opportunity for stimulus-specific modification of serotonin release. In some cases, primary sensory afferents and serotonergic cells are one and the same, thus allowing the sensory field to directly drive serotonin release. This is the case for the chemo/mechanosensory ADF neuron in *C. elegans* (Iwanir et al. 2016; Liu et al. 2019; Shao et al. 2019), select mechanosensory neurons in the antennae of cockroaches (Watanabe et al. 2014), and potentially auditory type II spiral ganglion afferents, as they express the serotonin transporter (Nielsen et al. 2006; Vyas et al. 2019). In other instances, serotonergic neurons are completely constrained to a sensory network, and therefore their activity is likely predominantly driven by sensory processing. For instance, several insect species have serotonergic neurons that make local projections within the optic lobes (Hamanaka et al. 2012; Homberg and Hildebrand 1989b; Leitinger et al. 1999), and the vertebrate retina possesses serotonergic amacrine cells (reviewed in Masson 2019) that contact retinal ganglion cells and bipolar cells.

Sensory Stimulus-Driven Serotonin Release

In addition to projecting to sensory and nonsensory regions (Gaudry 2018; Huang et al. 2019; Ren et al. 2019), many serotonergic neurons also receive input from sensory systems. In some cases, serotonergic neurons can receive sensory input locally within the networks that they are directly modulating. In *Drosophila* and moths, CSDn activity is influenced by odors (Hill et al. 2002; Zhang et al. 2019; Zhang and Gaudry 2016; Zhao and Berg 2009), via direct synaptic input from antennal lobe principal neurons (Berck et al. 2016; Coates et al. 2017; Sun et al. 1993; Zhang and Gaudry 2016). The organization of local input can even vary across sensory networks for a single neuron, as the CSDns can be excited and inhibited by a single odor due to local synaptic inputs to different neuronal compartments (Zhang et al. 2019). The raphe nuclei also have bidirectional connectivity, and in some cases sensory inputs arrive from cells that are relatively proximal to sensory transduction. Some retinal ganglion cells send collaterals to both the visual system and the DRN, although whether these retinal ganglion cells synapse directly onto serotonergic neurons remains unclear (Pickard et al. 2015). Inputs to serotonergic neurons in the DRN and MRN also originate from cortical and subcortical sensory regions including the inferior and superior colliculi or brain stem sensory nuclei (Ogawa et al. 2014; Pollak Dorocic et al. 2014). Furthermore, there are neurons in DRN and other raphe groups that respond to sensory stimuli across several modalities (Fornal et al. 1996; Gao and Mason 2000; Moriya et al. 2019; Rasmussen et al. 1984, 1986). Although the strongest sensory responses may occur in nonserotonergic raphe neurons, sensory responsiveness has been confirmed for serotonergic neurons themselves (Ranade and Mainen 2009; Ren et al. 2018; Waterhouse et al. 2004) and nonserotonergic DRN neurons may provide indirect sensory input to serotonergic neurons. Moreover, some serotonergic DRN neuron sensory responses are extremely short in latency, suggesting input from relatively early stages of sensory processing (Ranade and Mainen 2009). Thus, whether they are intrinsic to a network or span several networks, by having intimate access to the history of network activity serotonergic neurons can update their modulatory influence based on the stimulus regime or circuit state (Lizbinski and Dacks 2018).

Modality-Specific Serotonin Release

Variations in serotonergic neuron responses, as well as in their efferent connectivity, make it difficult to predict the conditions that elevate serotonin. Direct neurochemical analyses within sensory regions during behaviorally important events suggest that serotonin release within sensory regions is modality specific. For instance, serotonin levels in the electrosensory lateral line lobe of weakly electric fish increase in

response to a synthetic signal mimicking the presence of a conspecific, yet strong auditory stimuli have no effect (Fotowat et al. 2016). Likewise, in rat temporal and occipital cortices that correspond to auditory and visually responsive regions (respectively), serotonergic changes are modality specific. Here, auditory input only evokes changes in the temporal cortex, whereas visual input only evokes changes in the occipital cortex (Müller et al. 2007; Pum et al. 2008). Modality-specific influence on serotonin levels can also occur across several processing stages. For instance, auditory stimuli influence the levels of serotonin or its metabolites at multiple sites in the auditory system, including the brain stem, midbrain, and cortex (Cransac et al. 1998; Hall et al. 2010). In contrast, exposing a rodent to a stressful odor, a component of fox urine, does not influence serotonin in auditory regions (Hall et al. 2010). Together, these examples highlight the modality-specific nature of serotonin release.

