Review Article

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Neuromodulation of early sensory processing in the olfactory system

Neuromodulation der frühen sensorischen Verarbeitung im olfaktorischen System

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Abstract: At any given moment, we are continuously presented with information that is received from multiple sensory organs. Thus, our brain simultaneously processes enormous amounts of data in order to render an understanding of our environment. Adjustment of sensory processing is therefore important for tuning perception in a context-dependent fashion, i. e. to facilitate adequate behavioral responses by promoting the efficient sensory processing of relevant stimuli, while suppressing unimportant signals. The basic mechanisms that underlie the modulation of sensory information remain largely unknown, especially when considering early sensory circuits. Importantly, an ability to selectively manipulate these processes would offer great advantages for both basic and translational biomedical research. Here, we highlight the vertebrate olfactory bulb as a model system for early sensory processing and its utility in demonstrating the complexity of neuromodulatory actions.

Zusammenfassung: In jedem Moment sind wir von einer Vielzahl von Informationen umgeben, die gleichzeitig von mehreren Sinnen empfangen werden. Eine enorme Menge an Daten muss daher in unserem Gehirn gleichzeitig verarbeitet werden, um unsere Umwelt richtig zu verstehen. Eine Anpassung der sensorischen Verarbeitung ist wichtig, um unsere Wahrnehmung kontextabhängig optimieren zu können, d. h. um adäquate Verhaltensreaktionen zu ermöglichen, muss eine effiziente sensorische Verarbeitung relevanter Stimuli gefördert und unwichtige Signale unterdrückt werden. Die zugrundeliegenden Mechanismen der sensorischen Informationsmodulation sind, insbesondere in frühen sensorischen Schaltkreisen, weitgehend unbekannt. Die Fähigkeit, diese Prozesse selektiv manipulieren zu können, wäre sowohl für die Grundlagenforschung als auch die translationale biomedizinische Forschung von großem Vorteil. Hier betrachten wir das olfaktorische System der Vertebraten als Modellsystem für die Untersuchung früher sensorische Verarbeitung und demonstrieren die Komplexität neuromodulatorischer Vorgänge anhand dieses Systems.

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Introduction

Animals, including humans, live in an ever changing environment. In order to brave environmental changes, all organisms take up and process sensory information. However, it is becoming more and more apparent that sensory information is modulated in a situation-dependent fashion. There are many examples known, which demonstrate how our brain actively "tunes" sensory information. Most readers have probably already experienced some of these examples personally, e. g. the famous "cocktail-party effect" (McLachlan and Wilson, 2010) whereby despite strong background noise one can still listen to one's conversation partner or that things smell much stronger and more appetizing when we are hungry (Soria-Gomez et al., 2014). Disorders in sensory sensitivity adjustment can lead to mild symptoms such as over-reactiveness to certain stimuli (e. g. loud noise), whereas disorders in sensory filtering can cause severe conditions such as autism spectrum or attention deficit disorders. It is estimated that 1 out of 160 children worldwide suffers from a condition falling into the autism spectrum (www.who.int). Therefore, elucidating the mechanisms by which sensory information is modulated is one of the most important and challenging questions in modern neuroscience. The means by which these modulations are performed, we will

refer to as "neuromodulation", a concept we would like to discuss, and maybe redefine, within this article. In doing so, we will focus entirely on the olfactory system of vertebrates, illustrating the complexity of neuromodulation, and highlight the use of the olfactory system as a promising model in neuromodulation research.

Neuromodulation

Neuromodulation is a very ambiguous term. In medicine, neuromodulation is defined as a "field of science, medicine and bioengineering that encompasses implantable and non-implantable technologies, electrical or chemical, for the purpose of improving quality of life and functioning of humans" (Definition of the International Neuromodulation Society; www.neuromodulation.com). In neuroscience research, however, neuromodulation was, and in part still is, used to separate slower and more diffuse forms of neuronal communication from fast synaptic transmissions (see Bucher and Marder, 2013). Early on, it has been recognized that this definition might not be sufficient to comprise all forms of neuromodulation, rather defining it as "the alteration of cellular or synaptic properties by a neuron or a substance released by neurons"(Katz, 1999). We feel that this definition might still be too limited in scope as it excludes a vast amount of substances (not released by neurons) that can strongly modulate neuronal processing. Therefore, we prefer to use the term neuromodulation here for anything that alters neurons or neuronal processing, independent of the alterant's origin. This definition includes modulatory influences from endocrine sources, processes that are vital for the response of an animal to changes in its internal state.

