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Review

Cortical contributions to olfaction: Plasticity and perception

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Abstract

In most sensory systems, the sensory cortex is the place where sensation approaches perception. As described in this review, olfaction is no different. The olfactory system includes both primary and higher order cortical regions. These cortical structures perform computations that take highly analytical afferent input and synthesize it into configural odor objects. Cortical plasticity plays an important role in this synthesis and may underlie olfactory perceptual learning. Olfactory cortex is also involved in odor memory and association of odors with multimodal input and contexts. Finally, the olfactory cortex serves as an important sensory gate, modulating information throughput based on recent experience and behavioral state.

Keywords: Piriform cortex; Olfactory cortex; Odor perception; Odor discrimination; Odor memory

Contents

1. Introduction

If olfactory cortex is defined as that region of the brain that receives direct input from olfactory bulb second order olfactory neurons, then in terms of relative volume the olfactory cortex is a major component of many vertebrate brains. Olfactory cortex serves as a bidirectional interface between peripheral, largely analytical stages of sensory information processing and higher order, largely synthetic processing stages driving odor-guided behavior. The olfactory cortex receives direct input from olfactory bulb output neurons, as well as extensive input from neocortical and limbic regions conveying multisensory, state-dependent and memorial information. Subregions of the olfactory cortex are often highly interconnected, though there is some regional variation. The olfactory cortex projects to subcortical, limbic and neocortical regions involved in motivated behavior, autonomic reflexes and hormonal modulation. The olfactory cortex also projects back to the olfactory bulb, allowing online feedback modulation of cortical afferent activity. Current evidence suggests that the olfactory cortex is involved in coding odor quality and intensity as might be expected, but also is shaped by past experience to remember familiar odors and their meanings. Finally, the olfactory cortex may serve as a sensory gate, modulating sensory throughput based on past experience and current behavioral state.

This article is an overview of what constitutes the olfactory cortex, what is the synaptic organization of olfactory cortical areas, what is currently known about the sensory physiology of olfactory cortex and the role olfactory cortex may play in odor

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perception and behavior. The reader is also referred to more specialized, detailed reviews of many of these specific topics [1–7].

2. Where is olfactory cortex?

As in all other mammalian sensory systems, olfaction is subserved by multiple cortical areas organized with both hierarchical and parallel circuits. (It should be noted that although olfactory bulb projection sites are generally referred to as cortical, both cortical [pallial] and striatal [subpallial] components exist.) Most of these olfactory cortical areas are heavily interconnected with associational and feedback pathways. Olfactory cortex is traditionally defined as those cortical regions receiving direct input from the main olfactory bulb (the majority of anatomical terminology used here is from Ref. [6]). This definition holds for all vertebrates, though in fish and reptiles the target structures may not be truly cortical in organization. Thus defined, the olfactory cortex can be further subdivided into several major subregions, including the anterior olfactory cortex, tenia tecta, dorsal peduncular cortex, the piriform cortex, the olfactory tubercle (a striatal structure), the cortical amygdala, the agranular insula and the entorhinal cortex. In mammals these structures lie along the ventral and ventrolateral regions of the forebrain. In reptiles (snakes and lizards), the main olfactory bulb makes two major projections to the forebrain, the medial and lateral olfactory tracts, with target structures located in the ventral and lateral forebrain, roughly similar to mammals. In reptiles, the main olfactory bulb primarily projects to lateral cortex, a trilaminar cortical region along lateral/ventrolateral surface of the brain, as well as structures more ventromedial such as the olfactory tubercle [8,9]. In teleost fish such as catfish, the main olfactory bulb projects to a relatively large lateral terminal field in the forebrain, as well as smaller medial and central posterior regions [10]. Thus, in all vertebrates examined, olfactory information is rapidly distributed to multiple central targets.