Despite the canalization of serotonergic projections to sensory regions suggested by these studies, some DRN neurons that send projections into sensory regions also have projections into nonsensory regions, suggesting coregulation of functionally related brain regions. For example, single DRN neurons in the rat project to functionally related regions of sensory cortex and cerebellum (Waterhouse et al. 1986) or to sensory and motor areas related to whisker sensation and movement in the cortex, thalamus, or medulla (Lee et al. 2008). Coregulation of functionally related brain regions is also suggested by the projections of defined subgroups of dorsal raphe neurons. For example, block of serotonin release from select DRN neurons increases the expression of aggressive behaviors in mice and also alters nonsocial behaviors (Niederkofler et al. 2016). These neurons not only project to some nodes of social behavior networks but also provide prominent inputs to sites in the auditory brain stem and midbrain. Although serotonin release in response to multimodal stimuli has not been systematically examined across sensory regions, these studies suggest that DRN projections may be organized according to sensory modality.

Self-Regulation of Serotonin Release

In addition to the stimulus- and modality-dependent and -independent means of adjusting serotonin release discussed above, serotonin release can also be modified locally via autoreceptors or heteroreceptors (reviewed in Andrade et al. 2015; Belmer and Maroteaux 2019). In several rodent species, for instance, DRN and MRN neurons express inhibitory serotonin receptors (5-HTRs) (Adell et al. 2001; Moret and Briley 1997; Piñeyro et al. 1996; Starkey and Skingle 1994). Moreover, the activity of these serotonin autoreceptors and heteroreceptors is implicated in aggression (Nautiyal et al. 2015) and mood disorders (Donaldson et al. 2014; Nautiyal et al. 2016; Riad et al. 2017; You et al. 2016). At the cellular level, the activity of these 5-HTRs along a given serotonergic neuron's terminals can provide the means for cell-autonomous regulation of local serotonin release, without necessarily recruiting additional neurons. A similar theme may occur in the sea lamprey retina, where serotonergic amacrine cells in the retina express the inhibitory 5-HT1A receptor (Cornide-Petronio et al. 2015). In *Drosophila*, the CSDns express the inhibitory 5-HT1B receptor (Fig. 1*B*) and have several compartment-specific features, including synaptic connectivity (Zhang et al. 2019) and serotonin transporter expression (Kasture et al. 2019). Together these features of *Drosophila* CSDns provide several potential means for differential influence across networks. The inhibitory influence of serotonin on serotonergic neurons also appears to be mediated in an activity-independent and nonexocytotic manner (Mlinar et al. 2015), suggesting that the serotonergic network may self-regulate in a manner distinct from the context in which it affects other neurons.

Serotonergic Neurons Respond to Behavioral State and Context

In addition to sensory stimulus-driven responses, serotonergic neurons respond to complex stimuli, behavioral output, reward contingencies, and internal state. Much like the heterogeneous characteristics noted earlier (see above), raphe neurons as a population are markedly diverse in the stimuli to which they respond. In mammals, the activity of DRN neurons varies greatly in their responses to both behavioral outputs (Fornal et al. 1996; Heym et al. 1982; Jacobs et al. 2002; Jacobs and Fornal 1991) and more subtle stimulus qualities like reward contingencies based on recent experience. Subpopulations of DRN serotonergic neurons respond to reward, punishment, or learned predictors (Cohen et al. 2015; Li et al. 2016; Liu et al. 2014; Luo et al. 2016; Matias et al. 2017; Miyazaki et al. 2011a, 2011b, 2012; Stark and Scheich 1997). Furthermore, different stimulus features such as salience or valence can be encoded as bursts of spikes or changes in DRN tonic firing rate (Cohen et al. 2015). This heterogeneity likely reflects subpopulations of DRN neurons that support different behavioral functions. Frontal cortex- and olfactory bulb-projecting DRN neurons and amygdala-projecting DRN neurons differ in the brain regions from which they receive input. Moreover, the former are activated by reward and inhibited by punishment, whereas the latter are excited by both (Ren et al. 2018). Furthermore, the activation of raphe neurons is dependent upon environmental context. Serotonergic DRN neuron activity decreases with onset of movement in assays with low perceived threat but increases under high-threat conditions (Seo et al. 2019). Similarly, confinement within a small area, a mild stressor, increases serotonergic activity in the mouse auditory midbrain (Hall et al. 2010).

Social context can also influence serotonin release. Interactions with conspecifics increases serotonin release in the mouse auditory midbrain, in correlation with nonvocal behaviors such as social investigation or overall activity of the subjects, rather than the number of vocalizations produced (Hall et al. 2011; Hanson and Hurley 2014; Keesom and Hurley 2016). In male mice interacting with female partners, serotonergic activity correlates with female vocalizations that may indicate rejection, but this is a negative correlation (Keesom and Hurley 2016). Additionally, serotonin-auditory interactions are sensitive to prior experience. For example, the dynamics of serotonin release during some types of social interaction are also slower for individuals housed in isolation in early life (Keesom et al. 2017). These results suggest that serotonergic signaling is tied to the salience and valence of individual social interactions rather than being positively correlated with the sensory stimuli associated with that interaction. Finally, serotonergic neurons across taxa are also regulated by physiological contexts that

vary over relatively long timescales including hunger (Voigt and Fink 2015) and circadian rhythm (Cagampang and Inouye 1994; Corthell et al. 2013; Jacobs et al. 1981; Kloppenburg et al. 1999; Monti 2011; Trulson and Jacobs 1979). Thus, serotonergic neurons are influenced by both the animal's environment and broad behavioral states, both of which alter distinct aspects of temporal firing patterns.

