Chapter 8
Piriform Cortex and Olfactory Tubercle

Kensaku Mori

Abstract This chapter describes perspectives on the possible functional logic of neuronal circuits in the central olfactory system. The central olfactory system has multiplex pathways and loops that connect the olfactory bulb, olfactory cortex, neocortex, thalamus, ventral striatum, amygdala, hippocampus, and hypothalamus. Among the complex circuits, this chapter focuses on the possible functional differentiation of "olfactory bulb axon–Ib association axon (afferent) circuits" and "deep association axon (recurrent and top-down) circuits" in the piriform cortex. It is hypothesized that the activity of the former circuits is induced mainly by olfactory sensory inputs during the on-line inhalation phase of the sniff cycle, whereas activity of the latter circuits may occur mainly during the off-line exhalation phase. This chapter also discusses the possible function of motivation modules in the neuronal circuits of the olfactory tubercle.

Keywords Deep association axons • Endopiriform nucleus • Ib association axons • Medium-sized spiny neurons • Olfactory bulb • Olfactory tubercle • Orbitofrontal cortex • Piriform cortex • Thalamus • Ventral striatum

8.1 Introduction

Two types of projection neurons in the olfactory bulb, tufted cells and mitral cells, convey odor inhalation-induced signals to the olfactory cortex, which includes the piriform cortex and olfactory tubercle. In Chap. 7, Nagayama et al. described the hypothesis that the two types of projection neurons play distinct roles in sending sniff rhythm-paced odor signals from the olfactory bulb to the olfactory cortex during the inhalation phase. Tufted cells may provide specificity-projecting circuits

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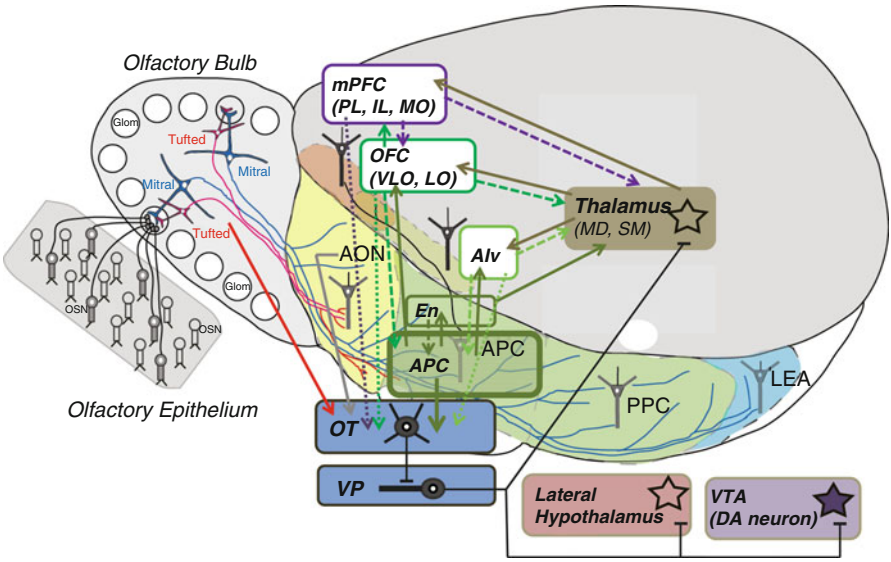

Fig. 8.1 Schematic diagram of central olfactory pathways and loops in the rodent brain. Areas in the olfactory cortex: *AON* anterior olfactory nucleus, *APC* anterior piriform cortex, *PPC* posterior piriform cortex, *LEA* lateral entorhinal area, *OT* olfactory tubercle. *En* endopiriform nucleus. Areas in the orbitofrontal cortex (*OFC*): *VLO* ventrolateral orbital cortex, *LO* lateral orbital cortex. Areas in the medial prefrontal cortex (*mPFC*): *PL* prelimbic cortex, *IL* infralimbic cortex, *MO* medial orbital cortex. *AIv* ventral agranular insular cortex. Thalamic nuclei: *MD* mediodorsal nucleus of thalamus, *SM* submedius nucleus of thalamus. *VP* ventral pallidum, *VTA* ventral tegmental area, *DA neuron* dopaminergic neuron. *Arrows* with *solid lines* indicate afferent excitatory synaptic connections; *arrows* with *broken lines* show top-down excitatory synaptic connections. T-shaped axonal terminals indicate inhibitory synaptic connections. *Glom* glomerulus, *OSN* olfactory sensory neurons. (Modified from Mori et al. 2013)

that send specific odor information to focal targets in the olfactory peduncle areas of the olfactory cortex with early-onset fast gamma synchronization. In contrast, mitral cells may give rise to dispersed-projection feed-forward "binding" circuits that transmit the response synchronization timing via their later-onset slow gamma synchronization to pyramidal cells across all parts of the piriform cortex as well as all areas of the olfactory cortex.

