Published in final edited form as:

Perception. 2017 ; 46(3-4): 320–332. doi:10.1177/0301006616663216.

The olfactory mosaic: bringing an olfactory network together for odor perception

Emmanuelle Courtiol and Donald A Wilson

Emotional Brain Institute, Nathan Kline Institute for Psychiatric Research, Orangeburg, USA and Department of Child and Adolescent Psychiatry, New York University Langone Medical Center, USA

Abstract

Olfactory perception and its underlying neural mechanisms are not fixed, but rather vary over time, dependent on various parameters such as state, task or learning experience. In olfaction, one of the primary sensory areas beyond the olfactory bulb is the piriform cortex. Due to an increasing number of functions attributed to the piriform cortex, it has been argued to be an associative cortex rather than a simple primary sensory cortex. In fact, the piriform cortex plays a key role in creating olfactory percepts, helping form configural odor objects from the molecular features extracted in the nose. Moreover, its dynamic interactions with other olfactory and non-olfactory areas are also critical in shaping the olfactory percept and resulting behavioral responses. In this brief review, we will describe the key role of the piriform cortex in the larger olfactory perceptual network, some of the many actors of this network, and the importance of the dynamic interactions among the piriform-trans-thalamic and limbic pathways.

Keywords

Piriform cortex; network; olfactory perception; limbic connection; thalamocortical; odor

Introduction

A mosaic is not defined by only one tile but rather by a specific assembly of tiles and depending on how those tiles are arranged, different mosaics can emerge. By analogy, the brain is like a sculptor, to perceive its environment, it does not rely only on one neuronal point but on an ensemble of different neuronal areas. Then, like a sculptor, it will use and dynamically re-arrange the network of neural areas involved to generate percepts and behaviors. This notion of network was well described by Walter J. Freeman: “*perception cannot be understood solely by examining properties of individual neurons, a microscopic approach that currently dominates neuroscience research. We have found that perception depends on the simultaneous, cooperative activity of millions of neurons spread throughout expanses of the cortex. Such global activity can be identified, measured and explained only if one adopts a macroscopic view alongside the microscopic one*” [(Freeman, 1991), p.78].

Dr. Freeman, who recently passed away (2016), was a precursor who introduced new concepts of neural dynamics in the understanding of perception and revealed them in the olfactory system (Freeman, 1960). The olfactory system was a perfect model to study those concepts due to its relative simplicity, unique anatomy with the first olfactory brain relay being only one synapse away from the external world and the presence of strong oscillatory network activity. Olfactory receptor neurons project directly to the olfactory bulb which in turn projects to the primary sensory areas including the piriform cortex (PCX), olfactory tubercle, olfactory peduncle, lateral entorhinal cortex and the cortical nucleus of the amygdala (Cleland & Linster, 2003; Haberly & Price, 1977; Price & Powell, 1971; Shepherd, Chen, & Greer, 2004). Freeman demonstrated that the olfactory bulb was not a passive relay in the olfactory pathway but rather a key area in a larger network producing the olfactory percept. He showed that the spatial pattern of olfactory bulb neural activity, recorded using an array of electrodes, “*did not reflect conformal mapping of odor stimulus to neural activity response, but were determined by state variables of the animal related to olfactory conditioning history*” [(Freeman & Schneider, 1982), p.44]. Those patterns of activity were especially dependent on centrifugal input and notably those of the PCX shaping the olfactory bulb output (Gray & Skinner, 1987; Martin, Gervais, Chabaud, Messaoudi, & Ravel, 2004; Neville & Haberly, 2003). The PCX is the largest of the olfactory cortical areas and receives direct input from olfactory bulb principal neurons. Following the principles of Freeman in the olfactory bulb, we will describe the PCX not only as a critical structure in olfactory perception but also as a central node in a larger network which includes, though is not limited to, the orbitofrontal cortex, the mediodorsal thalamic nucleus, the amygdala, and the entorhinal cortex.