In summary, the contexts for serotonin release are multidimensional and include both stimulus-dependent and -independent conditions. Anatomical and functional studies suggest that serotonergic neurons are sensitive to sensory events but are also influenced by factors such as internal state, motor activity, and the salience of stimuli with regard to prior events. From all this, it is reasonable to conclude that serotonin is capable of conveying information into sensory systems on the external context and internal state in which sensory events occur.

RECEPTOR BASIS OF COMMON MODULATORY EFFECTS

While serotonin clearly affects fundamental aspects of sensory processing, there are several paths by which these overall circuit outcomes can be achieved. Just as serotonergic neurons are themselves diverse, there is a diversity of serotonin receptors (5-HTRs) that vary in their affinity for serotonin, time course of action, and the secondary messenger system to which they couple (Nichols and Nichols 2008). This receptor diversity allows serotonin to differentially target neuronal populations that support distinct sensory computations across modalities (Fig. 1*C*).

Comparing Serotonin Receptors across Taxa

An array of 5-HTRs are encoded in nearly every animal genome (Azmitia 2007; Ishita et al. 2020; Moroz et al. 2014; Peroutka and Howell 1994; Ribeiro et al. 2005; Vleugels et al. 2015). The first 5-HTR emerged ~700–800 million years ago (Peroutka and Howell 1994), and there are seven major 5-HTR families in vertebrates (5-HT1–7) and at least three across the invertebrates (5-HT1, 2, and 7) (Table 2). However, there are notable clade-specific exceptions such as the MOD-1 ionotropic 5-HTR in *C. elegans* (Ranganathan et al. 2000), the 5-HT8 receptor in *Pieris rapae* (Qi et al. 2014), the 5-HT4 and 6 receptors in some mollusks (Kim et al. 2019; Nagakura et al. 2010; Tamvacakis et al. 2015, 2018), the nonfunctional 5-HT5B receptor subtype in humans (Grailhe et al. 2001), the absence of these receptors in the Ctenophora genome (Moroz et al. 2014), and the 5-HT4 receptor in *Apostichopus japonicus* (Wang et al. 2017). Invertebrate 5-HTRs are typically named for the vertebrate 5-HTR family with which they share the most sequence homology, but the pharmacological properties of these counterparts can differ. Methysergide, for example, acts as a broad-spectrum 5-HTR antagonist in vertebrates but agonizes or has no effect on select invertebrate 5-HTRs (Blenau et al. 2017; Dacks et al. 2013; Röser et al. 2012). There are 14 subtypes of vertebrate 5-HTRs (e.g., within the 5-HT2 family there are 5-HT2A–C), some of which can have several isoforms as a result of posttranscriptional modifications to the nascent 5-HTR transcript (Bockaert et al. 2006; Burns et al. 1997; Hannon and Hoyer 2008; Tanaka and Watanabe 2020; Vleugels et al. 2015). Conversely, invertebrate 5-HTR subtypes are generally encoded at distinct genomic loci, and each 5-HTR has a single predicted isoform (e.g., *Drosophila* 5-HTRs: Colas et al. 1995; Gasque et al. 2013; Saudou et al. 1992; Witz et al. 1990). Of these different 5-HTR subtypes, several (if not all) are expressed in olfactory, auditory, mechanosensory, visual, and gustatory centers of both vertebrates and invertebrates (Table 3). Moreover, reoccurring themes have begun to emerge wherein serotonin acts through these diverse receptors within these sensory modalities to modulate fundamental computations including breadth of responsive range, detection thresholds, and discriminating between stimuli.