This chapter describes perspectives on the possible functional logic of neuronal circuits in the piriform cortex and olfactory tubercle. For this purpose, I briefly summarize structural organization of afferent pathways in the olfactory cortex and large-scale neuronal pathways and loops that originate from the piriform cortex. The latter pathways include (1) piriform cortex → neocortex → piriform cortex loops, (2) piriform cortex → thalamus → neocortex → piriform cortex loops, and (3) piriform cortex → ventral-striatum (olfactory tubercle) — ventral pallidum — thalamus → neocortex → piriform cortex loops (in which → indicates excitatory synaptic connection and — indicates inhibitory synaptic connection) (Fig. 8.1).

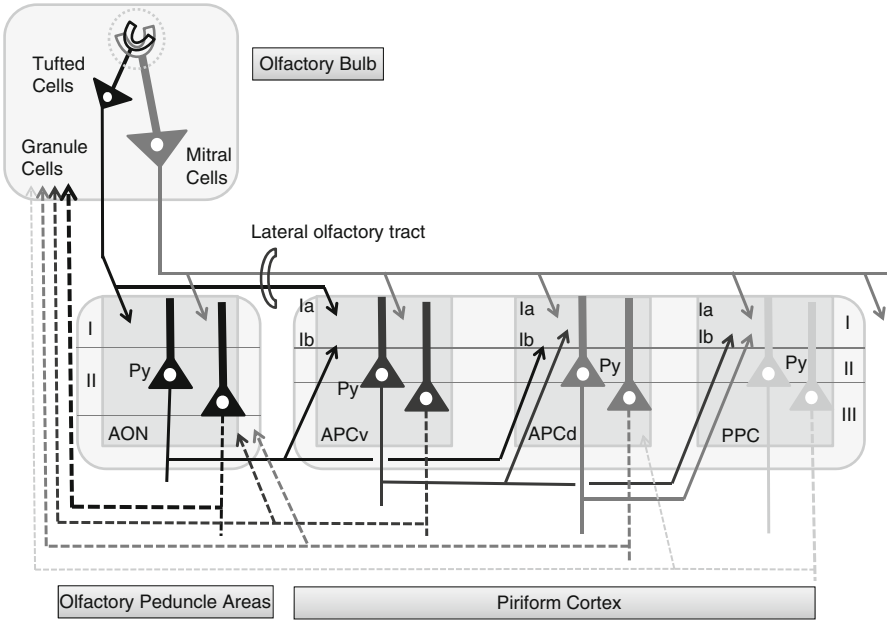

Fig. 8.2 Possible organization of afferent and top-down connections among olfactory bulb, anterior olfactory nucleus (*AON*), ventral subdivision of the anterior piriform cortex (*APCv*), dorsal subdivision of the anterior piriform cortex (*APCd*), and posterior piriform cortex (*PPC*). *Solid lines* with *arrowheads* indicate afferent axons of tufted cells and mitral cells and Ib association axons of pyramidal cells of the olfactory cortex. *Broken lines* with *arrowheads* show top-down collaterals of "deep association axons" of pyramidal cells that project to the deep layers of the olfactory bulb and AON. Layers in the AON: *I* layer I, *II* layer II. Layers in the piriform cortex: *Ia* layer Ia, *Ib* layer Ib, *I* layer I, *II* layer II, *III* layer III. *Py* pyramidal cell

The piriform cortex is the largest area of the olfactory cortex, composed of the anterior piriform cortex (APC) and posterior piriform cortex (PPC), although the definition of the boundary between the APC and PPC varies among researchers (Figs. 8.1, 8.2; see also Fig. 1.5 in Chap. 1) (Haberly 1983; Neville and Haberly 2004; Shipley and Ennis 1996). The anterior piriform cortex is further subdivided into ventral subdivision (APCv) and dorsal subdivision (APCd). Based on the direct afferent inputs from the olfactory bulb and the connectivity pattern of Ib association fibers of pyramidal cells in the olfactory cortex (Fig. 8.2), a major direction of afferent olfactory information flow is suggested as follows (Luskin and Price 1983a, b; Neville and Haberly 2004) : olfactory bulb (OB) → anterior olfactory nucleus (AON) → APCv → APCd → PPC (in which → indicates excitatory synaptic connection). The AON also send direct Ib association axons to the APCd. APCv also directly project Ib association axons to the PPC. In addition, each area of the piriform cortex project Ib and deep recurrent association fibers to its own area and other areas (Fig. 8.3). It should be noted that the bottom-up afferent pathways from the OB are typically associated with top-down feedback axonal projections, forming