Neuromodulation of early sensory processing

It is known that all neuronal circuits are subject to modulatory influence (e. g. Jacob and Nienborg, 2018). This modulation is most easily detected in sensory systems, where perception of a stimulus changes depending on factors such as mood or attention. As such, neuromodulation can be found across all sensory modalities (Reynolds and Chelazzi, 2004; Zelano and Sobel, 2005; Ferezou et al., 2006). Since neuromodulation occurs at all levels of processing (see e. g. Hurley and Hall, 2011), it is not always clear where the modulation of sensory information exactly happens; especially if only behavior is used as a measurable output. Additional levels of complexity arise from the multiplicity of potential neuromodulators that are present in every circuit and from the understanding that neuromodulation can be mediated not only by sources outside, but also within a given brain area; a concept termed extrinsic vs. intrinsic neuromodulation (see Lizbinski and Dacks, 2017). This plethora of modulating influences is the reason why in any system, it is hard to form a cohesive theory of neuromodulatory action ranging from the sensory uptake to the behavioral outcome.

In recent years new techniques including imaging and optogenetics (as later discussed in more detail) have been developed, significantly increasing our knowledge on neuromodulatory processes. Many studies using these techniques have so far focused on modulations in higher brain centers (Fu et al., 2014; Jacob and Nienborg, 2018). Neuromodulation of early sensory processing, however, might be of critical value for a general understanding of neuromodulatory processes in health and disease. This is because not only are modulations at early stages likely to affect all subsequent processing steps, but also because early sensory levels might be more accessible to pharmacological intervention compared to centers embedded deep inside the brain. As such, due to its accessibility and relative simplicity, we would like to introduce the olfactory bulb as an ideal model system to study neuromodulation of early sensory processing.

The olfactory bulb as model for neuromodulatory research

The sense of smell, though under-appreciated in human, is of critical importance to most animals (Sarafoleanu et al., 2009). Humans, who mostly navigate the world through vision, also rely heavily on olfaction (McGann, 2017). For example, there is strong evidence that humans use olfaction for food preference. Furthermore, olfaction exhibits pronounced subconscious effects, whereupon it has been shown to influence mood (Zald and Pardo, 1997) or mate choice (Thornhill et al., 2003).

The olfactory system, which from an evolutionary perspective is probably the oldest of all senses, displays some unique features compared to other sensory systems. For example, the olfactory cortex comprises only three layers and sensory information relayed to the olfactory cortex does not have to pass through the thalamus. This direct input of olfactory information to brain areas involved in mood and emotion (i. e. the amydgala, discussed below)

suggests a close relationship between olfactory and affective information processing (Soudry et al., 2011). However are also many similarities between olfaction and the other sensory systems. Information is taken up and relayed to higher brain centers after being heavily processed. Like in other sensory systems, this transformation from primary to a secondary representation is often "expansive", meaning that the number of principal neurons increases from lower to higher processing centers, typically leading to a sparse stimulus representation in downstream networks (Babadi and Sompolinsky, 2014).

Several recent technical developments have revolutionized neuroscientific and neuromodulatory research, most notably optogenetics, the control of neuronal activity and cell signaling by light, (see Spangler and Bruchas, 2017) as well as optophysiology, the optical recording of cell activity using different probes, e. g. for calcium (Chen et al., 2013), dopamine (Patriarchi et al., 2018) glutamate (Marvin et al., 2013; Marvin et al., 2018) or acetylcholine (Jing et al., 2018). These optical probes enable the monitoring of large neuronal populations simultanesously. In basic research settings, these techniques are usually combined with modern genetics and/or modified viruses to provide unparalleled specificity in targeting and manipulating cell populations of interest.

The olfactory bulb, due to its size and location in mice (see Figure 1) offers the possibility to apply these new techniques easily in living animals (Spors et al., 2012; Wachowiak et al., 2013). It is especially well-suited for studying early neuromodulatory processes in particular, since, in contrast to other sensory systems, early stations of sensory information processing are easily accessible. Moreover, the relative simplicity of this system, coupled to knowledge of its connectivity, should allow for easier formation of a holistic picture of neuromodulation. Also, for mice, the model animal of choice in many aspects of neuroscience, due to its susceptibility for genetic manipulation, olfaction is one of the most important senses. Taken together, these features render the mouse olfactory bulb a very appealing model system for the study of early sensory neuromodulation.