Serotonergic Modulation of Sensory Computations: Gain Control

Sensory systems employ several strategies to dynamically adjust the range of individual stimulus features that they encode. Given the ubiquity of serotonergic systems, it is not surprising that serotonin either modulates or plays a direct role in these processes. For instance, animals experience fluctuations in stimulus intensity as they navigate the world. In cases where the animal experiences intense sensory input (i.e., bright lighting, high odor concentration, etc.), the neurons may fail to properly encode the given stimulus as a result of saturation. Conversely, animals may fail to detect ecologically important stimuli (i.e., the scent of a predator) if they are present at low intensities. To overcome these hurdles, sensory systems typically use a suite of computations, such as "gain control" (reviewed in Carandini and Heeger 2012), to adaptively adjust the sensory input-to-output ratio of a network (Fig. 1*D*). Across modalities, 5-HTRs expressed by sensory afferents can enable direct serotonergic modulation of the gain of sensory input. For instance, chronic activation of nociceptive afferents in *Drosophila* larvae induces direct serotonergic inhibitory feedback mediated by 5-HT1B receptor that causes desensitization of afferents over the course of development (Kaneko et al. 2017). Additionally, although the receptor basis remains unknown, serotonin decreases sensory afferent activity in proprioceptor and mechanosensory networks (Gaudry and Kristan 2009; Nagata et al. 2019). Conversely, serotonin can activate excitatory 5-HTRs in photoreceptors to directly increase their excitability (Cheng and Frye 2020; Han et al. 2007; Pootanakit et al. 1999), therefore increasing the sensitivity of these sensory afferents.

Serotonergic Modulation of Sensory Computations: Sharpening and Broadening

In addition to directly acting on sensory afferents to modulate gain control, serotonin can indirectly modulate sensory afferents via local interneurons (LNs). For example, serotonin stimulates 5-HT2C-expressing LNs (juxtaglomerular cells) in the olfactory bulb to increase the amount of presynaptic inhibition exerted upon olfactory afferents (Petzold et al. 2009). In doing so, serotonin reduces the gain of olfactory afferent responses and thus the amount of sensory input entering the olfactory bulb (Petzold et al. 2009). Moreover, serotonin can also indirectly enhance presynaptic inhibition by activating 5-HT2A receptors expressed by excitatory LNs (external tufted cells), which in turn provide excitatory drive to inhibitory short axon and periglomerular cells (Brill et al. 2016; Liu et al. 2012). In this way, serotonin can further drive inhibitory inputs to sensory afferents as a means of decreasing sensory input. Serotonin similarly indirectly decreases the strength of sensory

Table 2. *Serotonergic receptors that have been molecular cloned and their intracellular effects assayed across members of various taxa*

Order	Species	Receptor Subtype	Response	Reference
Anaspideae	*Aplysia californica*	5-HT$_{ap1}$	Decrease cAMP	(Angers et al. 1998)
		5-HT$_{ap2}$	Decrease cAMP	(Barbas et al. 2002)
	Aplysia kurodai	5-HT$_{apAC1}$	Increase cAMP	(Lee et al. 2009)