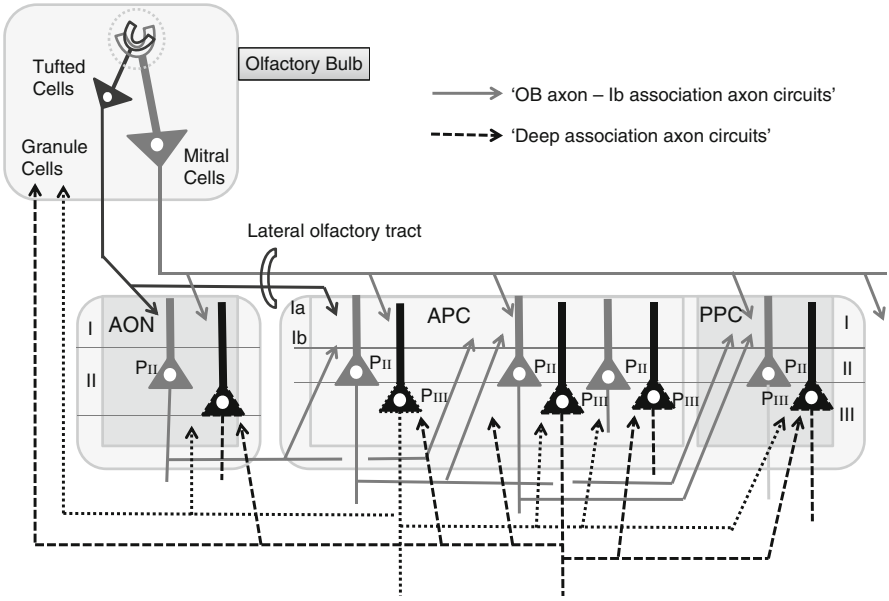

Fig. 8.3 Possible organization of "olfactory bulb (OB) axon–Ib association axon circuits" and "deep association axon circuits" in the olfactory cortex. *AON* anterior olfactory nucleus, *APC* anterior piriform cortex, *PPC* posterior piriform cortex. *PII* layer II pyramidal cells, *PIII* layer III pyramidal cells. "OB axon–Ib association axon circuits" are shown by *solid lines* with *arrowheads*; "deep association axon circuits" are indicated by *broken lines* with *arrowheads*. Endopiriform nucleus (not shown) is involved in the "deep association axon circuits". Layers in the piriform cortex: *Ia* layer Ia, *Ib* layer Ib, *I* layer I, *II* layer II, *III* layer III

neuronal loops, including OB → AON → OB loops and OB → APC → OB loops. The piriform cortex also sends top-down inputs to the AON (Figs. 8.2, 8.3).

The endopiriform nucleus (En) is located deep to the piriform cortex and reciprocally connected with the piriform cortex (Fig. 8.1) (see also Fig. 1.7 in Chap. 1), suggesting that the two regions form piriform cortex → En → piriform cortex loops. Pyramidal cells in the APC or neurons in the En project axons to higher association areas such as orbitofrontal cortex, thalamus, hypothalamus, and ventral striatum, including the olfactory tubercle (Fig. 8.1).

One of the major olfactory afferent streams beyond the APC is the information flow to the orbitofrontal cortex (OFC) and further to the medial prefrontal cortex (mPFC). The OFC receives multimodality sensory inputs including olfactory and gustatory inputs and is thought to be involved in conscious perception of the olfactory image of objects (Li et al. 2010; Plailly et al. 2008). In rodents, the OFC plays a key role in the sensory cue–reward association learning (Schoenbaum et al. 2007), whereas mPFC is important in action–outcome association learning.

The layer II pyramidal cells of the APC project axons directly to the layer I of the OFC. As described in Chap. 1, this projection from the APC to the orbitofrontal cortex is composed of two parallel pathways: APCv projects to the ventrolateral orbital cortex (VLO) and the APCd sends axons to the lateral orbital cortex (LO).

Neurons in the OFC send the information to the mPFC, which includes the prelimbic cortex (PL), infralimbic cortex (IL), and medial orbital cortex (MO).

In addition, the OFC project axons back to the APC. For example, the VLO send top-down axons to the APCv, indicating the presence of APCv → VLO → APCv loops. The LO project back to the APCd, forming the APCd → LO → APCd loops. APCd also directly and reciprocally connects with the ventral agranular insular cortex (AIv), forming the APCd → AIv → APCd loops. The posterior piriform cortex has reciprocal connections with AIv and the posterior agranular insular cortex (AIp) (see Fig. 1.7 in Chap. 1). Thus, the piriform cortex gives rise to piriform cortex → orbitofrontal cortex/agranular insular cortex → piriform cortex loops.

Neurons in the endopiriform nucleus project axons to the thalamus. Pre-endopiriform nucleus neurons (pEn) that are associated with the APCv project axons to the submedius nucleus of thalamus. The thalamocortical neurons in the submedius nucleus reciprocally connect with the VLO, forming thalamocorticothalamic loops. Because VLO project axons back to the APCv, these connections form APCv ↔ pEn → submedius nucleus ↔ VLO ↔ APCv loops (in which ↔ indicates reciprocal excitatory projections).

Endopiriform nucleus neurons that are associated with APCd project to the central segment of the mediodorsal nucleus (MDc) of the thalamus. Thalamocortical neurons in the MDc reciprocally connect with the LO and AIv. These connections thus form APCd ↔ En → MDc ↔ LO/AIv ↔ APCd loops. In summary, the piriform cortex gives rise to piriform cortex ↔ endopiriform nucleus → thalamus ↔ orbitofrontal cortex/agranular insular cortex ↔ piriform cortex loops.