In mammals, these different subregions of olfactory cortex differ in their projection patterns and local circuitry, thus creating a parallel, though interactive, organization to output from the olfactory bulb. In some cases, this parallel pathway may be initiated by different classes of olfactory bulb output neurons, with tufted cells projecting to more anterior sites and mitral cells projecting also to more posterior sites [11,12]. The known differences in physiology between these two output cell types [13,14], may further distinguish the type of information these parallel components of olfactory cortex process.

The piriform cortex, which is the largest component of the olfactory cortex can also be subdivided into anterior and posterior regions based on lamination patterns and local circuit characteristics [1]. The anterior piriform cortex can be further subdivided into at least a dorsal and ventral component [15], based on relative thickness of lamination patterns and intracortical association connection patterns. These differences in lamination can have important functional consequences as noted below.

In addition to the cortical areas receiving direct input from the main olfactory bulb, the olfactory system also has neocortical

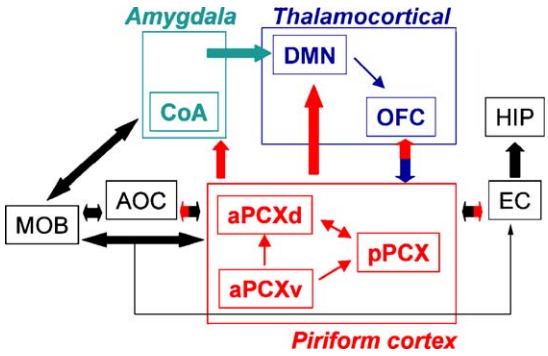

Fig. 1. A schematic representation of the major olfactory cortical areas for which some data on sensory processing exists, and their interrelationships. For simplicity, not all regions are shown, including olfactory tubercle and agranula insula of the pre-frontal cortex. MOB, main olfactory bulb; AOC, anterior olfactory cortex; aPXDd, dorsal anterior piriform cortex; aPCXv, ventral anterior piriform cortex; pPCX, posterior piriform cortex; CoA, cortical nucleus of the amygdala; DMN, dorsomedial nucleus of the thalamus; OFC, orbitofrontal cortex; EC, entorhinal cortex; HIP, hippocampus.

representation. The orbitofrontal cortex and insular cortex both receive input from the olfactory cortex [6]. The orbitofrontal cortex has direct, reciprocal connections with the piriform cortex [16] and also receives indirect piriform cortex input via the dorsomedial nucleus of the thalamus. The dorsomedial nucleus of the thalamus is also a target of amygdala input, and thus receives olfactory information from more than one source before relaying it to orbitofrontal cortex (Fig. 1).

3. Synaptic organization of olfactory cortex

In mammals, the lateral olfactory tract containing axons of olfactory bulb output neurons travels along the ventrolateral surface of the olfactory cortex. The lateral olfactory tract is clearly visible as far posterior as the border of the anterior and posterior piriform cortices. Axon collaterals leave the tract and terminate in the superficial layers of the olfactory cortex, Layer Ia. Both the thickness and termination density of lateral olfactory tract fibers varies substantially across the olfactory cortex [17] (Fig. 2). In olfactory tubercle, posterior piriform cortex and entorhinal cortex, olfactory tract axons form a very thin layer, terminating on the most distal apical dendrites of local pyramidal neurons. In regions of the anterior olfactory cortex and anterior piriform cortex, Layer Ia can be quite prominent, suggesting a more powerful role of cortical afferent input in driving activity of these regions.

Individual mitral/tufted cells appear to terminate in relatively small patches in the anterior olfactory cortex and piriform cortex [18,19], with mitral cells conveying information from different glomeruli (and thus from olfactory receptor neurons expressing different receptor genes) terminating in partially overlapping patches [20]. These patches are expanded to much larger termination zones in olfactory tubercle, entorhinal cortex and, most extremely in posterior piriform cortex [20]. It has been hypothesized that the overlap in mitral/tufted cell termination and potential convergence onto single cortical neurons may contribute to cortical synthesis of complex odorant stimuli into unitary perceptual odor objects.