Basommatophora	*Lymnaea stagnalis*	5-HT2	Increase IP_3	(Gerhardt et al. 1996)
Blattodea	*Periplaneta americana*	5-HT1	Decrease cAMP	(Troppmann et al. 2010)
Coleoptera	*Tribolium castaneum*	5-HT1	Decrease cAMP	(Vleugels et al. 2013)
		5-HT7	Increase cAMP	(Vleugels et al. 2014)
Decapoda	*Panulirus interruptus*	5-HT1A	Decrease cAMP	(Spitzer et al. 2008a)
		5-HT2B	Increase IP_3	(Clark et al. 2004)
	Procambarus clarkii	5-HT1A	Decrease cAMP	(Spitzer et al. 2008b)
		5-HT2B	Increase IP_3	
Diptera	*Aedes aegypti*	5-HT7	Increase cAMP	(Lee and Pietrantonio 2003; Pietrantonio et al. 2001)
	Anopheles gambiae	5-HT2 ("AGAP002229")	Increase Ca^{2+}	(Ngai et al. 2019)
		5-HT2 ("AGAP002232")	Increase Ca^{2+}	
	Calliphora vicina	5-HT7	Increase cAMP	(Röser et al. 2012)
		5-HT2A	Increase Ca^{2+}	
	Drosophila melanogaster	5-HT1A and 1B	Decrease cAMP	(Saudou et al. 1992)
		5-HT2A	Increase Ca^{2+}	(Colas et al. 1995; Gasque et al. 2013)
		5-HT2B	Increase Ca^{2+}	(Gasque et al. 2013)
		5-HT7	Increase cAMP	(Witz et al. 1990)
Hymenoptera	*Apis mellifera*	5-HT2A and 2B	Increase Ca^{2+}	(Thamm et al. 2013)
		5-HT7	Increase cAMP	(Schlenstedt et al. 2006)
Ixodida	*Boophilus microplus*	5-HT1	Decrease cAMP	(Chen et al. 2004)
Lepetellida	*Haliotis discus hannai*	5-HT1B	Decrease cAMP	(Kim et al. 2019)
		5-HT4	Increase cAMP	
Lepidoptera	*Bombyx mori*	5-HT1A	Decrease cAMP	(Xiong et al. 2019)
	Manduca sexta	5-HT2	Increase IP_3	(Dacks et al. 2013)
		5-HT7	Increase cAMP	
	Pieris rapae	5-HT1A and 1B	Decrease cAMP	(Qi et al. 2017)
		5-HT7	Increase cAMP	
		5-HT8	Increase Ca^{2+}	(Qi et al. 2014)
Primates	*Homo sapiens*	5-HT1A, 1B, 1D, 1E, 1F	Decrease cAMP	(Adham et al. 1993; Hamblin et al. 1992; McAllister et al. 1992; Stam et al. 1992; Stam et al. 1994; Weinshank et al. 1992)
		5-HT2A, 2B, 2C	Increase IP_3	(Kursar et al. 1994; Schmuck et al. 1994; Stam et al. 1992; Stam et al. 1994)
		5-HT4	Increase cAMP	(Blondel et al. 1998)
		5-HT5A	Inconclusive	(Grailhe et al. 2001)
		5-HT6	Increase cAMP	(Kohen et al. 1996)
		5-HT7	Increase cAMP	(Stam et al. 1997)
Rhabditidae	*Caenorhabditis elegans*	SER-1	Increase Ca^{2+}	(Hamdan et al. 1999)
		SER-4	Decrease cAMP	(Olde and McCombie 1997)
		SER-7	Increase cAMP	(Hobson et al. 2006)
Rodentia	*Mus musculus*	5-HT1A, 1B, 1D, 1F	Decrease cAMP	(Amlaiky et al. 1992; Charest et al. 1993; Maroteaux et al. 1992; Weydert et al. 1992; Yu et al. 1991)
		5-HT2A, 2B, 2C	Increase IP_3	(Foguet et al. 1992; Loric et al. 1992)
		5-HT4	Increase cAMP	(Claeysen et al. 1999)
		5-HT5A and 5B	Inconclusive	(Matthes et al. 1993)
		5-HT6	Increase cAMP	(Kohen et al. 2001)
		5-HT7	Increase cAMP	(Plassat et al. 1993)
	Rattus norvegicus	5-HT1A, 1B, 1D, 1F	Decrease cAMP	(Adham et al. 1993; Albert et al. 1990; Hamblin et al. 1992; Lovenberg et al. 1993)
		5-HT2A, 2B, 2C	Increase Ca^{2+}/IP_3	(Julius et al. 1988; Kursar et al. 1994; Pritchett et al. 1988)
		5-HT4	Increase cAMP	(Gerald et al. 1995)
		5-HT5A	Decrease cAMP	(Erlander et al. 1993; Thomas et al. 2000)
		5-HT5B	Inconclusive	(Erlander et al. 1993; Wisden et al. 1993)
		5-HT6	Increase cAMP	(Ruat et al. 1993a)
		5-HT7	Increase cAMP	(Ruat et al. 1993b; Shen et al. 1993)
Synallactida	*Apostichopus japonicus*	5-HT4	Increase cAMP	(Wang et al. 2017)