The piriform cortex also projects massively to the olfactory tubercle (Fig. 8.1). However, there is no direct feedback projection from the olfactory tubercle to the piriform cortex. Together with the accumbens nucleus, the olfactory tubercle forms the ventral striatum, which is thought to have a key role as an interface between sensory signals and motivational behaviors (Ikemoto 2007). Principal neurons in the olfactory tubercle are GABAergic medium-sized spiny neurons, and axons of the medium-sized spiny neurons terminate on GABAergic neurons in the rostral part of the ventral pallidum, forming the olfactory tubercle — ventral pallidum pathway (in which — indicates inhibitory synaptic connection).

The neurons in the ventral pallidum send inhibitory output to the lateral hypothalamus, ventral tegmental area, and most notably the MD and SM of thalamus (ventral pallidum — thalamus pathway). Because ventral pallidum neurons tonically inhibit target neurons in the thalamus, hypothalamus, and ventral tegmental area, activation of olfactory tubercle appears to disinhibit the target neurons. Thus the piriform cortex ↔ endopiriform nucleus → thalamus ↔ orbitofrontal cortex/agranular insular cortex ↔ piriform cortex loops are controlled by the piriform cortex → olfactory tubercle — ventral pallidum — thalamus pathways.

Besides these large-scale pathways and loops, the piriform cortex is known to give rise to the piriform cortex (cortical amygdaloid nuclei) → amygdaloid nucleus (including the bed nucleus of stria terminalis) pathways and the piriform cortex → entorhinal cortex → hippocampus pathways.

Looking at these large-scale pathways and loops in the central olfactory system (Fig. 8.1), it is tempting to raise questions of how and when in the sniff (respiration) cycle the olfactory information is transferred along each of these pathways and loops. Another interesting question is for what purpose the olfactory information is transferred along a variety of pathways and loops. Does each pathway or loop play distinct functional roles in the process of the odor input–behavioral output translation? Future studies are needed to answer these questions. In the following sections, I briefly summarize basic knowledge of neuronal circuits of the piriform cortex and olfactory tubercle, hoping that the knowledge is helpful for addressing important questions regarding the workings of the large-scale networks of the central olfactory system.

8.2 Neuronal Circuits in the Piriform Cortex

The piriform cortex is thought to use spatially distributed overlapping ensembles of active pyramidal cells to represent odors (Neville and Haberly 2004; Wilson and Sullivan 2011). At the level of the OB, individual glomeruli represent a single type of odorant receptor and thus respond to particular molecular features of odorants (Kikuta et al. 2013; Mori et al. 1999). On the other hand, individual neurons in the piriform cortex respond not to individual features but to combinations of features (Haberly 2001; Litaudon et al. 2003; Poo and Isaacson 2011; Wilson and Sullivan 2011; Yoshida and Mori 2007).

Piriform cortex neurons that respond to a given odor are dispersedly distributed across the wide space of the piriform cortex without spatial preference (Illig and Haberly 2003; Litaudon et al. 1997; Mitsui et al. 2011; Rennaker et al. 2007; Stettler and Axel 2009). As already stated, excitatory responses of individual neurons in the piriform cortex are tuned to specific combinations of stimulus odorants. The two characteristic properties of the piriform cortex ("sparse distribution of the odor-induced activity" and "selective odor tuning of individual neurons") resemble those of the hippocampus ("sparse distribution of CA1 pyramidal cells (place cells) that fire at a particular place" and "individual pyramidal cells have the property of well-tuned place cell"). Based on these properties and its characteristic anatomical structure, the hippocampus has been proposed to be a giant cortical module (Buzsaki 2006). Similarity between piriform cortex and hippocampus implies that the piriform cortex might also be categorized as a giant cortical module.

Recurrent axon collaterals of pyramidal cells in the piriform cortex form excitatory synaptic connections on dendrites of other pyramidal cells that are distributed widely in the piriform cortex (Fig. 8.3) (Chen et al. 2003; Franks et al. 2011; Haberly and Presto 1986; Johnson et al. 2000; Yang et al. 2004). These recurrent axon collaterals are classified into those that terminate in layer Ib (Ib association axons) and those that terminate in layers II and III (deep association axons). Association axons in the bottom-up afferent pathway tend to be dominated by the

