Chapter 1
Unique Characteristics of the Olfactory System

Kensaku Mori and Hiroyuki Manabe

Abstract The olfactory system in the brain plays key roles in the daily lives of humans and animals. This chapter briefly sketches the recent rapid progress in understanding the structure and function of the olfactory system and some unsolved important questions regarding this system. Olfactory perception occurs in discrete respirations (sniffs), and this chapter underscores the intimate relationship between the function of the olfactory system and the sniff rhythm. In addition, this chapter provides basic knowledge about the unique characteristics of the olfactory neural circuits, starting from olfactory sensory neurons in the nose through the olfactory bulb and olfactory cortex up to the orbitofrontal cortex and olfactory tubercle.

Keywords Exhalation • Inhalation • Motivational behaviors • Odor molecules • Odorant receptor • Olfactory bulb • Olfactory cortex • Orbitofrontal cortex • Sniff rhythm

1.1 From Odor Molecules to Behavioral Responses

One of the basic functions of the human brain is to process sensory information about the external world. This processing is done with reference to one's internal state to choose and evaluate salient objects so that one can express appropriate emotional, motivational, and behavioral responses. It is therefore natural for olfactory system researchers to ask "What is the neuronal circuit logic of the olfactory system that enables humans and animals to translate external odor information to necessary behavioral outputs?" However, understanding this translation

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(or understanding the input–output relationship) is no easy task. The difficulty originates from the tremendous diversity of odors in the world. It is estimated that the human nose can detect and discriminate more than 400,000 volatile compounds (odor molecules or odorants), each having a distinct molecular structure. Further, single objects emit a multitude of odor molecules—an apple, for example, emits an object-specific combination of more than 100 different odor molecules. The number of possible input patterns of odorants to the nose is beyond count. How does the olfactory system cope with these tremendously diverse input patterns, composed of an astronomically diverse range of odorant combinations?

As we discuss here, the discovery of the odorant receptor gene family by Linda Buck and Richard Axel (Buck and Axel 1991) triggered elucidation of the key logic of odorant coding (a type of combinatorial coding) at the level of the odorant receptors, olfactory sensory neurons in the nose, and glomeruli in the olfactory bulb. Before the identification of this key logic, relating each of the "innumerable odors" to each of the "large variety of percepts and behavioral responses" was considered almost impossible. However, the finding of the key logic encouraged us to speculate whether it might in fact be possible to relate any of "approximately 390 human odorant receptors" to any of "a large variety of percepts and behavioral responses."

The difficulty also originates from the diversity and complexity of percepts, motivational behaviors, and emotional behaviors. For example, while the detection of food odor may lead to food search behaviors followed by eating, the expression of these behaviors is also dependent on internal states such as hungriness and thirstiness. In response to predator odors, a good strategy for rodents is to escape from the danger, but there are numerous behavioral patterns for escape, including the fight or flight choice. Odors or pheromones from the opposite sex may lead to a variety of behavioral responses (Wyatt 2009), whereas distinct conspecific odors induce diverse social behaviors (Doty 1986). Furthermore, humans and mammals can learn to associate any neutral odorant with a reward or punishment, such that the odor can induce specific attractive or aversive behavior based on previous experience.

One possible strategy for the "odorant receptor input–behavioral output" translation is to form simple reflex-like neuronal connections (or so-called zombie-like connections) between olfactory sensory neurons in the nose and the motor circuits responsible for specific behavioral output. The spinal cord, brainstem, and midbrain contain a rich variety of reflex pathways (or short-circuit pathways) that connect somatosensory, gustatory, auditory, and visual inputs to motor outputs. In striking contrast, the olfactory system is unique among the five sensory systems in that it does not have direct connections with these regions and lacks simple reflex-like pathways. All axons of olfactory sensory neurons synapse with neurons in the olfactory bulb, which is developmentally an expansion forward of the cerebral cortex. In other words, olfactory sensory neurons directly connect with cerebral cortex networks.

Furthermore, the olfactory bulb and olfactory cortex lie in the telencephalic segment of the brain, which includes the neocortex, paleocortex, and basal ganglia.

Understanding the logic of olfactory sensory input–behavioral output translation therefore requires elucidation of the cortical and basal ganglia circuit mechanism. The discovery of odorant receptors led to rapid progress during the past two decades in understanding the mechanism of odorant coding at the level of odorant receptors, olfactory sensory neurons, and glomeruli in the olfactory bulb (Axel 1995; Buck and Axel 1991; Mori et al. 1999). Nevertheless, the question of how olfactory codes at the level of the glomeruli in the olfactory bulb are read by the olfactory cortex and higher association areas to translate the coded olfactory information into appropriate behavioral outputs remains largely unknown. We still lack an understanding of the functional logic of neuronal circuits in the olfactory cortex and higher association areas, and extensive exploration of the olfactory cortex and higher association areas in the paleocortex, neocortex, and basal ganglia has only recently begun. This new focus on these regions predicts rapid near-term progress in understanding the key logic of the neuronal circuits that translate the olfactory inputs to emotional, motivational, and behavioral output.

After providing an overall characterization of the structure and function of the olfactory system in Chap. 1, Kazushige Touhara summarizes in Chap. 2 recent progress in the state of knowledge about chemosensory signals, receptors, olfactory network, and behavioral outputs, and provides prospects for future progress and questions to be solved. Hitoshi Sakano describes his group's remarkable findings in the molecular and cellular mechanisms of olfactory map formation by olfactory sensory axons on the glomeruli in the olfactory bulb in Chap. 3. The structure and function of olfactory maps in the mammalian olfactory bulb is briefly described in Chap. 4. Although this book mostly describes the olfactory system of land mammals, there is also rapid growth in understanding the zebrafish olfactory system, which has become one of the most useful and important model organism in neurobiology. Yoshihiro Yoshihara describes the zebrafish olfactory system in Chap. 5. Masahiro Yamaguchi focuses on inhibitory interneurons in the olfactory bulb and discusses the functional roles of adult-born granule cell inhibitory interneurons in Chap. 6. Shin Nagayama, Kei Igarashi, Hiroyuki Manabe, and Kensaku Mori discuss how odor signals are conveyed from the olfactory bulb to the olfactory cortex in Chap. 7, focusing on parallel tufted cell and mitral cell pathways. Chapter 8 proposes possible structural and functional organization of the piriform cortex, olfactory tubercle, and orbitofrontal cortex. Finally, Noam Sobel summarizes olfactory system neurobiology and perception in humans in Chapter 9.