Neuroanatomy of the vertebrate olfactory bulb

The olfactory bulb is the first central processing station of olfactory information. Odorants are detected inside the nasal cavity by olfactory sensory neurons (OSN), primary sensory neurons that express a single type of olfactory receptor out of a repertoire of approximately 1200 receptors in mice (~ 350 in humans) (Glusman et al., 2001; Nei et al., 2008). Olfactory receptor neurons project an unbranched axon to the olfactory bulb. The cellular composition and synaptic buildup of the olfactory bulb is very well established (for review see Wachowiak and Shipley, 2006). Briefly, it consists of several layers harboring different cell types that together shape olfactory information (Figure 1). The outermost layer is the olfactory nerve layer. Axons of sensory neurons expressing the same type of olfactory receptor are sorted within this layer and enter the olfactory bulb. The functional unit, into which sensory neurons expressing the same olfactory receptor converge to form synapses with interneurons, as well as olfactory bulb output neurons is called a "glomerulus". The layer in which these glomeruli reside is the glomerular layer. Here, also some major types of interneurons can be found, most notably GABAergic periglomerular cells (PG), dopaminergic and GABAergic superficial short axon cells (SA), as well as glutamatergic external tufted cells (ET). The output neurons of the bulb are tufted and mitral cells (MTC) that reside in the external plexiform and the adjacent mitral cell layer, respectively. The granule cell layer, located below the mitral cell layer, is comprised of granule cells (GC), a major source of inhibition in the olfactory bulb.

Different forms of neuromodulatory sources for the olfactory bulb

Neuromodulatory cues can originate either from within a particular brain structure that is being modulated ("intrinsic neuromodulation") or from a remote area ("extrinsic neuromodulation", (see Lizbinski and Dacks, 2017). Intrinsic neuromodulatory processes within the olfactory bulb (OB) are extensive. They are present in all OB layers and examples range from a mechanism called presynaptic inhibition of olfactory sensory neurons, (most likely mediating a form of gain control; see Wachowiak and Shipley, 2006) to tonic inhibition of granule cells by other interneurons (Pressler and Strowbridge, 2006). Here, we will only discuss extrinsic influences in more detail and do so for the vertebrate olfactory bulb. In addition to modulatory sources from higher brain centers (centrifugal projections from neuromodulatory centers and cortical backprojections, something that can be summarized as "top-down" inputs) we will also discuss peptidergic and hormonal neuromodulation from sources outside the OB.