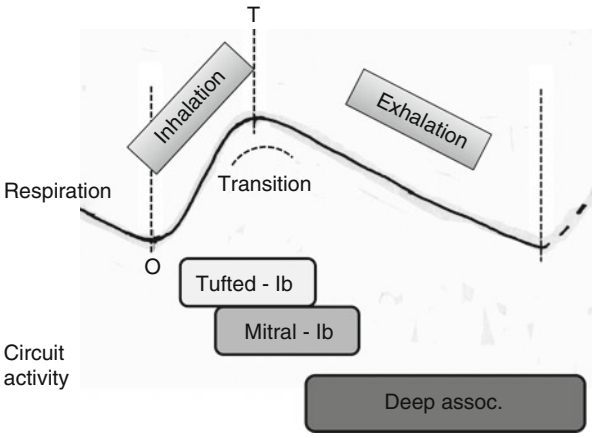

Fig. 8.4 "OB axon–Ib association circuit" activity is induced by olfactory sensory inputs during the inhalation phase (and the transition phase), whereas "deep association axon circuit" activity may occur mainly during the exhalation phase. *Upper trace* indicates the respiration cycle during awake resting state. Upward swing shows inhalation and downward swing indicates exhalation. *Abscissa* shows time (one sniff cycle is about 500 ms). *O* onset of inhalation, *T* period of transition from inhalation to exhalation. *Tufted–Ib*, activities of "tufted cell axon–IB association axon circuits" in the olfactory cortex. *Mitral–Ib*, activities of "mitral cell axon–Ib association axon circuits" in the olfactory cortex. *Deep assoc*, activities of "deep association axon circuits" in the olfactory cortex

Ib association axons, whereas those in the top-down pathway tend to be the deep association axons. For example, recurrent axons collaterals of pyramidal cells in the PPC terminate mostly on basal dendrites of other pyramidal cells in layer III of the whole piriform cortex, and only a small percentage of them terminate on apical dendrites in layer Ib (Haberly 2001).

As described in Fig. 8.2, a major direction of olfactory afferent information flow to the piriform cortex is OB → AON → APCv → APCd → PPC. The afferent stream of odor information is conveyed by axons of tufted and mitral cells in the OB (OB axons) and Ib association axons of pyramidal cells in the AON and piriform cortex. It should be underscored that both the OB axons and Ib association axons form excitatory synaptic terminals on apical dendrites (in layer I) of pyramidal cells in the piriform cortex, forming "OB axon–Ib association axon circuits" (Figs. 8.2, 8.3).

As discussed in Chap. 1, each sniff cycle consists of a sequence of the inhalation phase (or on-line phase) followed by the exhalation phase (or off-line phase). Odor-inhalation activates the OB axon–Ib association axon circuits during the inhalation phase, including the inhalation–exhalation transition phase, as shown in Chap. 7. In other words, OB axon–Ib association axon circuits are active mainly during the on-line inhalation phase of the sniff cycle (Fig. 8.4). Furthermore, the activity of OB axon–Ib association axon circuits during the inhalation phase consists of an early-onset fast gamma oscillation phase (mediated by tufted cell circuits) and a later-onset slow gamma oscillatory phase (mediated by mitral cell circuits) (Fig. 8.4).

Pyramidal cells in the piriform cortex also emit recurrent association axons that terminate in layers II and III of the piriform cortex and on neurons of the endopiriform nucleus. Because pyramidal cells in the piriform cortex extend basal dendrites in layers II and III, the deep association axons form excitatory synaptic terminals mainly on the basal dendrites of other pyramidal cells, forming the "deep association axon circuits" (Fig. 8.3). Hiroyuki Manabe and Kimiya Narikiyo in my laboratory recently found that the deep association axon circuits are active mainly during the later part of the long exhalation phase (off-line phase) of the sniff cycle in freely behaving animals. These results suggest that the OB axon–Ib association axon circuits and the deep association axon circuits in the piriform cortex are activated at different phases of the sniff cycle (Fig. 8.4).

Physiological analysis of the piriform cortex circuits during wakefulness and sleep also suggests the link between the activity of the deep association axon circuits and the off-line processing of olfactory information. During slow-wave sleep (off-line period) in which the OB axon–Ib association axon circuits are suppressed by behavioral state-dependent sensory gating (Murakami et al. 2005), numerous neurons in the APC generate synchronized spike activities that are associated with sharp waves (Manabe et al. 2011). Current source density analysis of the sharp waves indicated that the deep association axon circuits including the endopiriform nucleus are responsible for generating the synchronized spike discharges of APC neurons during slow-wave sleep. The sharp wave-associated synchronized discharges of APC neurons travel also to the deep layer (granule cell layer) of the olfactory bulb (Manabe et al. 2011) and to the deep layer of the olfactory tubercle (Narikiyo et al. 2013), sending synchronized synaptic inputs repeatedly to these regions during slow-wave sleep.

It is not well understood at present how the activity of the OB axon–Ib association axon circuits during the on-line inhalation phase is transmitted to the deep association axon circuits in the piriform cortex and generates the activity of the latter circuits that occurs mainly during the off-line exhalation phase. In addition, it is not clear what types of neurons in the piriform cortex are involved in the OB axon–Ib association axon circuits and the deep association axon circuits in the piriform cortex. For example, semilunar cells whose cell bodies are located in the superficial subdivision of layer II (layer IIa) of the piriform cortex appeas to be associated with the OB axon–Ib association axon circuits because these cells project apical dendrites widely to layer I and lack basal dendrites. Inhibitory interneurons in layer I such as large horizontal cells and layer Ia neuroglial cells (Bekkers 2013) might also be involved in the OB axon–Ib association axon circuits. Fast-spiking large multipolar cells are GABAergic inhibitory neurons whose somata are distributed in layers II and III (Suzuki and Bekkers 2012). Because they receive deep recurrent association axon inputs, they may be involved in the deep-association axon circuits in the piriform cortex. Further studies are needed to elucidate the neuronal substrates for the OB axon–Ib association axon circuits that works mainly during the inhalation phase and those for the deep association axon circuits that are activated during the later part of long exhalation phase.