1.2 Sniff Rhythm and Olfaction

Although it is controversial whether perception in general relies on discrete processing epochs, it is agreed that conscious olfactory perception occurs in discrete respirations (or sniffs) (Kepecs et al. 2006; Mainland and Sobel 2006; VanRullen and Koch 2003). Sniff rhythm appears to be a conductor orchestrating the mode of information processing globally across a wide variety of members

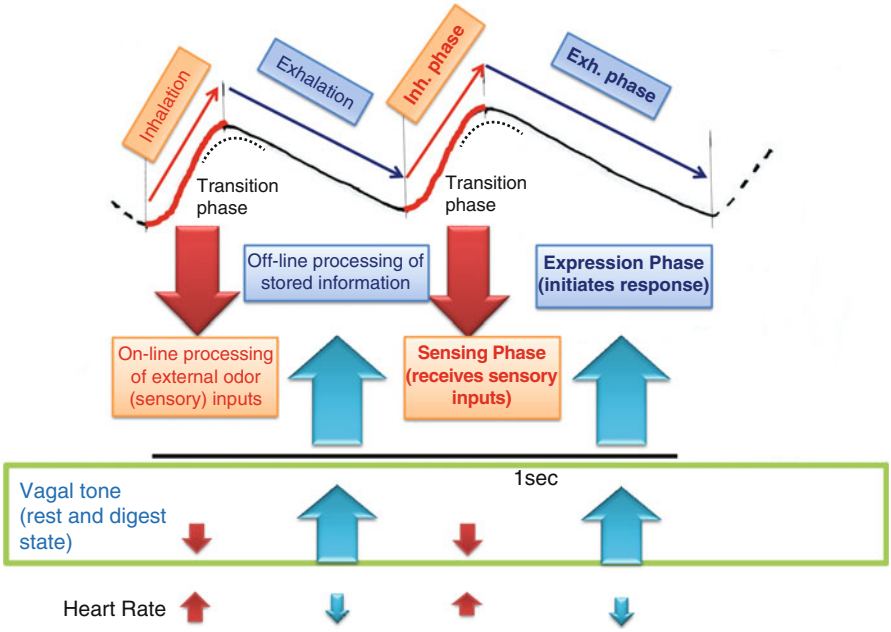

Fig. 1.1 Inhalation–exhalation sniff cycles. The *topmost trace* indicates the sniff rhythm of a rat (during awake resting) recorded with a thermocouple placed in the nasal cavity. *Upward swing of trace* indicates inhalation. *Broken line* indicates the phase of transition from inhalation to exhalation (*Exh.*). *Large* and *small arrows* below the respiration monitor illustrate possible functional state of the central olfactory system, the autonomic parasympathetic nervous system, and heart rate

(areas) of the central olfactory system. In land mammals, each respiration cycle consists of an inhalation phase followed by an exhalation phase (Fig. 1.1). During the inhalation phase, odorants in the external world are drawn, together with air, into the nasal cavity and thus activate olfactory sensory neurons in the nose.

Although it takes time for inhaled odorants to reach and then activate olfactory sensory neurons, the response of these neurons starts at the rising phase of the inhalation, continues during the rest of the inhalation phase, and then declines during the exhalation phase (Wachowiak 2011; Wilson and Sullivan 1999). This observation suggests that external odor input is processed on-line in the central olfactory system mostly during the inhalation phase, including the transition phase from inhalation to exhalation (Fig. 1.1). In this scenario, the inhalation phase is the time window for the central olfactory system to "explore" the external odor information. Because autonomic parasympathetic nervous system activity (so-called vagal tone) decreases during the inhalation phase, on-line processing of external odor inputs is associated with a decrease in parasympathetic activity and an increase in heart rate (Fig. 1.1).

In contrast, during the exhalation phase, particularly the latter part of a long exhalation, the central olfactory system is temporarily isolated from the external

odor world and processes olfactory information off-line. In parallel, parasympathetic nervous system activity increases during the exhalation phase, resulting in a decrease in heart rate. Because parasympathetic activity is thought to represent the "rest and digest" state of the body, we speculate that the exhalation phase is associated with the "rest and digest" state of the central olfactory system. We further speculate that the inhalation–exhalation sequence of a sniff cycle not only determines the timing of external odor information sampling but also regulates the mode of information processing in the central olfactory system. The inhalation phase might be a "sensing phase," specialized in the receipt of external sensory input, and the exhalation phase might be an "expression phase," specialized in the processing of stored information to initiate appropriate behavioral responses.

The working of the neuronal networks in the central olfactory system, particularly the information processing mode, therefore appears to depend heavily on the sniff cycle and rhythm. This is the case during wakefulness, especially during fast sniffs, in which animals actively explore the external odor world. However, during sleep states with slow respiration, the central olfactory system, particularly the olfactory cortex and higher association areas, is largely isolated from the external odor world by behavioral state-dependent sensory gating (Murakami et al. 2005). The information processing rhythm in the central olfactory system during sleep states is, if present, thus largely independent of the respiration rhythm.

In humans and animals, respiration rhythm varies precisely according to behavioral state, and each sniff rhythm has distinct behavioral correlates (Homma and Masaoka 2008; Manabe and Mori 2013). Figure 1.2 and Table 1.1 summarize the distinct sniff (or respiration) patterns that are induced during different behavioral states. The sniff rhythm in Fig. 1.2 was recorded with a thermocouple placed in the nasal cavity of a freely behaving rat. In addition, the sniff rhythm-paced neuronal activity in the olfactory system was monitored by recording local field potentials in the deep layer (granule cell layer) of the olfactory bulb, the first information processing center in the central olfactory system. The tight coupling between sniff rhythm and neuronal activity in the olfactory system underscores the critical importance of monitoring sniff cycles in analyzing the functional properties of the neuronal circuits in the olfactory system of freely behaving animals.