Brief review on PCX

The PCX is a three layered paleocortex that brings together input from the olfactory bulb and many other areas from the rest of the brain. It is a simple cortex, with Layer I composed of the pyramidal cell dendrites, olfactory bulb principal cell axons, as well as intrinsic intracortical association fiber axons. Layer II consists of the pyramidal cell body layer and Layer III is composed of pyramidal cell basal dendrites, somas of deep pyramidal cells and interneurons (Neville & Haberly, 2004). Based on its connectivity, cytoarchitecture, and activity, the PCX has been divided into two subdivisions: anterior and posterior (Haberly & Price, 1978; Kadohisa & Wilson, 2006b; Litaudon, Amat, Bertrand, Vigouroux, & Buonviso, 2003; Litaudon & Cattarelli, 1995).

In addition to receiving major input from the olfactory bulb, the PCX receives a variety of neuromodulatory inputs including acetylcholine and monoamines (Datiche & Cattarelli, 1996; Linster & Hasselmo, 2001). The PCX projects to a variety of cortical targets, including the orbitofrontal cortex, lateral entorhinal cortex and olfactory tubercle, as well as the amygdala and the mediodorsal thalamic nucleus (Chen et al., 2014; Haberly, 2001; Illig, 2005; Price, 1985; Shipley & Ennis, 1996). Importantly, the PCX has reciprocal connections with most of those areas which are involved in functions such as memory and emotion (Gottfried, 2010; Haberly, 2001; Illig, 2005).

PCX responses to various odorants can be observed in both anesthetized and awake animals at the single neuron level (Chen, Barnes, & Wilson, 2011; Litaudon et al., 2003; Rennaker, Chen, Ruyle, Sloan, & Wilson, 2007; Schoenbaum & Eichenbaum, 1995a; Wilson, 1998a) as well as in humans using fMRI (Gottfried, 2010; Sobel et al., 1998). Contrary to the olfactory bulb, odorants are not spatially represented in the PCX but are represented by ensemble patterns of neurons across the PCX (Cattarelli, Astic, & Kauer, 1988; Howard, Plailly, Grueschow, Haynes, & Gottfried, 2009; Illig & Haberly, 2003; Poo & Isaacson, 2009; Rennaker et al., 2007; Stettler & Axel, 2009). Odorant response in the PCX can quickly habituate (Sobel et al., 2000; Wilson, 1998a, 1998b) meaning that the PCX is able to serve as a filter of the olfactory input from background (Kadohisa & Wilson, 2006a). In addition, PCX neuron ensembles have been demonstrated to perform pattern completion – *where the response of an ensemble of neurons to a mixture can persist even if one component of that mixture is removed*- allowing perceptual stability (Barnes, Hofacer, Zaman, Rennaker, & Wilson, 2008). The PCX ensemble of neurons can also support odor discrimination learning – *with the activity in the PCX being progressively decorrelated between odors as rats/humans learn to discriminate or to associate the odor with an aversive stimulus* - which correlates with behavior (Chapuis & Wilson, 2011; Gottfried, 2010; Li, Howard, Parrish, & Gottfried, 2008; Wilson & Sullivan, 1994). Not only does the PCX support odor categorization, pattern completion and odor discrimination learning, but it has also been demonstrated that PCX neurons encode the value (e.g., rewarded/not-rewarded) associated to the odor (Calu, Roesch, Stalnaker, & Schoenbaum, 2007; Roesch, Stalnaker, & Schoenbaum, 2007). The information of both the identity and the value of the odor are contained in the temporal firing of PCX neurons (Gire, Whitesell, Doucette, & Restrepo, 2013). Importantly, PCX spiking activity has been demonstrated to display strong coupling with local field potential oscillations [LFP; (Litaudon, Garcia, & Buonviso, 2008)], and these oscillations have been shown to play a key role in encoding in the analogous regions of the insect olfactory system (Perez-Orive et al., 2002). At the network level, the PCX displays large fast LFP oscillations spontaneously and in response to odors (Bressler, 1984; Freeman, 1960; Kay & Freeman, 1998). Those oscillations have been shown to vary according to the animal's behavior and even to the past experience of the animal (Chapuis & Wilson, 2011; Freeman, 1960; Martin, Gervais, Messaoudi, & Ravel, 2006; Zibrowski & Vanderwolf, 1997). From the PCX single neuron activity or the LFP point of view, it is clear that the PCX is not encoding only the odor identity but rather multiple features of the odorant 'context'. This ability may come from the critical location of the PCX in the olfactory network, how and which areas of the network are recruited and how the PCX is able to dynamically be driven by and communicate with other brain areas depending on the learning, the state, the task demand, or the period of the task. As an example, in a conditioned odor aversion task, a network including olfactory bulb, PCX, basolateral amygdala and orbitofrontal cortex is activated but depending on the way the odor was sampled during acquisition, ortho vs. retronasally, the network can change and selectively include infralimbic and insular cortical areas during retrieval [(Chapuis et al., 2009); Fig. 1]. The olfactory network is dynamic and differential coupling between PCX and other neuronal areas seem critical (Wilson & Sullivan, 2011). We will briefly review two main axes of the extended olfactory network: the thalamocortical and limbic connections of the PCX.