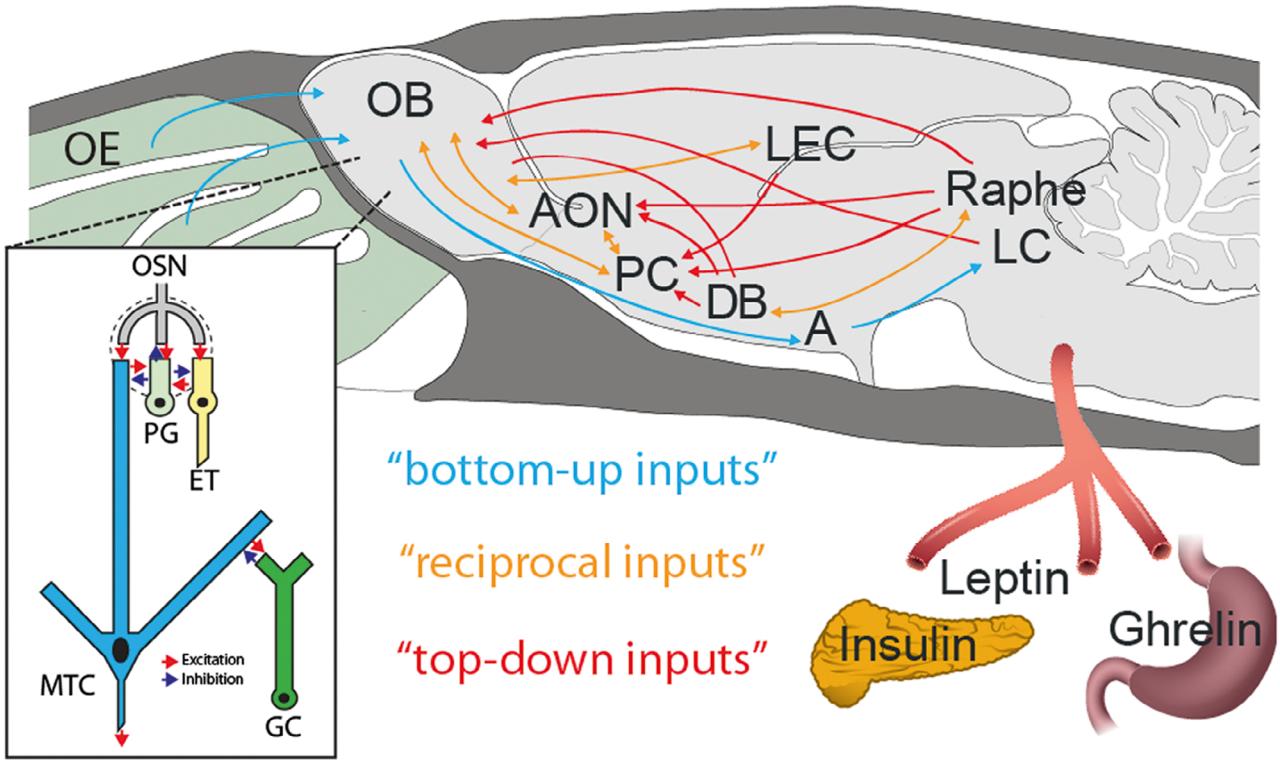

Figure 1: Diagram summarizing the neuromodulatory sources discussed in this review.
Olfactory sensory neurons (OSNs) located in the olfactory epithelium (OE) project axons into the olfactory bulb (OB). OSN axons synapse with projection neurons (mitral and tufted cells, MTC) and with interneurons (periglomerular, PG and external tufted, ET). MTC also make connections with granule cells (GCs) and PGs (simplified scheme). Brain regions receiving bottom-up information are marked with blue arrows, regions reciprocally-connected with orange arrows, and top-down inputs are marked with red arrows. AON, anterior olfactory nucleus; PC, piriform cortex; DB, diagonal band of broca; A, amygdala; LEC, lateral entorhinal cortex, LC, locus coeruleus. Courtesy of A.C. Puche, modified from (Aungst et al., 2003) and "The Rat Nervous System" 2nd Edition.

"Neuromodulatory" projections

The term "neuromodulatory brain centers" is used to describe relatively small pools of neurons which signal through neurotransmitters that are classically referred to as "neuromodulators". These centers include the locus coeruleus for noradrenergic projections, the *raphe nuclei*, for serotonergic projections, the band of broca for cholinergic projections and the ventral tegmental area for dopaminergic projections (Kandel, 2013). Each of these centers innervate a large variety of different brain structures that themselves are highly interconnected, thereby complicating the effort to understand effects of each of these modulatory centers on a particular circuit. Though several studies have attempted to assign discrete functions to each of the neurotransmitters, e.g. acetylcholine for mediating attentional processes (Parikh and Sarter, 2008; D'Souza and Vijayaraghavan, 2014), serotonin for influencing mood (Salomon and Cowan, 2013) and noradrenalin for controlling alertness (Waterhouse and Navarra, 2018), it has become apparent that their functions are far more complex and a complete understanding requires considering interactions between the neuromodulatory brain centers (e.g. cholinergic innervation of *raphe nuclei*, Kalen and Wiklund, 1989).

The olfactory bulb receives centrifugal projections from three different neuromodulatory centers: the locus coeruleus (LC), the horizontal band of broca (HDB) and the *raphe nuclei*.

Noradrenergic innervation of the OB by LC neurons is quite heavy (McLean et al., 1989). Behavioral studies have shown diverse functions for noradrenalin in the OB, ranging from lowered odor detection thresholds to odor learning and memory effects (see Linster and Escanilla, 2018). Recent physiological studies using imaging and electrophysiological recordings from OB neurons (Eckmeier and Shea, 2014; Manella et al., 2017) were able to shed light on the role of noradrenalin in signal-to-noise regulation, influencing OB input, modulating mitral cell spontaneous activity and increasing both the number and amplitude of sensory evoked responses.

One of the major influencers of neuromodulatory structures is the amygdala (which itself, however, does not belong to the classical neuromodulatory centers) (Price and Amaral, 1981; Retson and Van Bockstaele, 2013). The amygdala is a critical structure for emotional learning, valence coding and stress (Root et al., 2014; Gore et al., 2015; Maren, 2016). A recent study indicated amygdala connections to the LC as one major circuit by which the amygdala can shape early sensory processing (Fast and McGann, 2017). The amygdala must rely on indirect modulation pathways since, despite the direct input it receives from the OB (Haberly and Price, 1977; Schneider and Scott, 1983), no back projections to the OB have been reported.