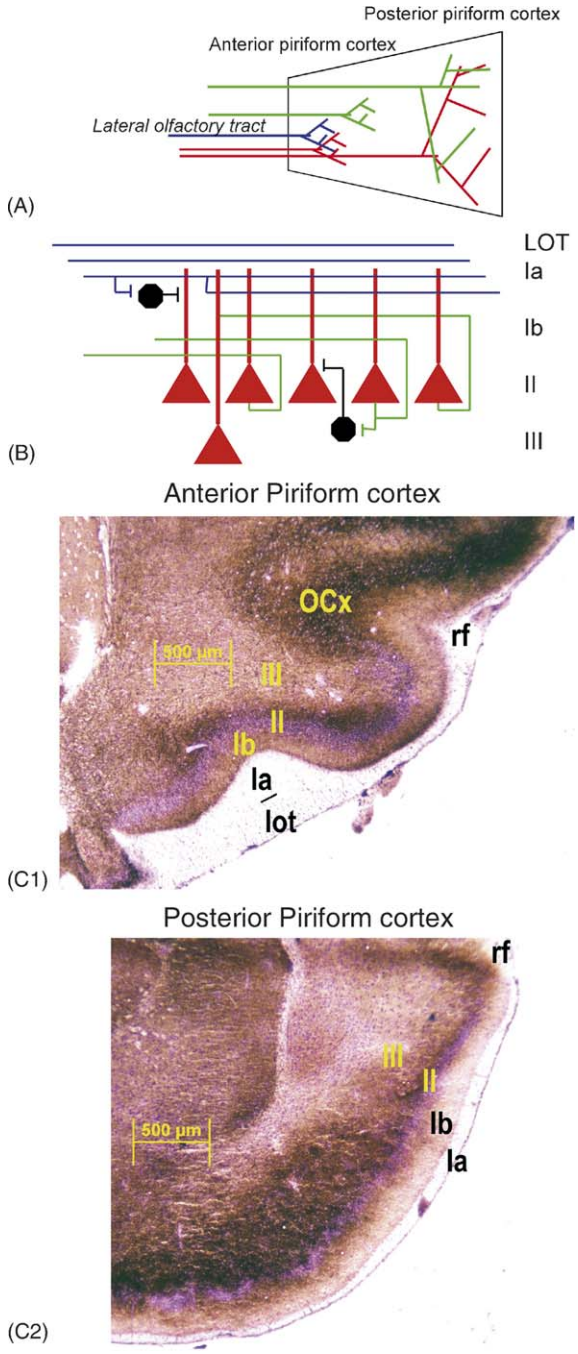

Fig. 2. Piriform cortex circuitry. (A) Mitral cells conveying odor receptor specific-input terminate in patches in the anterior piriform cortex that overlap with termination zones of mitral cells conveying information from other receptors. Mitral cell termination in the posterior piriform is more diffuse and overlapping. (B) A schematic representation of piriform circuitry emphasizing lamination of afferent (blue) and association (green) fiber terminations zones within the trilaminar cortical sheet. Association fibers derive from both local pyramidal neurons and commissural projections. Local feedforward and feedback inhibitory interneurons are shown black. (C) Coronal sections through the anterior and posterior piriform cortex stained with Timm stain for heavy metals which selectively stains intracortical association fiber axons brown. Sections are counterstained with cresyl violet. The proportional differences in association fiber input to neurons in dorsal anterior piriform and posterior piriform cortex relative to ventral anterior piriform cortex changes dramatically between these regions of the cortex. rf, rhinal fissure; OCx, orbital cortex (including orbitofrontal cortex); LOT, lateral olfactory tract.