During walking, running, and exploratory movements, rats make a series of small, brief, and rapid sniffs at the theta frequency range (6–10 Hz) (Fig. 1.2a). The local field potential in the olfactory bulb shows nested gamma oscillations superimposed on the sniff-paced oscillations of the theta frequency range. Here, we focus on the sniff-paced theta oscillations, leaving discussion of the gamma oscillations for Chap. 7. During the movement state, local field potentials in the hippocampus (or hippocampal EEG) are known to show theta oscillations (6–12 Hz). Because this hippocampal theta oscillation during the movement state is called the "translation-movement theta oscillation" (t-theta) (O'Keefe 2007), we call the theta sniffs "translation-movement theta sniffs" (t-theta sniffs).

When rats are immobile, showing no translation movement, but are in exploratory behavior with arousal and attention state, they show also a train of small, brief, and rapid sniffs of theta frequency range (3–8 Hz) followed by one or a few sniffs with a

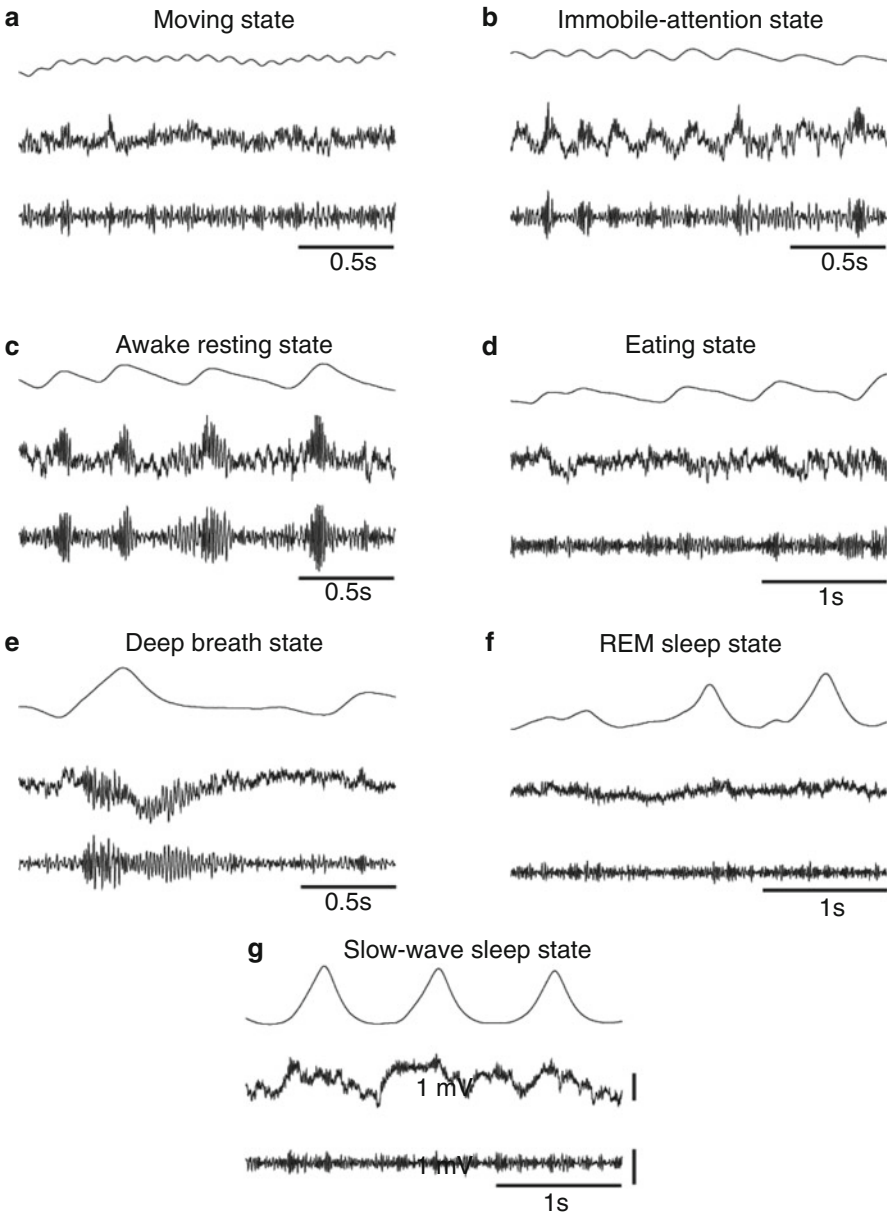

Fig. 1.2 Each sniff rhythm has distinct behavioral correlates. Simultaneous recordings of respiration rhythm (*topmost traces*; upward swing indicates inhalation), local field potential in the granule cell layer of the olfactory bulb (*middle traces*), and gamma oscillations of the local field potential (bandpass filtered, 30–140 Hz; *bottom traces*) during moving (**a**), during immobile-attentional state (**b**), during awake resting (**c**), during eating (**d**), during deep breath (**e**), during REM sleep (**f**), and during slow-wave sleep (**g**)

Table 1.1 Behavioral correlates of sniff rhythm

	Wakefulness					Sleep	
Behavioral state	Translation-movement state	Immobile-attention or arousal state	Awake resting state	Eating state	Deep breath state	REM sleep state	Slow-wave sleep state
Typical behavior	Walking, running, exploratory movement	Arousal, attention	Quiet sitting, grooming	Eating, drinking	Deep breath	Rapid eye movement, whisker movement	No movement
Respiratory (sniff) pattern	t-theta sniff (Fig. 1.2a)	a-theta sniff (Fig. 1.2b)	Resting slow sniff (Fig. 1.2c)	Eating slow sniff	Deep sniff	Irregular respiration (Fig. 1.2f)	Regular slow respiration (Fig. 1.2g)
Hippocampal EEG	t-theta oscillation	a-theta oscillation	LIA with SPW/ripples	LIA with SPW/ripples	LIA during exhalation phase	REM-theta oscillation	LIA with SPW/ripples

relatively long exhalation phase (Fig. 1.2b). During the theta frequency sniffs, rats show synchronization between sniff and whisking (rapid movements of vibrissae), with vibrissae protraction during the brief inhalation and vibrissae retraction during the brief exhalation (Welker 1964). Local field potential in the olfactory bulb shows the sniff rhythm-paced theta oscillatory activity with superimposed nested gamma oscillations. During this behavioral state, hippocampal EEG shows theta oscillations (4–9 Hz), which are called "immobile attention-related theta oscillations" (a-theta). Accordingly, the theta sniffs during this behavioral state can be classified as "attention-related theta sniffs" (a-theta sniffs).