The OB also receives serotonergic innervation from a large number of neurons of the median and dorsal *raphe nuclei* (McLean and Shipley, 1987; Steinfeld et al., 2015). However, despite this knowledge, its effects on olfactory perception are far from clear. One reason might be the recently-reported dual transmitter release of serotonin and glutamate from *raphe nuclei* derived fibers (Liu et al., 2014). Moreover, serotonergic fibers innervate broad areas of olfactory cortex like e. g. the piriform cortex (Lottem et al., 2016). Recent physiological studies have reported several cellular effects: serotonin was shown to increase baseline as well as odorant-evoked responses in periglomerular and superficial short axon cells (Brunert et al., 2016) and to modulate mitral cell activity in a heterogeneous fashion (Hardy et al., 2005; Brunert et al., 2016; Kapoor et al., 2016) (Figure 2).

Cholinergic modulation in the OB has been implicated in enhanced odor coding by OB output neurons, and in improved odor discrimination ability (Doty et al., 1999; Cleland et al., 2002; Mandairon et al., 2006; Chaudhury et al., 2009; Devore and Linster, 2012; Li and Cleland, 2013; Chan et al., 2017). Studies that used electrical basal forebrain stimulation to investigate modulation effects at the level of the OB (Kunze et al., 1991, 1992; Zhan et al., 2013; Bendahmane et al., 2016), were unable to discriminate between modulation effects caused by cholinergic and GABAergic neurons (which themselves project to the OB). A study using optogenetic activation of cholinergic neurons in basal forebrain reported inhibition of spontaneous activity and preferential suppression of weak sensory responses in MTCs, sharpening their odorant response spectra (Ma and Luo, 2012). However, the neural pathways underlying this modulation remain unclear because basal forebrain cholinergic neurons target olfactory cortical areas, which themselves strongly modulate OB circuitry (Woolf et al., 1984; Carlsen et al., 1985; Linster et al., 1999; Zimmer et al., 1999; Boyd et al., 2012; Markopoulos et al., 2012; Otazu et al., 2015). By contrast, optogenetically activating cholinergic axons directly in the OB, was shown to add an excitatory bias to MTCs: the enhancement of MTC odorant responses occurred independent of the strength or even polarity of the odorant-evoked response (Rothermel et al., 2014) (Figure2). The observation that a direct stimulation of cholinergic OB inputs modulates OB activity distinctly from that of non-selectively activating cholinergic HDB neurons is consistent with the idea that indirect pathways from HDB to the OB may differentially contribute to cholinergic modulation of early sensory processing. For example, cholinergic axons in both piriform cortex and anterior olfactory nucleus can be observed after viral expression in HDB, and both of these secondary cortical areas can, in turn, modulate OB processing. This example demonstrates that results from neuromodulatory experiments, even when using similar techniques, must be interpreted carefully.

Cortical top-down modulation

Cortical top-down areas primarily release glutamate instead of classical neuromodulators, but can be equally as complex. Similar to classical neuromodulatory inputs, most brain areas receive cortical top-down inputs from multiple sources. In general, cortical areas receiving bottom-up neural signals from primary sensory areas mostly also return top-down cortical input to these areas. The olfactory bulb receives cortical top-down inputs from at least 3 different sources (Matsutani and Yamamoto, 2008): the lateral entorhinal cortex (LEC), the anterior olfactory nucleus (AON) and the piriform cortex (PC).

The lateral entorhinal cortex receives (Igarashi et al., 2012) and transfers olfactory information from the olfactory bulb to the hippocampus (Steward and Scoville, 1976). It is involved in olfactory discrimination learning and the integration of olfactory information (Staubli et al., 1984; Chapuis et al., 2013). Recently, two spatially segregated types of feedforward (to hippocampus) and feedback neurons, which send direct connections either to piriform cortex or the OB, have been identified in the LEC (Leitner et al., 2016).

The AON sends a majority of cortical top-down projections to the olfactory bulb (Carson, 1984; Shipley and Adamek, 1984) and has been implicated in a range of different functions, including serving as the first site of integrated odor percept formation, reconstructing olfactory memory traces (Haberly, 2001), social interaction (Wacker et al., 2011; Oettl et al., 2016), controlling food intake (Soria-Gomez et al., 2014), episodic odor memory (Aqra-