Olfactory cortical Layer Ib lies just deep to Layer Ia and includes intracortical association and commissural axons and their terminations. The boundary between Layers Ia and Ib is remarkably distinct, and the relative thickness of these two layers is shaped by postnatal experience in a competitive manner [21,22]. The intracortical association fibers are axon collaterals of cortical pyramidal cells, with branches of individual pyramidal cells traveling both anterior and posterior for several millimeters in rats [23,24]. Axon collaterals of individual cells appear broadly distributed, without the degree of patchiness evident in mitral/tufted cell axons in anterior piriform cortex. A single pyramidal cell may contact up to 3000 other pyramidal neurons within the piriform cortex [25]. Furthermore, an individual axon and its collaterals may travel to several subregions of olfactory cortex, as well as to orbitofrontal cortex and back to the olfactory bulb [23].

The lamination of cortical afferent and association fiber input to olfactory cortex results in afferent input to the distal dendrites and association input to the proximal and basal dendrites of cortical pyramidal cells. Given the electrotonic characteristics of piriform cortical apical dendrites, this results in association fiber input being at least as influential on cortical pyramidal cell activity as afferent input, if not more so, depending on the specific location within cortex [26]. For example, in posterior piriform cortex, where afferent input is less dense and limited to a very narrow superficial zone, association fiber input should be the dominant factor in driving these cells. This is an important distinction when interpreting the degree to which cortical neural activity reflects ‘simple’ cortical afferent input or more highly ‘complex’ intracortical processing. Furthermore, the differences in relative density of afferent and association fiber synapses and in local network connectivity between different areas within the piriform cortex and within different regions of the greater olfactory cortex most likely lead to functional heterogeneity of olfactory cortical subregions which are just now beginning to be explored.

There are several subclasses of principle neurons within the piriform cortex. Layer II of the olfactory cortex is composed of the somata of pyramidal neurons with apical dendrites extending into Layer Ia and for the majority of cells, basal dendrites extending into Layer III. A subclass of pyramidal neurons with somata located in the superficial Layer IIb, semilunar cells, lack basal dendrites and have dendrites with large spines primarily located in Layer Ia. Interestingly, survival of semilunar cells is exquisitely sensitive to olfactory bulb input, with dramatic, selective apoptosis occurring within hours after olfactory bulbectomy and within days after naris occlusion [27–29]. No apoptosis is detected in other pyramidal cell types in piriform cortex in the same condition. The third class of pyramidal cells are situated deeply in Layer III, with dendrites extending to Layer Ia. Layers III and II pyramidal cells differ in their electrophysiological characteristics (e.g., deep pyramidal cells have a lower spike threshold than superficial pyramidal cells [30]). The differential role of these three principle cell types, however, in information processing and sensory coding have not been explored.

In addition to pyramidal neurons, there are several classes of inhibitory interneurons mediating both feedforward and feed-

back inhibition of pyramidal cells. Inhibition is directed at both somatic and dendritic compartments, regulates pyramidal cell excitability, responsiveness to afferent input, magnitude of NMDA-mediated currents and controls spike timing [31-34].

Finally, olfactory cortex is a major target of many modulatory inputs including acetylcholine, norepinephrine and serotonin. These inputs have differential effects on pyramidal cells versus interneurons [35,36], afferent versus association fiber synapses [37,38] and modulate cortical synaptic plasticity [39] and response to sensory input [40,41]. Interestingly, the anterior piriform cortex also appears to be directly sensitive to basal amino acid levels and is a critical site for regulation of amino acid dietary intake [42,43].

This circuitry – patchy afferent input and diffuse, often dominant association fiber network – creates an ideal substrate for a content addressable and/or distributed memory system [34,44,45]. A problem faced by olfaction is that most biological odors are complex mixtures, varying in intensity, and almost always experienced against changing backgrounds. However, despite this potential variation in stimulus input, the olfactory system allows perception of relatively stable, highly synthetic perceptual objects. The synaptic organization of the olfactory cortex may directly contribute to this perceptual outcome. Put very simply, it is hypothesized that prior experience with odors (i.e., a specific pattern of afferent input) modifies synaptic strength of association fiber synapses (e.g., through associative long-term potentiation) such that subsequent exposure to that stimulus, or exposure to a slightly degraded version of that stimulus (e.g., background odors present) allows the cortex to recreate (remember) the stimulus as a whole. In addition, the close association of olfactory cortex with limbic circuits and frontal cortex means that these synthetic percepts often include integral multimodal and hedonic components.