When rats are in the awake resting state sitting quietly, they show a slow low-frequency sniff pattern (~2.5 Hz on average), with a sniff cycle consisting of a slow inhalation followed by a longer exhalation. The longer exhalation phase may reflect the dominance of the "rest and digest" state of the olfactory system. Local field potential in the olfactory bulb exhibits sniff rhythm-paced slow oscillations with superimposed nested gamma oscillations (Fig. 1.2c). In contrast, the hippocampal EEG typically shows large irregular amplitude activity (LIA) with sharp wave/ripple events, which are thought not to be driven by external sensory inputs but to be generated internally based on memory traces stored during preceding movement or exploratory behavior (Buzsaki 2006).

Eating foods is a typical daily olfactory behavior, and rats show slow low-frequency sniffs with a relatively long exhalation phase during eating and drinking (Fig. 1.2d). During the exhalation phase, rats sometimes stop respiration for a short period, which may correspond to the respiration-absent period for swallowing (swallowing apnea). The long exhalation phase of the eating slow sniff is a unique time window in which the central olfactory system receives strong retronasal odor stimulation from foods in the mouth (Gautam and Verhagen 2012). Hippocampal EEG exhibits LIA with sharp wave/ripple events during this behavioral state.

If you breathe slowly and deeply, your mind becomes calm. Rats also sometimes show slow and deep breathing with an extremely long exhalation phase or apnea phase, as exemplified in Fig. 1.2e. In synchrony with the large inhalation, the olfactory bulb shows prominent gamma oscillations superimposed on a large slow potential. Rich oscillatory activity also appears during the exhalation phase, in which the olfactory bulb does not receive direct olfactory sensory inputs. The hippocampal EEG shows LIA with sharp waves/ripples during the exhalation phase, but these events are typically absent during the inhalation phase (Manabe 2008).

During a sleep episode, rats show several cycles of slow-wave sleep and rapid eye movement (REM) sleep. They show very regular slow respiration of large amplitude during the slow-wave sleep state, but strikingly irregular respirations with a wide variety of amplitude during REM sleep. During these sleep states, the olfactory bulb does not show sniff-paced oscillations of local field potential. During slow-wave sleep states, the olfactory bulb shows slow irregular waves, but their occurrence is largely independent of respiration rhythms. The hippocampal EEG

shows characteristic theta oscillations during REM sleep (REM-theta) and LIA with sharp waves/ripples during slow-wave sleep.

In this way, as each hippocampal EEG pattern has distinct behavioral correlates, so also does each sniff rhythm. Researchers with rich experience in studying rat olfactory behavior tell us that they can correctly guess the behavioral state of the rat by monitoring the sniff pattern, even without direct observation of the rat's behavior. Furthermore, the sniff rhythm depends on motivational state and the type of motor activity. If the information processing rhythm in the central olfactory system of a rat occurs in synchrony with its sniff rhythm, what is the function of this rhythm in olfactory information processing? And if sniff rhythm is a key to olfactory information processing, what types of information are processed at different phases of a sniff cycle?

As already stated, each sniff cycle consists of an inhalation phase (on-line phase) followed by an exhalation phase (off-line phase). Figure 1.2 shows that several types of nested oscillatory activity occur sequentially in the olfactory bulb at fixed phases of an inhalation–exhalation sniff cycle. The nested gamma oscillations during the inhalation phase (including those that occur just after the end of inhalation) are thought to reflect neuronal activities that are induced directly by the odor inhalation. As shown in Fig. 1.2, however, a large amount of nested oscillatory activities in the olfactory bulb sometimes also occurs during the subsequent long-exhalation phase or off-line "rest and digest" phase. Such nested oscillatory activities occur also in the olfactory cortex and higher olfactory centers during the long exhalation phase up to the initial part of the next inhalation, in which the central olfactory system is nearly disengaged from the external odor world (see Chap. 8).

Odor information is conveyed from the olfactory bulb to the olfactory cortex via two types of projection neurons, tufted cells and mitral cells (see Chap. 7). A sniff cycle can be divided into an inhalation phase and exhalation phase (Fig. 1.1). At which phase of the sniff cycle do tufted cells and mitral cells send odor information to the olfactory cortex? Recent studies by Igarashi et al. (2012) and Fukunaga et al. (2012) indicate that tufted cells and mitral cells send odor information at different phases of the respiration cycle. During the inhalation phase, including the inhalation–exhalation transition phase (on-line "exploratory" phase), a subset of tufted cells start to respond with spike discharges at the rising phase of inhalation, which is followed by the later-onset burst discharges of many mitral cells during the inhalation–exhalation transition phase (see Chap. 7). The initial on-line processing of odor inputs by tufted cells during the inhalation phase might mediate initial fast responses or initial detection of an inhaled odor. The later-onset on-line processing by mitral cells might be important for later integration processes in the olfactory cortex (see Chaps. 7 and 8).