8.3 Plasticity of Recurrent Association Fiber Synaptic Connections Among Pyramidal Cells in the Piriform Cortex

Piriform cortex networks have been described as containing a combinatorial, auto-associative array capable of content addressable memory (Haberly 2001; Wilson and Sullivan 2011). Both Ib and deep recurrent association axons of pyramidal cells in the piriform cortex form excitatory synaptic connections on dendritic spines of other pyramidal cells that are distributed widely in the piriform cortex (Figs. 8.3, 8.5) (Chen et al. 2003; Haberly and Presto 1986; Johnson et al. 2000; Yang et al. 2004). It has been proposed that Ib and deep association axon synaptic connections among pyramidal cells in the piriform cortex form networks with an iterative recurrent reexcitatory pattern that can store input patterns from the OB by plastically changing their synaptic connections (Barkai et al. 1994; Haberly 2001; Marr 1971; Neville and Haberly 2004; Wilson and Sullivan 2011).

Based on the idea of spike timing-dependent plasticity (Feldman 2012), it can be speculated that during the learning or storage of input patterns the association axon synaptic connections would be strengthened between pyramidal cells with different odorant-tuning specificity that are coactivated by odor inhalation, whereas the association axon synaptic connections would be weakened between activated and nonactivated pyramidal cells (Fig. 8.5). After learning the olfactory input pattern, the strengthened association axon synaptic connections could temporally synchronize the spike activity of those coactivated pyramidal cells with different odorant-tuning specificity when the same or similar input patterns arrive from the olfactory bulb (Neville and Haberly 2004). Computer modeling studies showed that the recurrent association axon networks can store and retrieve multiple input patterns that may include olfactory images of numerous different objects (Barkai et al. 1994). The recurrent association axon connections among pyramidal cells can thus provide a mechanism for feedback binding of coactivated pyramidal cells based on the memory traces of previously stored input patterns.

Based on the foregoing considerations, Mori, Manabe, Narikiyo, and Onisawa hypothesized that the late-onset synchronous gamma oscillatory inputs from mitral cells cause temporal “binding” of the spike activities of numerous pyramidal cells with different tuning specificity that are coactivated via tufted cell axon–Ib association axon pathways during odor inhalation (Mori et al. 2013) (Fig. 8.5). The mitral cell-induced spike synchronization of pyramidal cell activities would facilitate the strengthening of the association axon synaptic connections among the coactivated pyramidal cells during the storage of input patterns that are provided by tufted cell–Ib association axon pathways. In summary, Mori et al. proposed a model in which mitral cell pathways provide feed-forward binding circuits, sending the spike synchronization timing to facilitate the storage of olfactory sensory inputs patterns by causing the spike synchronization of coactivated pyramidal cells at the gamma frequency, and thus strengthening association axon synaptic connections among coactivated pyramidal cells with different tuning specificity.