4. Olfactory cortex physiology

The olfactory cortex and other, second-order cortical regions receiving olfactory input are where the analytical chemistry that occurs within the nose is translated into the incredibly information- and emotion-rich experience that is olfaction. Based on lesion, functional imaging and electrophysiological data in humans and other animals, primary and secondary olfactory cortical areas contribute to: odor stimulus identification and recognition [46–57], intensity coding [58,59]; stimulus localization [60–62]; stimulus cross-modal associations [63–65]; stimulus hedonics [47,49,66–69]; habituation and other forms of sensory gating [70–74]. Some of these functions are localized to specific regions or even sub-regions of olfactory cortex (e.g., Refs. [75,76]), and some cortical functions may be lateralized, at least in humans [77]. Given the breadth of these identified cortical functions, understanding the sensory physiology of the olfactory cortex is a necessary prerequisite for understanding olfactory perception.

Individual neurons in piriform cortex and the orbitofrontal cortex respond to multiple odors [78–80], and piriform cortex neurons can display odorant receptive fields similar to mitral/tufted cells when tested with homologous odorant series [80]. In both anesthetized [71,76] and unanesthetized [56] rat piriform cortex, excitatory responses appear most common (though see Ref. [54]). Low spontaneous activity rates may reduce detection of suppressive responses, though even in intracellular recordings odorant-evoked purely hyperpolarizing responses are relatively rare [71,81]. Both piriform cortex odorant-evoked responses and spontaneous activity are often strongly in phase with respiration, and hyperpolarization can be observed between respiratory cycles (see Fig. 3). Odorant evoked depolarization can reach amplitudes of 20 mV or more, with instantaneous firing frequencies of greater than 100 Hz [71]. This pattern of odorant-evoked activity – high frequency bursts in phase with a theta frequency respiratory cycle – is ideal for inducing associative synaptic plasticity which, as discussed below may be critical for cortical function and odor discrimination.

In contrast to the olfactory bulb, cells responding to particular odorants are widely scattered in the piriform cortex [82,83], though there may be some regional variation in odorant specific responsiveness in anterior piriform cortex [51]. In the first demonstration of odor-evoked spatial patterns in the piriform cortex [51] – after many repeated failed attempts to detect such patterns [82,83] – the observed odorant topogra-