Extended olfactory network

Cortico/Thalamo-cortical network

Orbitofrontal-piriform cortical connections—The orbitofrontal cortex has reciprocal connections with the PCX, especially the anterior PCX (Haberly, 2001; Illig, 2005). A number of functions have been ascribed to the orbitofrontal cortex including decision making, reward valuation, and working memory (Bechara, Damasio, & Damasio, 2000). The orbitofrontal cortex may also be a critical site for multisensory convergence underlying aspects of flavor processing due to its sensitivity to olfactory, gustatory, visual and mouth feel sensory inputs (Kadohisa, Rolls, & Verhagen, 2005). During odor discrimination tasks, orbitofrontal cortex single-units modify their firing activity in response to approach to the sampling and goal ports, as well as during odor sampling itself (Feierstein, Quirk, Uchida, Sosulski, & Mainen, 2006; Schoenbaum & Eichenbaum, 1995a, 1995b). Thus, the orbitofrontal cortex and PCX are active during many of the same sensory-behavioral moments, but contribute different kinds of information to the overall perceptual outcome (Howard, Kahnt, & Gottfried, 2016).

Of particular interest here is that the orbitofrontal-PCX connection is dynamic. Thus, knowing this cortical connectome, even in detail (Chen et al., 2014), only provides the first step toward understanding how these regions interact. For example, the gamma band LFP coupling between the PCX and orbitofrontal cortex can be present during wakefulness, but does not occur during sleep periods (Mori, Manabe, Narikiyo, & Onisawa, 2013). In addition to this state dependence, the PCX-orbitofrontal cortex connection is also experience-dependent. In fact, Cohen, Wilson, and Barkai (2015) compared changes in synaptic input to the PCX from the olfactory bulb and from the orbitofrontal cortex during odor rule learning. Odor rule (or set) learning occurs when animals are trained on a difficult odor discrimination task. Odor rule learning results in a myriad of synaptic and biophysical changes within the PCX (Barkai, 2014; Saar, Reuveni, & Barkai, 2012), but also modifies synaptic connectivity between the PCX and some of its monosynaptic partners. Specifically, during acquisition of odor rule learning the olfactory bulb synaptic input to the PCX was potentiated, and simultaneously the orbitofrontal cortex input to the PCX was depressed [(Cohen, Wilson, et al., 2015); Fig. 1]. Upon acquisition of criterion performance and initial training of the next odor pair (switching to a new odor pair results in very rapid conditioning), both pathways returned to basal synaptic strength. Pseudo-trained animals showed no change in either pathway over the course of repeated, daily odor exposure. One interpretation of these results is that during active, difficult odor discrimination training, the PCX is most strongly influenced by sensory input, and is able to suppress top-down signals from orbitofrontal cortex that may interfere with odor coding. A similar phenomenon may occur in the lateral entorhinal cortex input to PCX described in the limbic connections section below.

In addition to the direct PCX-orbitofrontal cortex pathway, both structures are also involved in a larger triad including the thalamus that can be dynamically recruited during the olfactory task.

Olfactory trans-thalamic connections—While it is generally assumed that olfaction is independent from the thalamus, evidence since the 1980's has returned the thalamus, specifically the mediodorsal thalamic nucleus, to the olfactory pathway. This nucleus receives direct input from primary olfactory areas, including the PCX, and secondary olfactory areas (Bay & Cavdar, 2013; Price & Slotnick, 1983). The mediodorsal thalamus also has reciprocal connections with the orbitofrontal cortex forming the olfactory trans-thalamic pathway (Krettek & Price, 1977).