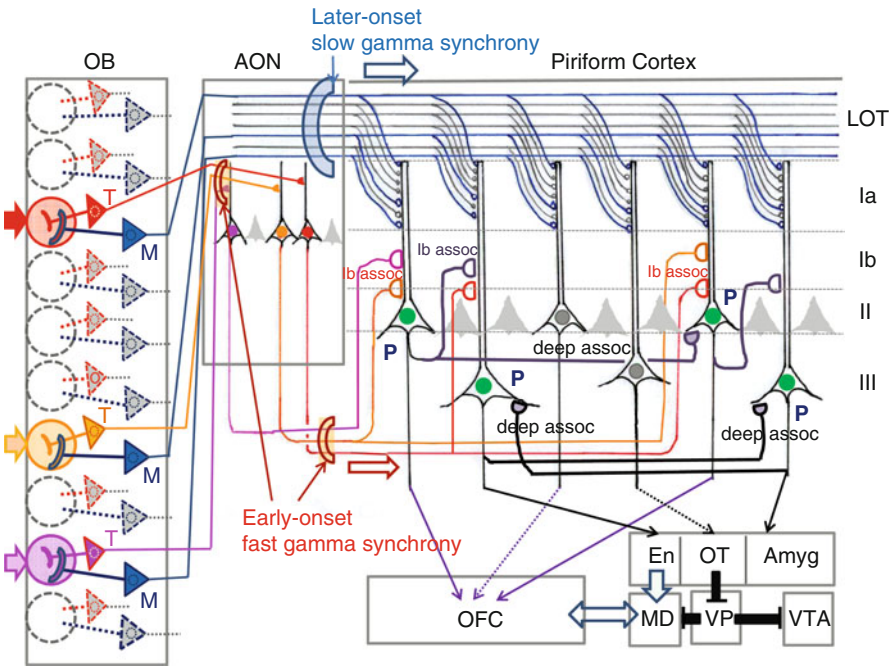

Fig. 8.5 Schematic diagram of possible functional differentiation between the tufted cell pathway and mitral cell pathway in odor information processing in the neuronal circuits of the piriform cortex. In this model, *red*, *yellow*, and *pink* glomeruli are assumed to be activated simultaneously by an odor inhalation. Activated tufted cells (*T*; shown by *red*, *orange*, or *pink*) send the odor information with early-onset fast gamma synchrony to specific target pyramidal cells in the anterior olfactory nucleus (*AON*), which in turn send the information presumably with fast gamma synchrony with specific target pyramidal cells in the piriform cortex. Activated mitral cells (*M*, shown by *blue*) provide dispersedly-projecting feed-forward binding circuits transmitting the spike synchronization timing with later-onset slow gamma synchrony to whole pyramidal cells in the piriform cortex. Pyramidal cells (*P*) in layer II of the anterior piriform cortex project axons directly to the orbitofrontal cortex (*OFC*). Pyramidal cells in the piriform cortex form recurrent association axon synaptic connections (*Ib assoc*. and *deep assoc*.) with other pyramidal cells, forming feedback binding circuits. These pyramidal cells project axons also to the endopiriform nucleus (*En*), olfactory tubercle (*OT*), and amygdaloid nuclei (*Amyg*). Neurons of the endopiriform nucleus send axons to the mediodorsal nucleus (*MD*) of thalamus. The MD provides thalamocortical projections to the OFC, and OFC sends feedback corticothalamic connections to the MD. Neurons in the OT send inhibitory output to the ventral pallidum (*VP*), which sends inhibitory output to the MD and ventral tegmental area (*VTA*). *Ia*, *Ib*, *II*, *III* are layers in the piriform cortex. Pyramidal cells with *green nucleus* in the piriform cortex indicate neurons coactivated by an odor inhalation. Recurrent collateral excitatory synaptic connections (*deep assoc*) among these neurons form feedback binding circuits. (Modified from Mori et al. 2013)

If this scenario is correct, the next question is to which neuronal circuits the coactivated pyramidal cells of the piriform cortex send the synchronized spike outputs. Because the olfactory tubercle receives association fiber inputs from virtually all parts of the piriform cortex, the olfactory tubercle is one of the candidate targets that receive the synchronized inputs from the piriform cortex.

8.4 The Olfactory Tubercle Is Part of the Ventral Striatum and Receives Axonal Projection from the Olfactory Bulb, Piriform Cortex, and Frontal Cortex

The olfactory tubercle is an area of the olfactory cortex and part of the ventral striatum that has a key role in a variety of motivational behaviors (Heimer 2003; Heimer et al. 1987; Ikemoto 2003, 2007; Switzer et al. 1982). The olfactory tubercle has a layered structure that consists of superficial layer I, dense cell layer (layer II), and deep layer (layer III), although these layers have undulations and are interrupted by CAP-like regions and islands of Calleja (Fig. 8.6) (Millhouse 1987; Millhouse and Heimer 1984). Although the olfactory tubercle has a cortex-like layered structure, it has a striatum-like organization consisting of GABAergic medium-sized spiny neurons (MSNs) as major output neurons (Millhouse and Heimer 1984).

The olfactory tubercle contains cortex-like regions and CAP regions (Fig. 8.6). In the cortex-like region, two types of MSNs (dopamine D1 receptor-expressing MSNs and D2 receptor-expressing MSNs) are intermingled. These MSNs extend apical dendrites superficially in layer I and basal dendrites in layers II and III. In the CAP region, smaller MSNs (dwarf cells) are packed in the layer II (dense cell layer). In the CAP region, layer Ib is very thin and apical dendrites of the smaller MSNs are distributed mostly in layer Ia. In both CAP and cortex-like regions of the olfactory tubercle, axons of MSNs make inhibitory synaptic connections on dendrites of neurons in the rostral part of the ventral pallidum (Fig. 8.6) (Heimer et al. 1987; Luskin and Price 1983a; Newman and Winans 1980; Tripathi et al. 2013).

Tufted and mitral cells in the olfactory bulb project axons to layer Ia of the olfactory tubercle and form excitatory synaptic connections on the spines of apical