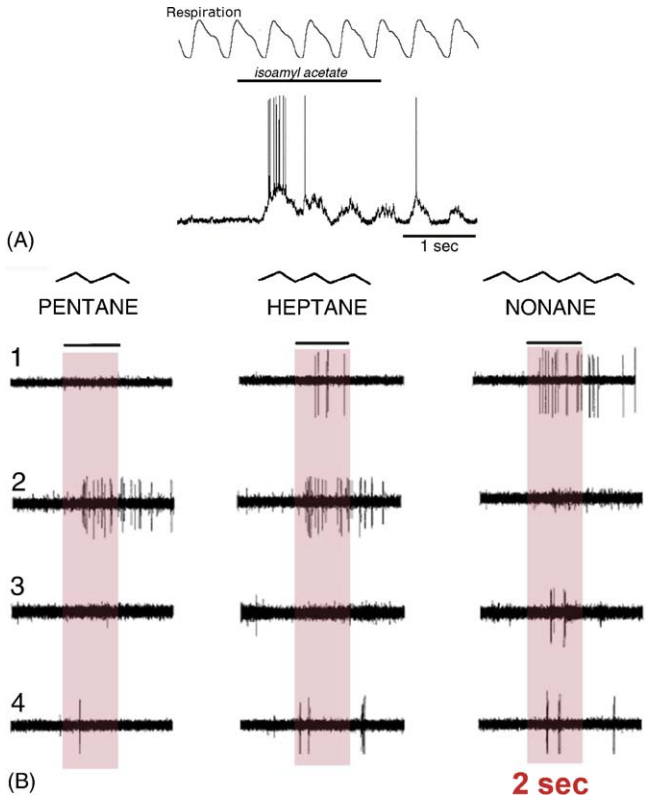

Fig. 3. Examples of anterior piriform cortex neural responses to odorant stimulation. (A) An intracellular recording from a layer II/III neuron in anterior piriform cortex showing odor-inhalation-evoked depolarizations that rapidly adapt over successive inhalations. Note the high-frequency subthreshold membrane potential oscillations riding on top of the respiratory entrained potentials. (B) Responses of four different piriform cortical neurons to 2 s stimuli presented during the red shaded region. Note that, similar to reports of olfactory receptor neurons and mitral/tufted cells, piriform cortical neurons respond differentially to odorants varying along a specific dimension such as carbon chain length.

phy is subtle in anterior piriform. Using a quantitative analysis of odorant-evoked *c*-fos patterns in mice, Zou et al. [51] found that individual odorants activate neurons across large (20–25%), overlapping portions of the anterior piriform cortex, and that odorant-evoked cortical spatial patterns are similar between hemispheres and across animals. Odor-specific spatial patterns of cortical activity might be predicted based on the patchy termination of afferent input [20], as would a muting and expansion of such patterns given the broad distribution of intracortical association fibers [23].

Odorant intensity may also influence spatial patterns of activation within the piriform, with more intense odorants activating larger regions of cortex [51,59], and with more anterior sites showing lower thresholds than more posterior sites [59]. Sugai et al. [59] used both intrinsic signal imaging and single-unit recording in guinea pig anterior piriform cortex to examine the spatial distribution of odorant activation with different odorants and intensities. They found, as did Zou et al. [51] that as intensity increased the spatial extent of cortical activation expanded, and further that this expansion moved preferentially in a caudal direction. This latter point may be indicative of the differential input from tufted and mitral cells to anterior and posterior olfactory cortical regions, and the distinct physiology of these two afferent cell types [11,13,14]. For example, tufted cells tend to have lower thresholds and are more sensitive to olfactory nerve input than mitral cells [13,14].

Finally, subregions of olfactory cortex may differ in their discrimination abilities. In response to a defined series of odorants, neurons in posterior piriform cortex [76] and orbitofrontal cortex [78] are reported to be more selective than cells in anterior piriform cortex, possibly suggesting increasing odorant discrimination abilities as information is synthesized and refined as it moves through cortex.

Olfactory cortex odor responses, synaptic physiology and neurocircuitry are all strongly influenced by previous odor stimulation [84]. For example, cortical odorant-evoked responses show rapid, odorant-specific adaptation in humans and rats [56,70,71] (see below). In addition, work in our laboratory has demonstrated that odorant discrimination ability of individual piriform cortical neurons is modified by previous odorant exposure. Specifically, cortical neurons exposed to novel binary mixtures show strong cross-adaptation between those mixtures and their components, suggesting poor discriminability. Prior exposure to the binary mixture however, reduces subsequent cross-adaptation to the components [85], suggesting that the mixture is now treated by cortical neurons as distinct from its components. The effects of odorant experience on cortical odorant discrimination can be blocked by cortical application of scopolamine, a cholinergic muscarinic receptor antagonist [86]. Importantly, prior odorant experience also enhances behavioral odor discrimination (olfactory perceptual learning) in rats [87] and humans [88], which can also be prevented by scopolamine [87]. Although mitral/tufted cells in the olfactory bulb do show experience-induced changes in odorant responses [89] and odorant receptive fields [90], they do not appear capable of discriminating familiar mixtures from their components in the same manner as piriform cortical neurons [85].