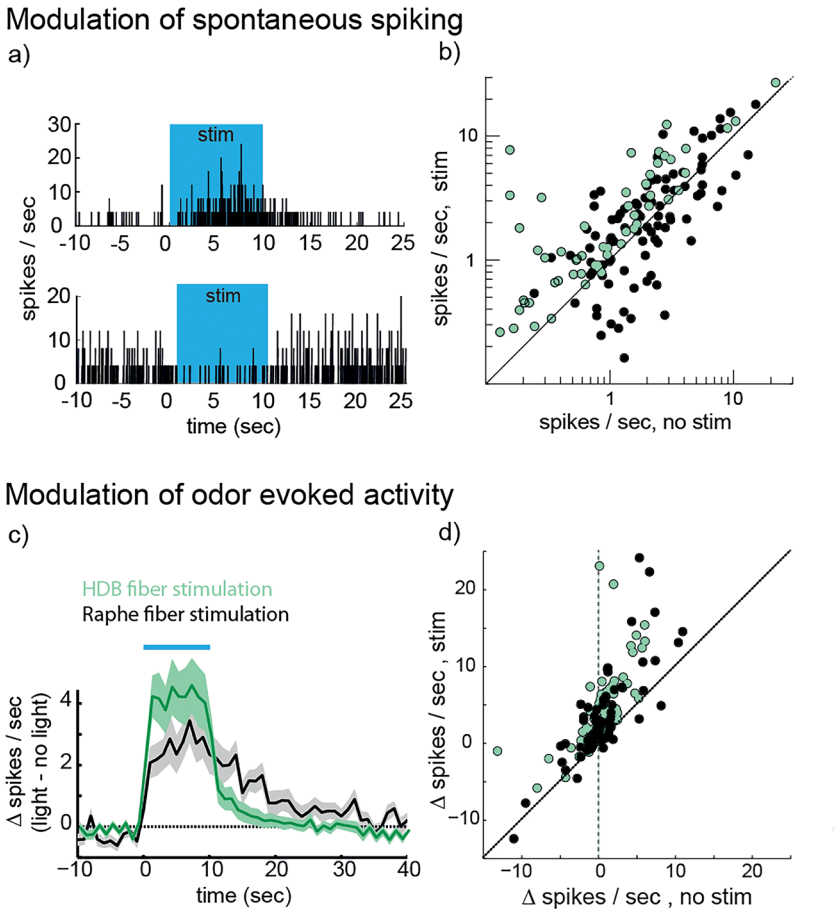

Figure 2: Diagram comparing the effects of cholinergic and serotonergic modulation on OB output activity in anesthetized mice. a) Exemplary rate histograms of two presumptive mitral/tufted cells (MTC) illustrating the effects of optically stimulating *raphe nuclei*-derived fibers in the OB on spontaneous activity (measured in the absence of inhalation). Note the qualitatively different effects in these two units. b) Plot of spontaneous firing rate of individual units before (no stim) and during (stim) optical stimulation of serotonergic (black circles) or cholinergic fibers (green circles) in the OB. c) Time course of effects of optical serotonergic (black trace) or cholinergic (green trace) fiber stimulation on odorant-evoked spike rate, averaged across all units. d) Plot of odorant-evoked changes in MTC spiking (Δ spikes/sniff) in the absence of (no stim) and during (stim) optogenetic stimulation of serotonergic (black circles) or cholinergic (green circles) afferents to the OB. Serotonergic and cholinergic fiber stimulation was performed in separate experiments. Effects on OB output neuron activity 1) are depending on the neuromodulatory center being activated, 2) display relatively fast on and offset kinetics that are center specific, and 3) can vary with sensory input (spontaneous compared to odor-evoked activity). In summary, these data support the idea that different neuromodulatory systems can modulate OB processing in distinct ways, even working in concert or independent of sensory inputs, in order to modulate sensory processing in a context-dependent fashion. For detailed material and methods please see (Rothermel et al., 2014; Brunert et al., 2016).

bawi and Kim, 2018) and integrating activity within and between the two OBs (Schoenfeld and Macrides, 1984; Lei et al., 2006; Kikuta et al., 2010; Esquivelzeta Rabell et al., 2017; Grobman et al., 2018). To date, very few studies have investigated the influence of centrifugal AON projections on OB circuit function; one study demonstrated that optogenetically activating these inputs, depolarizes as well as disynaptically inhibits MTCs, thereby enabling precisely timed spikes in a population of MTCs and shaping of OB output (Markopoulos et al., 2012). By selectively expressing the calcium-sensitive protein GCaMP in AON projection neurons, another study imaged fluorescence signals from AON axon terminals in the OB (Rothermel and Wachowiak, 2014). Using two-photon imaging, different odorants were shown to activate different subsets of centrifugal AON axons, pointing to a surprising richness in the representation of odor information by cortical feedback to the OB. Furthermore, this study revealed insights into the complexity and interplay between different top-down systems: activating classical neuromodulatory centers (the basal forebrain in this case) drove AON inputs to the OB independent of odorant stimulation. These results

demonstrate that top-down centers can also serve as a descending relay for other systems, as previously discussed for the amygdala-locus coeruleus circuit.