It should be noted that many mitral cells also show burst discharges during the later part of the exhalation phase. Why do many mitral cells show spike discharges during the exhalation phase? What is the functional role of the neuronal activities of the central olfactory system during the off-line "rest and digest" phase? Olfactory researchers have no clear answers to these questions. One can only speculate that

during the exhalation phase the central olfactory system is engaged in off-line processing of odor information that is stored during the preceding inhalation phase. The off-line processing of odor information might be used to initiate adequate behavioral outputs. In addition, off-line processing might also be important in inducing specific emotional and motivational states in the brain. Furthermore, the olfactory system processes retronasal odor inputs from foods in the mouth during the off-line exhalation period, presumably for the evaluation of foods. Off-line processing is discussed in more detail in Chap. 8.

Once you detect rhythms in music, you anticipate subsequent tones in the next rhythmic cycle. From this, we further speculate that once humans or animals detect the sniff rhythm (or once the cerebral neocortex actively elicits the sniff rhythm), off-line processing might be used in anticipating particular types of odor inputs during subsequent inhalation. Monitoring the respiration cycle provides a unique opportunity to differentiate neuronal activities in the on-line processing of odor inputs from those in off-line processing, which occur at distinct time windows.

In all sensory systems, including the olfactory system, distinction between on-line processing and off-line processing also occurs over a much longer time scale, that is, on-line processing during wakefulness and off-line processing during sleep. In the olfactory system, on-line processing during inhalation and off-line processing during exhalation occur alternatively throughout the period of wakefulness. During sleep, in contrast, off-line processing may continually occur irrespective of respiration rhythm, as described in Chap. 8. In other words, there are at least three distinct time windows for information processing in the central olfactory system: during wakefulness, there is a constant alternation of on-line processing of odor inputs at the inhalation phase and off-line processing of olfactory information at the exhalation phase, whereas continuous off-line processing occurs during sleep.

Sensory neuroscience has been markedly successful in advancing knowledge of neuronal circuit mechanisms in the on-line processing of sensory inputs. In contrast, progress in understanding the mechanisms of off-line processing of sensory information is relatively slow. Future studies of the central olfactory system will substantially contribute to advancing our knowledge of this latter point.

1.3 Unique Characteristics of Olfactory Pathways

In this section, we briefly review the characteristic structural organization of the central olfactory pathways in the brain, starting from the olfactory sensory neurons in the olfactory epithelium of the nose (Fig. 1.3). Olfactory information from the external world is carried in a vast variety of odorants, small volatile compounds with a molecular mass less than 300 Da. Odorants are drawn into the nasal cavity during the inhalation phase of the respiration. They are received by odorant receptors expressed on the cilial surface membrane of olfactory sensory neurons (Buck and Axel 1991).

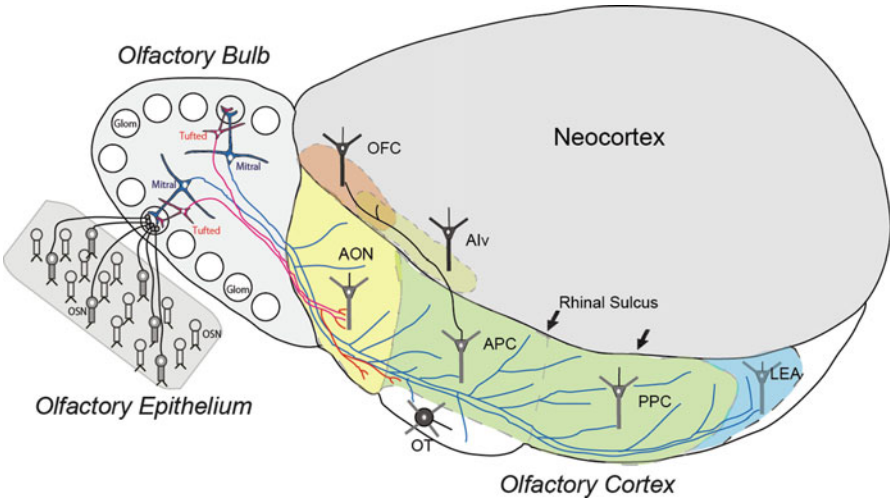

Fig. 1.3 Olfactory pathways to the orbitofrontal cortex in rodents. A schematic diagram of the lateral view of the rodent brain illustrates the neuronal pathways from olfactory sensory neurons through the olfactory bulb and olfactory cortex to the orbitofrontal cortex. *AIv* ventral agranular insular cortex, *AON* anterior olfactory nucleus, *APC* anterior piriform cortex, *Glom* glomerulus, *LEA* lateral entorhinal cortex, *OFC* orbitofrontal cortex, *OSN* olfactory sensory neuron, *OT* olfactory tubercle, *PPC* posterior piriform cortex. Axons of tufted cells are shown by *red*; those of mitral cells are shown by *blue*. (Modified from Mori et al. 2013)

In the mouse olfactory system, each olfactory sensory neuron expresses only one type of functional odorant receptor among a repertoire of more than 1,000 different odorant receptor types, a phenomenon called the "one cell–one receptor" rule. Each olfactory sensory neuron projects a single axon (olfactory axon) to a single glomerulus in the olfactory bulb, which has approximately 1,800 glomeruli spatially arranged around its surface (Fig. 1.3). Axons of numerous olfactory sensory neurons expressing the same type of odorant receptor converge onto two target glomeruli located at fixed positions in the olfactory bulb (see Chap. 3). Each glomerulus therefore represents a single type of odorant receptor (the "one glomerulus—one receptor" rule).

Within each glomerulus of the olfactory bulb, olfactory axons form excitatory synaptic connections on the terminal tufts of primary dendrites of two types of projection neurons, tufted cells and mitral cells (Figs. 1.3 and 1.4). Because of the one glomerulus—one receptor rule, all the olfactory axons and all the sister tufted and mitral cells that project to a single glomerulus form a functional module (glomerular module or glomerular unit) that represents a single type of odorant receptor (Mori and Sakano 2011; Shepherd et al. 2004). For information on the synaptic organization of the olfactory bulb, we refer readers to Shepherd et al. (2004).