The experience-dependent synthesis of odorant components by cortical circuits into unique odor objects distinct from those components may be a major function of olfactory cortex in odor perception. Both humans and animals treat complex odor mixtures as single entities and have limited ability to identify components within those mixtures [91,92]. This synthetic processing of odors has been compared to face or object recognition in vision, and the piriform cortex may play a critical role in this synthetic/configural processing [34,93].

In addition to synthesizing co-occurring odorant features into stored representations of odor objects, the olfactory cortex and orbitofrontal cortex also appear to be involved in storing memories of odors and their non-olfactory associations. Neurons in both the olfactory cortex and orbitofrontal cortex respond to a variety of contextual and non-olfactory stimuli within a behavioral training paradigm [54,65,94]. For example, neurons in both anterior piriform cortex and orbitofrontal cortex respond to non-olfactory stimuli associated with approaching the odor sample port, or water reward port, or while drinking water [54,65]. This multimodal convergence within olfactory cortical areas may contribute to the unique perceptual properties of odors, including their mixture with taste in flavor sensations and their often strong emotional content. Furthermore, the multimodal convergence appears to not be ephemeral, but rather leads to long-lasting changes in cortical circuit function and structure, presumably contributing to the long-term memory of the experienced odors.

For example, Barkai and co-workers have used an olfactory discrimination task to identify changes induced in the piriform cortex. Repeated odor discrimination learning can lead to rule learning, wherein new odor pairs are learned often within a single trial [95]. Recording from in vitro slices obtained from animals at different stages of rule learning, Barkai's laboratory has demonstrated changes in both synaptic and membrane biophysics that correlate with learning [96,97]. Furthermore, dendritic spines on piriform cortical pyramidal neurons are also modified. Spines along the proximal dendrites, receiving intracortical association fiber input are increased in density, while the density of distal dendritic spines, receiving afferent input is decreased [98]. These results further emphasize the importance of intracortical association connections in storing sensory representations. While afferent input can demonstrate use-dependent plasticity [99,100], association connections appear more plastic [98,101]. It should also be noted that in other behavioral paradigms, there appear to be differences in plasticity and learning associated changes between anterior and posterior piriform [53,102], with posterior regions showing greater plasticity, though this is an area in need of further study.

The above findings suggest that the olfactory cortex and orbitofrontal cortex serve important roles in odor discrimination, formation of synthetic odor objects, and in odor memory. A final identified role for olfactory cortex is as a sensory gate – modulating olfactory information throughput based on recent stimulation history and behavioral state. As noted above, the piriform cortex rapidly adapts to odorants, with response depression occurring within seconds of odor onset [70,71] (see Fig. 4). This adaptation is of cortical origin because it occurs despite relatively main-