"Response" indicates the in vitro consequences of receptor activation. IP_3, inositol trisphosphate.

Table 3. *Serotonin receptor subtype expression within auditory, mechanosensory, gustatory, olfactory, and visual processing centers across vertebrates and invertebrates*

Sensory System	Order	Receptor Subtype	Method	Reference
Audition/mechanosensation	Anaspidea	5-HT7	In situ hybridization	(Lee et al. 2009)
	Araneae	5-HT1	In situ hybridization	(Sukumar et al. 2018)
	Diptera	All subtypes	Transgenics	(Howard et al. 2019)
	Decapoda	5-HT1	Immunohistochemistry	(Fickbohm et al. 2005)
	Rodentia	5-HT1A, 1C, 2	In situ hybridization	(Wright et al. 1995)
		5-HT2A, 2C	Immunohistochemistry	(Li et al. 2003)
		5-HT4A	Immunohistochemistry	(Suwa et al. 2014)
		5-HT1B, 1D, 1F	In situ hybridization	(Bruinvels et al. 1994)
		5-HT2A	Immunohistochemistry	(Cornea-Hébert et al. 1999)
		5-HT2A	Immunohistochemistry	(Basura et al. 2008)
		5-HT2B	Immunohistochemistry	(Tadros et al. 2007)
		5-HT2	Autoradiography	(Malgouris et al. 1993)
		5-HT1A	In situ hybridization and autoradiography	(Chalmers and Watson 1991)
		5-HT1A	In situ hybridization	(Pompeiano et al. 1992)
		5-HT7	Autoradiography	(To et al. 1995)
		5-HT1A. 1B	Immunohistochemistry	(Peruzzi and Dut 2004)
Gustation	Blattodea	5-HT1	Immunohistochemistry	(Troppmann et al. 2010)
	Decapoda	5-HT1, 2	Immunohistochemistry	(Vázquez-Acevedo et al. 2009)
		5-HT1	Immunohistochemistry	(Spitzer et al. 2005)
	Diptera	5-HT1A	Transgenics	(Luo et al. 2012)
		5-HT1A, 1B, 2A, 7	Transgenics	(Huser et al. 2017)
		5-HT1B	Transgenics	(Liu et al. 2015)
	Hymenoptera	5-HT7	In situ hybridization	(Schlenstedt et al. 2006)
	Orthoptera	5-HT1A, 1B	Immunohistochemistry	(Shao et al. 2010)
	Rhabditida	5-HT7	Transgenics	(Hobson et al. 2006)
	Rodentia	5-HT2A	Immunohistochemistry	(Cornea-Hébert et al. 1999)
		5-HT4A	Immunohistochemistry	(Suwa et al. 2014)
		5-HT2	Autoradiography	(Malgouris et al. 1993)
Olfaction	Decapoda	5-HT1	Immunohistochemistry	(Spitzer et al. 2005)
		5-HT2	Immunohistochemistry	(Vázquez-Acevedo et al. 2009)
	Diptera	All subtypes	Transgenics	(Sizemore and Dacks 2016)
		5-HT1A, 1B, 2A, 7	Transgenics	(Huser et al. 2017)
	Hymenoptera	5-HT7	In situ hybridization	(Schlenstedt et al. 2006)
		5-HT1A	Immunohistochemistry	(Thamm et al. 2010)
	Lepidoptera	5-HT1	Immunohistochemistry	(Dacks et al. 2013)
	Orthoptera	5-HT1A, 1B	Immunohistochemistry	(Shao et al. 2010)
	Rhabditida	SER-5 (5-HT6-like)	Transgenics	(Harris et al. 2010)
	Rodentia	5-HT2	Autoradiography	(Pazos and Palacios 1985)
		5-HT3	In situ hybridization	(Tecott et al. 1993)
		5-HT1A, 1C, 2	In situ hybridization	(Wright et al. 1995)
		5-HT1E	Immunohistochemistry	(Klein and Teitler 2012)
		5-HT4A	Immunohistochemistry	(Suwa et al. 2014)
		5-HT1C	In situ hybridization	(Mengod et al. 1990)
		5-HT2A	Immunohistochemistry	(Cornea-Hébert et al. 1999)
		5-HT1B	In situ hybridization	(Voigt et al. 1991)
		5-HT2A	Immunohistochemistry	(Hamada et al. 1998)
		5-HT1B, 1D, 1F	In situ hybridization	(Bruinvels et al. 1994)
		5-HT2	Autoradiography	(Malgouris et al. 1993)
		5-HT2A. 2C	Immunohistochemistry	(Li et al. 2003)
Vision	Carnivora	5-HT1	Autoradiography	(Mower 1991)
		5-HT1	Autoradiography	(Skangiel-Kramska and Kossut 1992)
		5-HT1A, 1C, 2, 3	Autoradiography	(Dyck and Cynader 1993)
	Cypriniformes	5-HT1A, 1B	In situ hybridization	(Norton et al. 2008)
	Decapoda	5-HT1, 2	Immunohistochemistry	(Vázquez-Acevedo et al. 2009)
		5-HT1	Immunohistochemistry	(Spitzer et al. 2005)
	Diptera	All subtypes	Transgenics	(Sampson et al. 2019) (preprint)
	Hymenoptera	5-HT1A	Immunohistochemistry	(Thamm et al. 2010)
		5-HT7	In situ hybridization	(Schlenstedt et al. 2006)
	Lagomorpha	5-HT1A, 7	In situ hybridization	(Chidlow et al. 1998)
	Orthoptera	5-HT1A, 1B	Immunohistochemistry	(Shao et al. 2010)
	Petromyzontiformes	5-HT1A	In situ hybridization	(Cornide-Petronio et al. 2015)
	Primates	5-HT1, 2	Autoradiography	(Rakic et al. 1988)
		5-HT1, 2	Autoradiography	(Rakic and Lidow 1995)
		5-HT1A, 2	Autoradiography	(Impieri et al. 2019)
		5-HT1B, 2A	In situ hybridization	(Watakabe et al. 2009)

Continued

Table 3.— *Continued*

Sensory System	Order	Receptor Subtype	Method	Reference
	Rodentia	5-HT1A, 1C, 2	In situ hybridization	(Wright et al. 1995)
		5-HT1A	Immunohistochemistry	(Zhou et al. 2019)
		5-HT2A, 2C	Immunohistochemistry	(Li et al. 2003)
		5-HT4A	Immunohistochemistry	(Suwa et al. 2014)
		5-HT2A	Immunohistochemistry	(Cornea-Hébert et al. 1999)
		5-HT1B, 1D, 1F	In situ hybridization	(Bruinvels et al. 1994)
		5-HT1F	In situ hybridization	(Adham et al. 1993)

afferent input in the *Drosophila* antennal lobe by enhancing presynaptic inhibition (Dacks et al. 2009; Gaudry 2018) and the strength of projection neuron (PN) responses by enhancing postsynaptic inhibition (Suzuki et al. 2020). Altogether, these examples highlight the different mechanisms by which serotonin regulates the resolution with which sensory networks encode stimulus intensity.