The olfactory cortex is defined as those areas that receive direct synaptic input from projection neurons in the olfactory bulb (Fig. 1.5) (Neville and Haberly 2004; Price 1985; Wilson and Sullivan 2011). Individual mitral cells have large cell bodies in the mitral cell layer and send axons in a dispersed manner to virtually

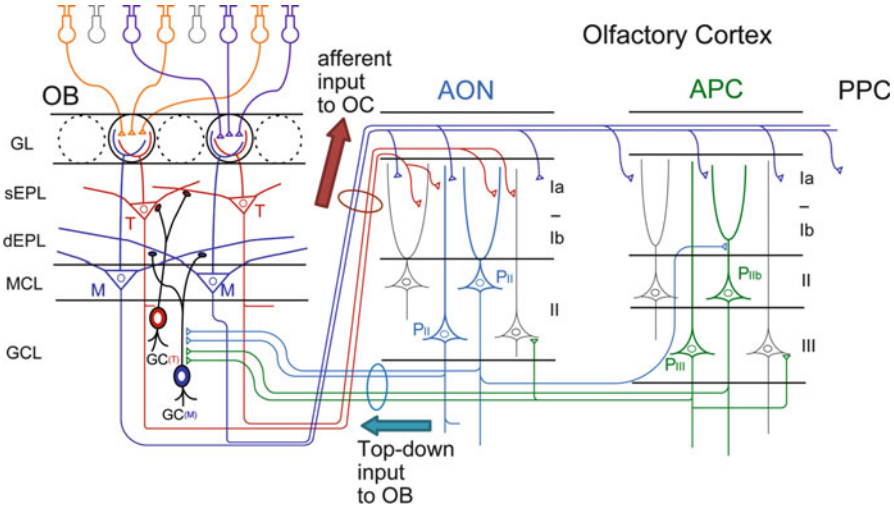

Fig. 1.4 Schematic diagram of the neuronal circuit of the olfactory system shows connectivity of olfactory sensory neurons in the olfactory epithelium (*upper left*), projection neurons and local interneurons in the olfactory bulb (*OB*), and pyramidal cells in the anterior olfactory nucleus (*AON*) and anterior piriform cortex. *GL* glomerular layer, *sEPL* superficial part of the external plexiform layer, *dEPL* deep part of the external plexiform layer, *MCL* mitral cell layer, *GCL* granule cell layer, *T* tufted cell, *M* mitral cell, *GC*(*T*) tufted cell-targeting granule cell, *GC*(*M*) mitral cell-targeting granule cell, *PII* pyramidal cell in layer II of the AON, *PIIb* pyramidal cell in layer IIb of the APC, *PIII* pyramidal cell in layer III of the APC, *PPC* posterior piriform cortex. (Modified from Yamaguchi et al. 2013)

all areas of the olfactory cortex, including the piriform cortex (anterior and posterior piriform cortex), areas in the olfactory peduncle (anterior olfactory nucleus, tenia tecta, and dorsal peduncular cortex), olfactory tubercle, cortical amygdaloid nuclei (nucleus of the lateral olfactory tract, anterior cortical amygdaloid nucleus and posterolateral cortical amygdaloid nucleus), and lateral entorhinal area (Figs. 1.4, 1.5, and 1.6) (Haberly and Price 1977; Igarashi et al. 2012; Luskin and Price 1983; Neville and Haberly 2004; Shipley and Ennis 1996). Tufted cells have smaller cell bodies that are distributed in the external plexiform layer (EPL). Each tufted cell projects axons selectively to focal targets in the olfactory peduncle areas, the rostroventral part of the anterior piriform cortex, and rostrolateral parts of the olfactory tubercle (see Chap. 7).

Except for the olfactory tubercle, all areas of the olfactory cortex have a pyramidal cell-based cortical organization (Figs. 1.4 and 1.6) (Neville and Haberly 2004). Each of these areas has a relatively simple cortical structure, typically with three distinct layers (I, II, and III). Axons of olfactory bulb projection neurons (afferent input) form excitatory synaptic connections (in layer Ia) on the apical dendrites of layer II and layer III pyramidal cells (Figs. 1.4 and 1.6). The pyramidal cells send association fibers to form excitatory synapses on neurons in the same area and in other areas of the olfactory cortex and higher association areas. In the