The piriform cortex is the primary location where the percept of "odor objects" is thought to be formed (Gottfried, 2010; Wilson and Sullivan, 2011). Piriform inputs to the OB seem to mainly activate granule cells (Price and Powell, 1970; Pinching and Powell, 1972; Davis et al., 1978; Davis and Macrides, 1981; Boyd et al., 2012), which in turn inhibit OB output neurons (Balu et al., 2007; Strowbridge, 2009; Boyd et al., 2012). More recently, top-down projections from piriform cortex in the OB were visualized (Boyd et al., 2015; Otazu et al., 2015), demonstrating that an inactivation of piriform cortex decorrelates mitral, but not tufted cells odor responses (Otazu et al., 2015). These studies did not observe that different odorants activated different subsets of top-down fibers (as demonstrated for the AON), but rather found a general relay of odor information back to the OB, highlighting the unique role of the AON in sensory information processing.

Hormonal and Peptidergic Neuromodulation

Neuromodulation in the OB can also occur via molecules other than classical neurotransmitters (see Table 1). These substances can be subdivided into hormones (signaling molecules of different chemical structure that are secreted in the body and transported via the bloodstream) and neuropeptides (small protein-like molecules released by neurons to communicate with each other). The nomenclature used can be confusing as many of these signaling molecules can act both systemically as hormones, as well as locally in the brain as neurotransmitters (see McClard and Arenkiel, 2018). Therefore, the functional context in which they are discussed, is important.

Hormones, with receptors expressed in the OB, have different sources within the body, e. g. insulin, which is released by pancreatic beta cells in response to feeding state in a glucose-dependent manner (Henquin, 2011), or ghrelin, which is an appetite-stimulating hormone produced primarily by the stomach (Kojima et al., 1999). Importantly, certain blood molecules can more easily pass into the OB compared to other brain areas, since the blood-brain barrier at the OB is more permeable (Ueno et al., 1996). Additionally, density of the capillary network in the glomerular layer is one of the highest reported for the entire brain (Lecoq et al., 2009). Furthermore, there are specialized transport systems for specific hormones (e. g. insulin) that increase the local concentration within the OB (Banks et al., 1999). Thus far, the functions of OB-active hormones have been linked to the metabolic regulation of food intake (see Palouzier-Paulignan et al., 2012). The olfactory system is known for its major contribution to the hedonic evaluation of food (affecting food choice and consumption) and it seems reasonable that olfaction would be modulated according to foraging needs. To date, olfactory-modulating substances including ghrelin, which acts as an orexigenic molecule (i. e. stimulating food uptake), insulin and leptin, which act as anorexigenic molecules (i. e. inhibiting food uptake), and adiponectin, which can regulate insulin sensitivity have been identified. Thoroughly investigated in this respect is insulin, which causes an increase in firing frequency in OB mitral cells and an inhibition of spike adaptation (Fadool et al., 2000). As a substrate, the voltage-activated K+ channel Kv1.3 has been identified which, when phosphorylated by insulin, causes a change in mitral cell excitability.

The number of neuropeptides with modulatory function in the OB is large, however most of them are generated locally within the OB: e. g. pituitary adenylate cyclase-activating polypeptide (PACAP, Irwin et al., 2015) or the circadian rhythm-mediating vasoactive intestinal polypeptide (VIP, Miller et al., 2014). Some neuropeptides like substance P or enkephalins have been observed both locally, as well as in axonal fibers within the OB (Halasz and Shepherd, 1983) and their resulting effects within the OB can not be clearly assigned to either extrinsic or intrinsic sources. Furthermore, neuropeptide-secreting fibers from multiple brain centers project to the OB. One example includes calcitonin gene-related peptide (CGRP)-containing fibers from the trigeminal ganglion, which potentially reduce the activity of OB interneurons, thus mediating an interaction between trigeminal and odorant sensations (Genovese et al., 2016). Another prominent example is oxytocin, which is important for social recognition, and has been shown to induce maternal behavior in female rats when infused into the OB (Yu et al., 1996). Oxytocin release in the forebrain originates from neurons in the paraventricular nucleus of the hypothalamus. It has been recently reported that same-sex social recognition in mice is dependent on oxytocin. In this study oxytocin was shown to activate AON cells projecting to the OB, thereby modulating mitral cell firing (Oettl et al., 2016). However, cells positive for oxytocin receptor can also be found in deeper layers of the OB (see http://www.gensat.org/imagenavigator.jsp?imageID=31777), thereby also potentially enabling direct modulation effects.