Mediodorsal thalamic neurons have been shown to display responses to different odorant categories (Courtiol & Wilson, 2014, 2016; Imamura, Onoda, & Takagi, 1984; Kawagoe et al., 2007; Yarita, Iino, Tanabe, Kogure, & Takagi, 1980). Moreover, odor presentation induces the emergence of LFP beta frequency oscillations in urethane-anesthetized rats (Courtiol & Wilson, 2014). Our lab demonstrated that the emergence of beta oscillations in the mediodorsal thalamus follows those in the PCX and that a subset of thalamic neurons can fire in phase with PCX beta oscillations in anesthetized rats (Courtiol & Wilson, 2014). As reported in other PCX targets (Manabe, Kusumoto-Yoshida, Ota, & Mori, 2011; Wilson & Yan, 2010), we also observed that the relationship between the mediodorsal thalamus and PCX is state-dependent with increased coherence during slow wave activity compared to fast wave activity (Fig. 1).

Functionally, the roles of the mediodorsal thalamus in olfaction are still not clearly defined, although studies of mediodorsal thalamic damage in both humans and animal models demonstrate its contribution in various tasks: from perception and learning to discrimination (Courtiol & Wilson, 2015; Sapolsky & Eichenbaum, 1980; Tham, Stevenson, & Miller, 2009). The contribution of the mediodorsal thalamus in this large spectrum of functions suggests that it may be differentially involved in the olfactory network depending on the task demand. As an example, while rats with mediodorsal thalamic damage are not impaired to perform simple odor discrimination task, they require more trials to attain performance in more challenging olfactory discrimination tasks (Eichenbaum, Shedlack, & Eckmann, 1980; Slotnick & Kaneko, 1981; Staubli, Schottler, & Nejat-Bina, 1987). The dynamic recruitment of the mediodorsal thalamus in olfaction was further highlighted in humans in an odor attention task. Using fMRI, Plailly, Howard, Gitelman, and Gottfried (2008) demonstrated that the network coherence from PCX to mediodorsal thalamus and from mediodorsal thalamus to orbitofrontal cortex is enhanced during selective attention to odors. The changes of coupling within the olfactory trans-thalamic pathway were also observed at the single trial level. We recorded mediodorsal thalamic single-units and LFPs in PCX and orbitofrontal cortex in rats performing a two-alternative odor choice discrimination task [(Courtiol & Wilson, 2016); Fig. 1]. We not only demonstrated that mediodorsal thalamic units display odorant selectivity in this task but also that the connectivity within the olfactory trans-thalamic pathway depends on the task period with enhanced mediodorsal thalamus-PCX coupling during odorant sampling and enhanced mediodorsal thalamus-orbitofrontal cortex coupling during the decision/goal approach compared to baseline and pre-sampling periods.

Thus, the olfactory network is more extended and distributed than was originally thought, and can transiently include the thalamus depending on the state, the task demand and the

period of the task. As we will describe in the next section, this dynamic holds true for another important olfactory axis: the PCX-limbic connections.

Limbic connections

The PCX has very strong reciprocal connections with a number of classical limbic regions. In fact, the PCX is included as a component of the limbic system in early descriptions (Papez, 1937). Two regions that have received particular attention in terms of their inter-relationship with the PCX and odor coding and perception are the amygdala and lateral entorhinal cortex.

While several groups have examined olfactory related processes within these structures, here our attention is on how they dynamically interact with the PCX and how activity in these regions shapes PCX function. Activity in the amygdala, especially the basolateral (Al Ain et al., 2016; Grace & Rosenkranz, 2002) and cortical nuclei (Root, Denny, Hen, & Axel, 2014) of the amygdala is shaped by innate and learned odor valence and odor intensity (Anderson et al., 2003). The basolateral amygdala receives direct input from the PCX, and sends a reciprocal connection back to the anterior and posterior PCX. The strongest amygdala input is to the posterior PCX in rodents (Majak, Ronkko, Kemppainen, & Pitkanen, 2004).