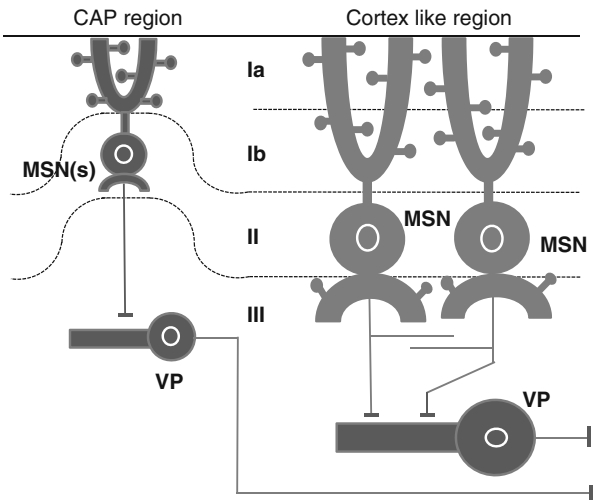

Fig. 8.6 Principal neurons and neuronal circuits in the olfactory tubercle and ventral pallidum (*VP*). Olfactory tubercle can be subdivided into CAP region (*left*) and cortex-like region (*right*). *MSN* medium-sized spiny neuron in the cortex-like region, *MSN*(*s*) smaller MSN (dwarf cells) in the CAP region. Layers in the olfactory tubercle: *Ia* layer Ia, *Ib* layer Ib, *II* layer II (dense cell layer), *III* layer III

dendrites of MSNs (Price 1973). Association axons originated from pyramidal cells in the piriform cortex terminate in layers Ib, II, and III of the olfactory tubercle (Luskin and Price 1983a; Price 1973). Based on the classification of Ib association axons and deep association axons in the piriform cortex, the association axon inputs from the piriform cortex pyramidal cells to the olfactory tubercle can be classified into two subsets: "Ib association axon inputs" and "deep association axon inputs." The Ib association axon inputs may reflect the OB axon–Ib association axon circuit activity and may terminate on apical dendrites (in layer I) of MSNs whereas the deep association axon inputs may be associated with the activity of deep association axon circuits in the piriform cortex and mainly terminate on basal dendrites (layers II and III) of MSNs.

The olfactory tubercle is thought to contain motivation behavior modules that function as gateways for odor information to induce specific motivation behaviors (Ikemoto 2007). In line with this idea, Koshi Murata in my laboratory found, in mice, that the regions or modules within the olfactory tubercle do not represent odors but rather are activated when mice show specific motivational behaviors. Activation of MSNs in a specific motivation behavior module may lead to the expression of the motivational behavioral outputs via the olfactory tubercle — ventral pallidum — thalamus/hypothalamus/ventral tegmental area pathways (Heimer et al. 1987; Zahm and Heimer 1987; Zahm et al. 1987) (Figs. 8.1, 8.6). This observation suggests that the olfactory sensory pathways to the olfactory tubercle provide an excellent model neuronal circuit for analyzing the neuronal mechanism of the odor input–behavioral output translation.

There are multiple neuronal pathways from the olfactory sensory neurons to the olfactory tubercle (Fig. 8.1). First, tufted and mitral cells in the olfactory bulb project axons directly to the olfactory tubercle, forming direct pathways from the olfactory bulb. Second, the olfactory tubercle receives association axon inputs from many areas of the olfactory cortex including the AON, tenia tecta, piriform cortex, cortical amygdaloid nuclei, and entorhinal cortex, forming the OB → olfactory cortex → olfactory tubercle pathways. In these pathways, odor signals are first processed in the neuronal circuits of the olfactory cortex, possibly in reference to olfactory memories, and then the processed results are sent to the motivation behavior modules in the olfactory tubercle.

Third, the olfactory tubercle receives inputs from the amygdaloid nuclei, thus forming the OB → olfactory cortex (including cortical amygdaloid nuclei) → amygdala → olfactory tubercle pathways. Fourth, the olfactory cortex receives inputs from the OFC and mPFC, thus forming OB → olfactory cortex → frontal cortex → olfactory tubercle pathways. Thus, odor signals are processed first in the olfactory cortex and then in the frontal cortex. After the integration of olfactory signals with other sensory and motor signals, the frontal cortex may send the signal to the olfactory tubercle. Therefore, multiplex parallel pathways rather than a single pathway convey olfactory information from the olfactory bulb to the olfactory tubercle (Fig. 8.1).

Furthermore, neurons in the ventral pallidum, which receives inputs from the olfactory tubercle, project axons to the ventral tegmental area. Dopaminergic

neurons in the ventral tegmental area are involved in the expectancy of reward and project axons densely back to the olfactory tubercle.

At present, it is unclear how these multiple olfaction-related pathways to the olfactory tubercle work during the inhalation–exhalation sniff cycle. It is a great challenge of future studies to understand the function and its neuronal mechanism of each pathway as well as those that coordinate the functions of these multiple pathways to the olfactory tubercle.

The foregoing speculations regarding the multiple parallel neuronal pathways to the olfactory tubercle can be extrapolated to many other pathways and loops in the central olfactory system. Intensive research on the piriform cortex, olfactory tubercle, and higher association areas has started only recently, and a number of important questions remain unanswered or even questions themselves remain unknown. Recent studies suggest that there will be a rapid acceleration of the understanding of the structure and function of the large-scale networks in the central olfactory system in the near future. Finally, neuronal circuits in the central olfactory system provide an excellent model system with which to study the functional organization of the cortical, thalamic, and basal ganglia networks for the translation of external sensory information to appropriate motivational and emotional behaviors.

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