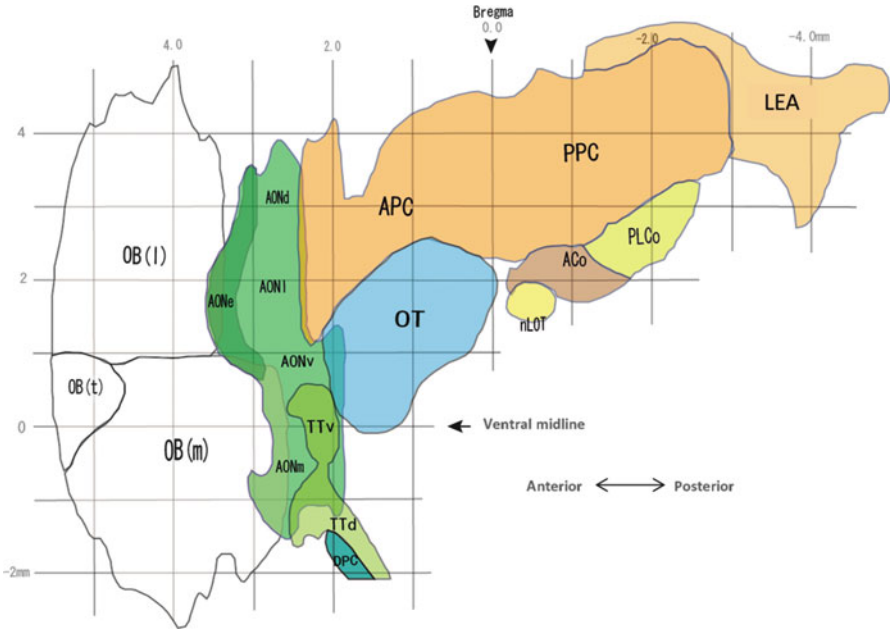

Fig. 1.5 Unrolled flattened map of olfactory bulb (*OB*) and olfactory cortex (*ventral view*). The unrolled map of the olfactory cortex was reconstructed based on the coronal sections of the mouse brain shown in Paxinos and Franklin (2001); that of the olfactory bulb was reconstructed by OCAM-labeled coronal sections shown in Nagao et al. (2000). *OB*(*l*) lateral map of the olfactory bulb, *OB*(*m*) medial map of the olfactory bulb, *OB*(*t*) tongue-like region of the olfactory bulb, *AONe* anterior olfactory nucleus pars externa, *AONd* dorsal part of the AON, *AONl* lateral part of the AON, *AONv* ventral part of the AON, *AONm* medial part of the AON, *TTv* ventral tenia tecta, *TTd* dorsal tenia tecta, *DPC* dorsal peduncular cortex, *APC* anterior piriform cortex, *OT* olfactory tubercle, *nLOT* nucleus of lateral olfactory tract, *ACo* anterior cortical amygdaloid nucleus, *PLCo* posterolateral cortical amygdaloid nucleus, *PPC* posterior piriform cortex, *LEA* lateral entorhinal area. Different areas of the olfactory cortex are shown by different colors

afferent pathways (Figs. 1.4 and 1.6), direct afferent input from the olfactory bulb terminates in layer Ia of the piriform cortex, whereas association fiber inputs terminate mainly in layer Ib (Neville and Haberly 2004). Pyramidal cells in layers II and III of the anterior olfactory nucleus and anterior piriform cortex also massively project collateral axons of the association fibers to the olfactory bulb, and thus form top-down feedback pathways (Fig. 1.4).

Figure 1.7 illustrates the major olfactory afferent pathways from the piriform cortex to the neocortex. Pyramidal cells in layer II of the anterior piriform cortex (APC) project axons to the orbitofrontal cortex (OFC), which includes the ventrolateral orbital cortex (VLO) and lateral orbital cortex (LO). These pyramidal cells also project axons to the ventral agranular insular cortex (AIv) of the neocortex. The projection from the APC to the OFC/AIv is composed of two parallel pathways (Ekstand et al. 2001): pyramidal cells in the ventral part of the APC (APCv) project axons to the VLO, and those in the dorsal APC (APCd) send axons to the LO and AIv.

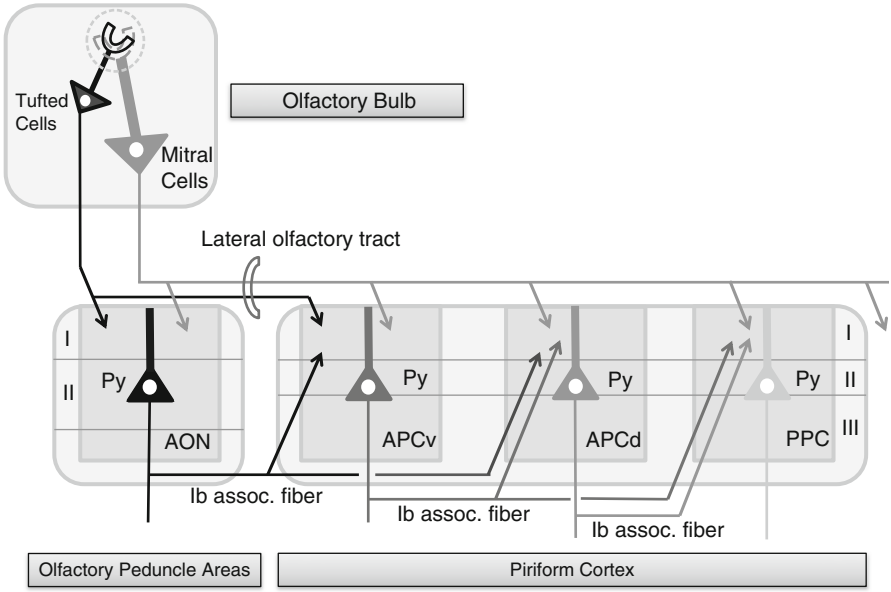

Fig. 1.6 Olfactory afferent pathways from the olfactory bulb through the anterior olfactory nucleus to the three subdivisions of the piriform cortex. Tufted cell axons and mitral cell axons form two types of direct afferent pathways from the olfactory bulb and terminate in the superficial part of layer I (layer Ia) of the olfactory cortex. *AON* anterior olfactory nucleus, *APCv* ventral subdivision of the anterior piriform cortex (APC), *APCd* dorsal subdivision of the APC, *PPC* posterior piriform cortex. Ib association fiber afferent pathways (*Ib assoc. fiber*) are also shown by *arrows* that terminate in the deep part of layer I (layer Ib). *Py* pyramidal cell; *I*, *II*, and *III* indicate layers I, II, and III, respectively, of the olfactory cortex

The olfactory pathway to the OFC/AIv is unique in that the orbitofrontal cortex is only three synapses (olfactory bulb, APC, and OFC synapses) distant from olfactory sensory neurons. However, in addition to the direct projection from the APC to OFC/AIv, indirect transthalamic pathways are also present (Fig. 1.7). The APCd projects axons to the endopiriform nucleus (En), which projects axons to the mediodorsal nucleus (MD) of the thalamus. Thalamocortical neurons in the MD project axons to the LO and AIv. The APCv connects with the pre-endopiriform nucleus (pEn), which projects axons to the submedius nucleus (SM) of the thalamus. Thalamocortical neurons in the SM send axons to the VLO.