Table 1: Extrinsic neuromodulation of the OB.
List of the more prominent examples of extrinsic neuromodulators in the olfactory bulb with their point of origin and their cellular effects within the olfactory bulb. Note that this list is not exhaustive. For many of the listed modulators so far just the receptor presence within the OB has been demonstrated while the modulatory outcome is still unknown.

Neuromodulator	Primary Source	Effect on OB circuit	Publications
Classical Neuromodulatory Projections			
Acetylcholine	Horizontal dorsal Band of Broca (HDB)	Modulation of various cells types	(D'Souza and Vijayaraghavan, 2014)
Noradrenalin	Locus coeruleus (LC)	Increase in signal-to-noise ratio	(Linster and Escanilla, 2018)
Serotonin	Dorsal and Median *raphe nuclei* (RN)	Modulation of various cell types	(Lizbinski and Dacks, 2017)
Cortical Feedback Projections			
Glutamate	Piriform cortex	Activation of granule cells, thereby decorrelation of mitral cell output	(Boyd et al., 2012) (Otazu et al., 2015)
Glutamate	Anterior olfactory nucleus	Monosynaptic activation and disynaptic inhibition of MCs enabling precise spike timing	(Markopoulos et al., 2012)
Glutamate	Entorhinal cortex	Unknown	--
Hormones			
Ghrelin	Stomach	Unknown	--
Insulin	Pancreas	Increase in mitral cell firing frequency	(Fadool et al., 2000)
Leptin	Adipose tissue	Unknown	--
Adiponectin	Adipose tissue	Regulation of insulin receptor expression	(Miranda-Martinez et al., 2017)
Neuropeptides			
Oxytocin	Paraventricular nucleus (PVN) of the hypothalamus	Unknown	--
Orexins	Lateral hypothalamus	Unknown	--
Calcitonin gene-related peptide (CGRP)	Trigeminal ganglion	Reduces the activity of OB interneurons to mediate interaction between trigeminal and olfactory sensations	(Genovese et al., 2016)
Relaxin-3	Nucleus incertus	Unknown	--

Research potential of the olfactory system for sensory neuromodulation

Research on neuromodulation in the olfactory bulb is still in its beginning stages. This is probably due to the fact that the olfactory system has received less attention than other sensory systems, which are considered more significant to humans. Therefore, and especially in combination with new tools in the fields of optogenetics and optophysiology, research on the olfactory bulb as a model system for neuromodulation of early sensory processing, has much untapped potential.

One example is the modulation of sensory processing by attention. While cholinergic neuromodulation has been classically associated with attentional processes, recent data indicate that activity of noncholinergic HDB neurons (GABAergic or glutamatergic) is more strongly correlated with attention, whereas cholinergic neuron activity is correlated with reward and punishment, as well as outcome expectations (Hangya et al., 2015). To further complicate things, even a neurotransmitter co-transmission of HDB neurons has been recently reported (Case et al., 2017). In contrast to deep brain areas, more exposed structures like the olfactory bulb enable simple activity visualization in top-down fibers using optophysiological probes (Rothermel and Wachowiak, 2014). Therefore, they have enormous potential to solve long outstanding questions in the field, e. g. what task(s) engage(s) which top-down system(s).

Another example is the ability to visualize responses of single cells of the OB over an extended time period. Work on early sensory processing in other systems often requires deep brain electrophysiology. However, following individual cells over an extended time period is challenging using this technique. By using high resolution two-photon imaging in the olfactory bulb, cells of interest can be unambiguously identified between recording sessions, and therefore modulatory influences like experience can be investigated on a single cell level (Kato et al., 2012).

In addition, the olfactory system has received much attention recently in the field of artificial intelligence and machine learning. Despite its simplicity, or maybe because of it, olfactory system-based artificial neural networks perform much faster and better at classifying objects in a noisy environment than commonly used visual system-based artificial neural networks (see Srinivasan et al., 2018). This further highlights the need to achieve a deeper understanding of sensory processing in the olfactory system.

Summary

Neuromodulatory processes in sensory systems are of critical importance, enabling all organisms to survive in an ever changing environment. This review provides a short overview on the best understood neuromodulatory systems, using the olfactory bulb as a model system for early sensory processing. It is intended to highlight the complexity of the topic as well as to emphasize the need for further research. Broadening the general definition of neuromodulation enables the inclusion of more modulatory factors, which are of vital importance. We believe that substantial progress in the field of neuromodulation can only be achieved if different fields of expertise (e. g. hormonal and neuronal; different sensory systems) work in close collaboration. In conclusion, we envision an open and interdisciplinary field of neuromodulation, which includes fields and topics ranging from basic to clinical research.

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