As observed in the thalamocortical network, PCX-amygdala connectivity is state dependent with for example, higher coherence between the PCX and basolateral amygdala (as well as neocortex), during slow wave compared to fast wave activity [(Wilson, Hoptman, Gerum, & Guilfoyle, 2011; Wilson & Yan, 2010); Fig. 1]. In addition, activity in the amygdala can also shape the ongoing PCX odor response. Indeed, using *in vitro* optogenetics to selectively stimulate basolateral input fibers within the PCX, Luna and Morozov (2012) demonstrated that both interneurons and pyramidal cells are targets of excitatory amygdala input in layers Ib, II and III. This suggests that amygdala activation, for example in response to emotional stimuli including odors, could have complex effects on PCX odor coding. In fact, using *in vivo* optogenetics to selectively stimulate basolateral input fibers within the PCX of anesthetized mice, our lab found that activation of amygdala efferent fibers significantly modulates posterior PCX single-unit responses to artificial, novel odorants (Sadrian & Wilson, 2015). In accord with the diversity of cellular targets of amygdala inputs, the effect on odor responses was heterogeneous, with some single-units showing enhancement of odor-evoked responses and some (the majority) showing odor response suppression. Odor fear conditioning modifies PCX single-unit odor responses (Chen et al., 2011) in rodents and PCX BOLD signals in humans (Li et al., 2008). The fact that amygdala activation also modulates PCX responses raises the possibility that these learned PCX responses may reflect both changes within the PCX itself, as well as plasticity of amygdala input modulation. We are currently examining plasticity of the basolateral amygdala pathway to the PCX and its role in shaping responses to odors with learned hedonic associations.

A second major source of limbic feedback to the PCX is the lateral entorhinal cortex. The entorhinal cortex receives direct input from the olfactory bulb and PCX and is generally considered to be the primary source of input to the hippocampal formation. However, the lateral entorhinal cortex also sends a strong projection back to the PCX and olfactory bulb (Shiple & Adamek, 1984). Recent work has demonstrated that separate populations of

lateral entorhinal cortex layer II neurons project to the hippocampal formation and back to the olfactory system (Leitner et al., 2016). Furthermore, the neurons projecting back to the olfactory system express more broad odor tuning (less selective) than those projecting to the hippocampal formation (Leitner et al., 2016). As with the amygdala input, entorhinal inputs are believed to target both pyramidal cells and interneurons.

Importantly again, the coupling among the olfactory bulb, PCX and entorhinal cortex axis is dynamic (Chabaud, Ravel, Wilson, & Gervais, 1999; Chabaud et al., 2000; Kay & Freeman, 1998), with, for example, coherence between the PCX and the lateral entorhinal cortex varying across the trial of a two-odor discrimination task [(Boeijinga & Lopes da Silva, 1989); Fig. 1]. In addition to these coherence studies, the lateral entorhinal cortex has also been demonstrated to influence the PCX activity. Aspiration lesions of the entorhinal cortex increase odor-evoked PCX activity [e.g., immediate early gene labeling; (Bernabeu, Thiriet, Zwiller, & Di Scala, 2006)] and enhance simple odor learning such as conditioned odor aversion (Ferry, Oberling, Jarrard, & Di Scala, 1996). These results suggest a strong top-down suppression of PCX activity by the entorhinal cortex. Consistent with this hypothesis, our lab has demonstrated that reversible silencing of the lateral entorhinal cortex enhances both PCX single-unit activity in anesthetized animals, and odor-evoked LFPs in animals performing an odor discrimination task [(Chapuis et al., 2013), Fig. 1]. How does this loss of top-down suppression affect odor perception? Bilateral reversible suppression of lateral entorhinal cortical activity reversibly impairs fine odor discrimination in a well-learned two-odor choice task that is known to not be hippocampal-dependent (Otto, Schottler, Staubli, Eichenbaum, & Lynch, 1991), but has no effect on gross odor discrimination (Chapuis et al., 2013). This suggests that top-down signals from lateral entorhinal cortex may shape signal:noise or other aspects of ensemble coding in PCX necessary for fine odor perception.