In addition to compensating for large variations in stimulus intensity, animals may also need to adjust their ability to resolve different stimuli. At the neuronal level, sensory systems use inhibition and lateral excitation to sharpen or broaden the resolution with which they encode stimulus identity (reviewed in Martin et al. 2011). Not surprisingly, serotonin also targets these aspects of sensory encoding (Fig. 1*E*). Such is the case in the inferior colliculus, where serotonin sharpens auditory neurons' responses to primary sound frequencies by decreasing their responsiveness to frequencies both within and outside of the central range (Hurley and Pollak 2001). In the piriform cortex, serotonin sharpens neuronal representations of odors by decreasing their spontaneous activity but leaving their odor-evoked responses unaffected (Lottem et al. 2016).

In these instances, serotonin hones the neurons' responses, whether by narrowing the receptive range or by decreasing spontaneous activity. However, serotonin can also broaden the receptive range of neurons in a given sensory system. For instance, in the vertebrate retina serotonin can decrease lateral inhibition by activating inhibitory 5-HTRs expressed by amacrine cells, therefore broadening the number of retinal ganglion cells that are responsive to a given stimulus (Trakhtenberg et al. 2017; Zhou et al. 2019). In the olfactory bulb, serotonin enhances feedforward excitation to mitral cells from interneurons via the 5-HT2A receptor (Brill et al. 2016; Huang et al. 2017; Liu et al. 2012). The combined actions of both serotonin and glutamate released by DRN neurons increase the sensitivity of tufted cells and decorrelate odor-evoked responses of mitral cells, presumably increasing the separation of representations of different odors (Kapoor et al. 2016). Within the *Drosophila* antennal lobe, serotonin could potentially affect the breadth of odor-evoked representations, as a specialized population of excitatory interneurons can broaden odor-tuning (Huang et al. 2010; Shang et al. 2007; Yaksi and Wilson 2010) and these neurons express excitatory 5-HTRs (Sizemore and Dacks 2016). Serotonin can also directly modulate the excitability of second-order neurons within a sensory system, thus potentially influencing tuning breadth. Exogenous application of serotonin increases the excitability of antennal lobe output neurons (Dacks et al. 2006b; Kloppenburg et al. 1999; Kloppenburg and Hildebrand 1995; Zhang and Gaudry 2016). This effect, however, is at least partially polysynaptic and depends on the method of delivery, as activation of *Drosophila* CSDns can have little to no effect on the odor-evoked responses of output neurons depending on the glomerulus (Zhang and Gaudry 2016). This discrepancy could arise from cell class-specific receptor expression in the antennal lobe (AL) (Sizemore and Dacks 2016), differences in binding affinities of the 5-HTRs for serotonin (Gasque et al. 2013), or differences in the time course of receptor activation and inactivation. Regardless, there appear to be a variety of means by which serotonin can affect the resolution with which stimulus identity is encoded.

Serotonergic Regulation between Sensory Information Streams

By its combined action on different neural types within a sensory circuit, serotonin can functionally regulate the balance among different streams of information within sensory regions. For example, in the superficial layers of the superior colliculus, serotonin acting via 5-HT1A receptors decreases the responses of single postsynaptic neurons to stimulation of both ascending and descending visual pathways (Mooney et al. 1996). In contrast, activation of 5-HT1B receptors largely decreases responses to stimulation of the ascending visual pathway, likely by decreasing transmitter release presynaptically. Endogenous serotonin release could therefore favor descending over ascending visual streams via these two inhibitory serotonin receptor types. In the dorsal cochlear nucleus (DCN), the high density of serotonergic fibers in cell groups that receive descending and multisensory input is proposed to regulate the convergence of multimodal information at the level of the principal cells (fusiform cells) in this nucleus (Klepper and Herbert 1991). As in the superior colliculus, serotonin acts on multiple types of excitatory and inhibitory DCN neurons through different classes of receptors (Tang and Trussell 2015, 2017). Serotonin postsynaptically increases the excitability of fusiform neurons through 5-HT2A and 5-HT7 receptors. At the same time, serotonin presynaptically decreases the amplitude of excitatory potentials from auditory nerve fibers through 5-HT1A receptors and increases the excitability of inhibitory interneurons through 5-HT2 receptors. This causes responses of the principal neurons of the DCN to stimulation of auditory-only pathways to be dampened, whereas responses to stimulation of multisensory pathways are enhanced. In multiple sensory cortices, serotonin also has neuron-specific, receptor-specific, or layer-specific effects (Foehring et al. 2002; García-Oscos et al. 2015; Jang et al. 2012; Lee et al. 2018; Torres-Escalante et al. 2004; Xiang and Prince 2003). These selective effects may alter the balance between different sources of information such as inter- and intracolumnar inputs or intralayer versus feedforward sources of input (Cervantes-Ramírez et al. 2019; Xiang and Prince 2003).