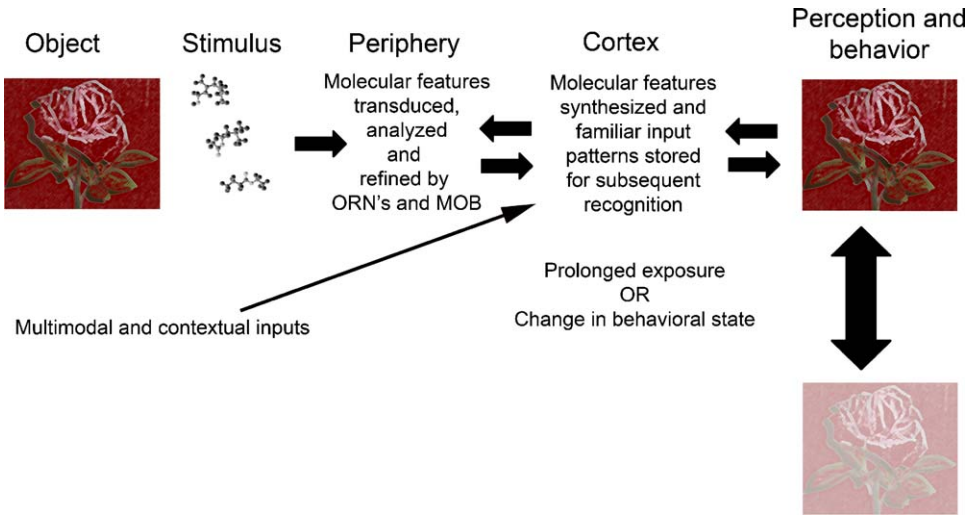

Fig. 4. Summary of the hypothesized role of the olfactory cortex in odor perception. Based on both anatomical and sensory physiological evidence, the olfactory cortex synthesizes co-occurring odorant features, extracted by the receptor sheet and olfactory bulb into unique odor objects. This synthesis involves synaptic plasticity and allows subsequent exposure to familiar combinations of odor features to be processed as odor objects. Perceptual odor objects may include multimodal components. The olfactory cortex also functions as a sensory gate, modulating information throughput based on recent stimulation history and behavioral state.

tained input from the olfactory bulb [71]. Cortical odor adaptation is associated with afferent synaptic depression and this depression is mediated by pre-synaptic group III metabotropic glutamate receptors on mitral/tufted cells axon terminals [100]. Blockade of these receptors in vitro prevents afferent synaptic depression [100], and in vivo prevents habituation of a simple odor-evoked reflex [103] and reduces habituation of odor investigation [107]. Together these findings argue that odor habituation is largely a cortical phenomenon, despite the adaptation that occurs more peripherally. Piriform cortical adaptation is also highly odorant-specific, and recent work suggests that this adaptation allows separation of odorants from background [104], similar to figure-ground separation in other sensory systems.

In addition to adaptation, information flow through cortical circuits can also be gated by arousal or attention. In urethane anesthetized rats, for example, neocortical activity can alternate between slow-wave and fast-wave states, putatively comparable to slow-wave sleep and a more alert behavioral state, respectively. Using single-unit and intracellular recording techniques, Murakami et al. [74] have reported that piriform cortical neurons are far more responsive to odors and afferent input during fast-wave states than during slow-wave states. Similar shifts were not observed in olfactory bulb evoked activity. This state-dependent shift is associated with a relative hyperpolarization of cortical neurons during the slow-wave state, which may occur as the result of changes in modulatory input from brainstem and basal forebrain nuclei. In accordance with this hypothesis, Bouret and Sara [41] have reported that stimulation of the locus coeruleus (as might occur during arousal or enhanced attention) enhances piriform cortical unit activity entrainment to afferent input and odor responsivity. Thus, through processes such as adaptation and state-dependent changes, cortical output for a given afferent input may vary, directly controlling odor-guided behaviors.

5. Summary

As in other sensory systems, increasing evidence suggests that the penultimate computations necessary for olfactory stimulus discrimination and perception occur within cortical circuits. Odorant stimulation evokes dispersed activation of neurons within the olfactory cortex [51,82], in contrast to the highly odor specific spatial patterns of activation within the olfactory bulb. Through overlapping afferent inputs and a broad intracortical association fiber system, the olfactory cortex synthesizes odorant features extracted and refined by more peripheral circuits into unique configural odor objects. This synthesis requires experience and neural plasticity–without prior experience or with synaptic plasticity disrupted, both cortical and behavioral odor discrimination are impaired [85,87]. In addition to learning new odor objects, the olfactory cortex and orbitofrontal cortex are involved in memory for past odors and their multimodal associations [2,94]. Finally, the olfactory cortex is a critical mediator of olfactory sensory gating, involved in both habituation and state-dependent modulation of odor responsiveness [74,103].

In addition to these intracortical processes, it must be emphasized that the olfactory cortex sends strong feedback projections to the olfactory bulb. Odor responses within the olfactory bulb have long been known to be modulated by centrifugal inputs [105,106]. Thus, future work should not only focus on how and what the olfactory cortex adds to olfactory information processing, but also on how olfactory cortical processing shapes its own afferent input from the olfactory bulb.

Acknowledgements

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