Both the amygdala and lateral entorhinal cortex inputs to PCX target lamina containing intracortical association fibers (Wilson & Sullivan, 2011). Synapses in this fiber pathway display robust NMDA-dependent synaptic plasticity (Kanter & Haberly, 1990) and are selectively (compared to afferent input from the olfactory bulb) modulated by neuromodulators such as norepinephrine and acetylcholine (Hasselmo & Bower, 1992; Hasselmo, Linster, Patil, Ma, & Cekic, 1997). Selective suppression of intracortical association fiber synapses reduces odor-evoked responses (Poo & Isaacson, 2011) and impairs odor memory acuity (Barnes & Wilson, 2014). Together, these findings suggest that the efficacy of both basolateral amygdala and lateral entorhinal cortex inputs to PCX should be experience-, state- and task-dependent. For example, while basolateral amygdala input can modulate PCX odor responses even in naïve, anesthetized animals (Sadrian & Wilson, 2015), prior association between odors and emotional outcomes may modify the strength of this modulation. Furthermore, periods of high arousal, or tasks requiring high attention are known to affect cholinergic and noradrenergic release (Hasselmo & McGaughy, 2004). High acetylcholine levels suppress intracortical association fiber synapses (Hasselmo & Bower, 1992). This suppression might shift the relative effectiveness of input to the cortex toward the olfactory bulb (and ongoing odor input from the environment) and away from top-down input from the lateral entorhinal cortex known to be less odor selective (Leitner et al., 2016). During subsequent periods of low arousal or especially during post-training slow-wave sleep, the balance of input effectiveness can then shift away from the nose and back to top-

down signals as those synapses are released from suppression. Preliminary data from our lab exploring state and task dependent changes in identified top-down inputs to PCX support this hypothesis.

Conclusion

The olfactory network is not static; it can change over the course of milliseconds to hours to days (Fig. 1) and dynamically recruit different areas of the brain to appropriately respond to its environment. Here we selectively reviewed a few of the many network components and changes occurring within the olfactory network focusing on the PCX, which in the light of the many functions in which it is involved, may be considered as an associative cortex rather than a primary sensory cortex (Haberly, 2001). As knowledge of the olfactory system increases, the more its complexity and dynamics are revealed. In fact, in addition to the ipsilateral targets and inputs of the PCX, it is important to recognize that the PCX is a bilateral structure with a strong reciprocal interconnection via the anterior commissure (Schwob & Price, 1984) and via commissural fibers originating in layer II of the PCX (Haberly & Price, 1978). Recent work from our lab by Cohen, Putrino, and Wilson (2015) has demonstrated that even the efficacy of these crossed connections is plastic and can be modulated in a state- and task-dependent manner. Thus, the dynamic networks involved in shaping odor perception can also be extended and include bilateral components.

Acknowledgments

Funding

The authors declare no conflicting financial interests.

This work was supported by grants from the National Institute on Deafness and Other Communication Disorders R03DC014540 to EC and R01DC003906 to DAW.

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Some examples of the dynamic of the olfactory network

Figure 1. A simplified representation of changes in the recruitment and coupling within the olfactory network depending on the way an odor is experienced, the period of a trial, the state, or past experience

Blue arrows represent the direction of the connection between the PCX and other brain areas and circled black arrows mean that the connection strength between those structures is variable. From the left to the right, the olfactory network recruited during retrieval depends on the way the odor was sampled during olfactory conditioning. Odors activate the olfactory bulb which in turn activates the PCX. Top: the network involved in olfactory discrimination can evolve during the course of a trial. Middle: During slow wave activity (e.g., nonREM sleep) the connectivity between PCX and MDT, BLA and neocortex is increased compared to fast wave (e.g., waking/REM) activity. During slow wave activity the PCX is also hypo-responsive to odors but sends strong projections back to the OB and other neocortical and limbic sites (Manabe et al., 2011; Wilson et al., 2011). Bottom: experience also shapes the connectivity within the olfactory pathway with, for example changes in connection strength between PCX and OB, OFC and LEC. Bilateral linkage between the bilateral PCX is also modified by olfactory experience.

OB: olfactory bulb, PCX: piriform cortex, OFC: orbitofrontal cortex; BLA: basolateral amygdala; MDT: mediodorsal thalamic nucleus; LEC: lateral entorhinal cortex; Il: infralimbic cortex; IC: insular cortex.

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