Serotonergic Metamodulation across Sensory Systems

In addition to acting on fast synaptic transmission within a given sensory system, serotonin can also act on other modulatory neurons that influence sensory processing. Indeed, all sensory systems are influenced by multiple neuromodulators released from intrinsic or extrinsic neurons (Berg et al. 2009; Carlsson et al. 2010; Chalasani et al. 2010; Hurley et al. 2004; Iwano and Kanzaki 2005; Jacob and Nienborg 2018; Lizbinski et al. 2018; Nässel 2018; Nässel and Zandawala 2019; Schofield and Hurley 2018). Neuromodulators released by a given modulatory neuron can also influence other modulatory neurons within the network. Collective changes in concentration over time of each neuromodulatory molecule reflect the overall "modulatory tone" of any given sensory network. These changes in modulatory tone might therefore reflect dramatic shifts in the animal's behavior state as it relates to a given sensory experience. Individual modulators, such as serotonin, can therefore profoundly alter networkwide activity by simply adjusting existing modulatory circuitry present in a given sensory network.

Serotonin influences GABAergic modulation in both vertebrate and invertebrate primary olfactory systems (reviewed in Lizbinski and Dacks 2018), and peptidergic modulation by serotonin is likely present across taxa. For instance, interneurons of the vertebrate sensory cortex that release vasoactive intestinal peptide (VIP) also express the excitatory 5-HT3 ionotropic receptor (Cardin 2018; Lee et al. 2010; Rudy et al. 2011). Activating 5-HT3 receptors in VIP interneurons causes a hyperpolarization in 5-HT3-negative inhibitory interneurons, which subsequently disinhibits pyramidal neurons (Jiang et al. 2015; Pfeffer et al. 2013; Takesian et al. 2018). Moreover, serotonergic stimulation of VIP interneurons also produces a latent, $GABA_B$ receptor-mediated hyperpolarization in these same pyramidal cells (Takesian et al. 2018). Therefore, by acting through these interneurons serotonin can have a large impact on network dynamics and even modulate distinct aspects of sensory processing (for example see Pi et al. 2013). Moreover, the activity of the VIP interneurons appears to be at least one determinant for the changes observed in the activity of visual cortex circuitry according to the animal's ongoing behavioral state (Batista-Brito et al. 2017; Bennett et al. 2013; Fu et al. 2014; Pakan et al. 2016; Polack et al. 2013). Collectively, these results suggest that there may be a serotonin-induced contingency switching module in visual cortex wherein the animal's locomotor activity induces serotonergic activation of VIP interneurons. Then, perhaps after some epoch after behavior initiation, negative feedback terminates this serotonin-induced module.

CONCLUDING REMARKS

Here we have presented numerous examples of serotonin's capacity for adjusting sensory processing at nearly every stage of signaling. Regardless of modality or species, serotonergic systems are heterogeneous at the level of individual neurons, as well as diverse at the level of whole populations. Moreover, the suite of serotonin receptors further expands the means with which serotonin affects select features, such as odor coding. These heterogeneous features of the serotonin system allow for widespread, nuanced effects of serotonin on sensory processing that vary in a context-dependent manner. Subsequently, these heterogeneous features also complicate assignments of a singular role for serotonin. However, serotonergic modulation is widespread throughout the animal kingdom, and currently the majority of our understanding regarding the cellular mechanisms underlying serotonergic modulation of sensory processing comes from a handful of organisms (i.e., rodents, fruit flies, etc.). By comparing across modalities and diverse taxa, we can reveal convergent adaptations that reveal fundamental molecular, cellular, and network mechanisms of sensory modulation. Similar approaches might also reveal divergent adaptations that reveal the selective pressures that sculpt neuromodulation.

Future directions for understanding the role of serotonin in sensory processing include the following:

- How does the full extent of serotonergic neuron diversity vary from animal to animal, and what factors contribute to this variation?
- How do the properties of serotonergic neurons and expression patterns of 5-HTRs change in response to different external and/or internal demands?
- How much of the context-dependent effects of serotonin arises from the heterogeneous nature of serotonergic neurons, and how much arises from different 5-HTR expression motifs?
- How does 5-HTR autoreceptor and heteroreceptor activity influence serotonergic modulation of sensory processing?
- To what extent are 5-HTRs expressed in specific neuronal compartments, and what are the consequences of 5-HTR distribution patterns for sensory processing?

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

T.R.S. conceived and designed research; T.R.S. and A.D. prepared figures; T.R.S., L.M.H., and A.D. drafted manuscript; T.R.S., L.M.H., and A.D. edited and revised manuscript; T.R.S., L.M.H., and A.D. approved final version of manuscript.

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