The direct projection from the piriform cortex to the neocortex shows broad topographical organization (Figs. 1.7 and 1.8) (Ekstand et al. 2001; Ray and Price 1992). The APCv projects to the VLO, the most rostral target area of the neocortex. The APCd directly sends axons to the LO and AIv. Pyramidal cells in the posterior piriform cortex (PPC) project axons to the AIv and posterior agranular insular cortex (AIp). The OFC in turn projects axons back to layer III of the piriform cortex. This top-down projection also shows broad topography, as shown in Fig. 1.7

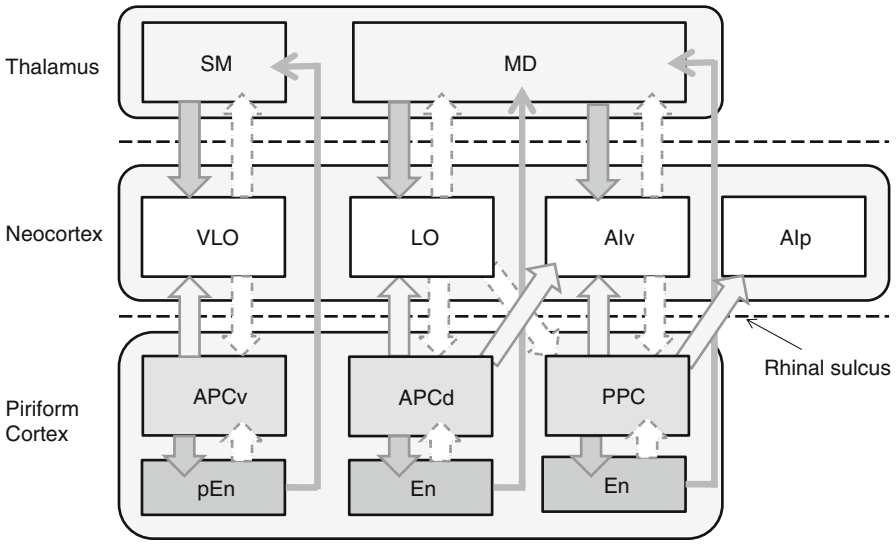

Fig. 1.7 Direct and transthalamic pathways from the three subdivisions of the piriform cortex to the neocortex. Ventral subdivision of the anterior piriform cortex (*APCv*), dorsal subdivision of the anterior piriform cortex (*APCd*), and posterior piriform cortex (*PPC*) form distinct pathways to the neocortex. *VLO* ventrolateral orbital cortex, *LO* lateral orbital cortex, *AIv* ventral agranular insular cortex, *AIp* posterior agranular insular cortex, *SM* submedius nucleus of thalamus, *MD* mediodorsal nucleus of thalamus, *pEn* pre-endopiriform nucleus, *En* endopiriform nucleus. *Solid arrows* indicate afferent axonal connections; *broken arrows* show top-down connections

(Illig 2005). The lateral entorhinal cortex has reciprocal connections with the perirhinal cortex (Fig. 1.8) (Amaral and Lavenex 2007).

The olfactory cortex is a key structure that sends olfactory sensory information not only to the neocortex but also to other higher association areas (Fig. 1.8). For example, the lateral entorhinal cortex sends axons to the hippocampus, forming olfactory afferent pathways to the hippocampus. The piriform cortex and cortical amygdaloid nuclei have rich connectivity with the amygdaloid nuclei, forming olfactory afferent pathways to the amygdala. The piriform cortex and other areas of the olfactory cortex also project to the lateral hypothalamus, forming the olfactory afferent pathways to the hypothalamus.

The olfactory tubercle is unique among areas of the olfactory cortex and thus appears to be functionally distinct from other areas of the olfactory cortex. Although it has a cortical organization, principal neurons in the olfactory tubercle are GABAergic medium spiny neurons (Millhouse and Heimer 1984). These medium spiny neurons do not send association fibers to other areas of the olfactory cortex but send inhibitory output to the neurons in the ventral pallidum. The ventral pallidum neurons are GABAergic neurons that send inhibitory outputs to neurons in the mediodorsal nucleus of the thalamus, dopaminergic neurons in the ventral tegmental area, and neurons in the lateral hypothalamus. Together with the accumbens, the olfactory tubercle forms the ventral striatum (Heimer 2003;

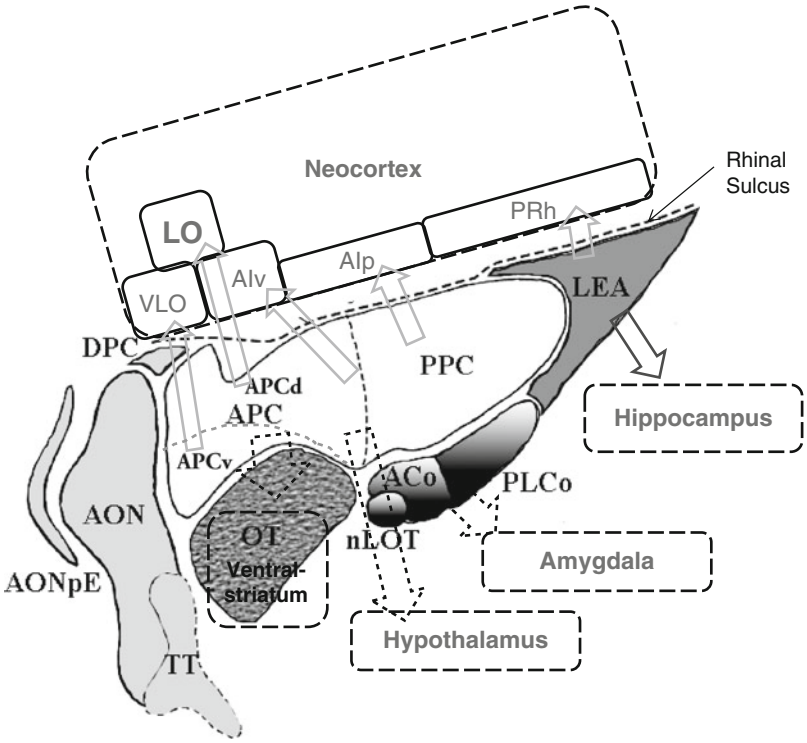

Fig. 1.8 Major olfactory afferent pathways from the olfactory cortex to the neocortex, hippocampus, amygdala, hypothalamus, and ventral striatum. Unrolled map of areas in the olfactory cortex is reconstructed based on Fig. 1.5. Olfactory peduncle areas include anterior olfactory nucleus (*AON*), anterior olfactory nucleus pars externa (*AONpE*), tenia tecta (*TT*), and dorsal peduncular cortex (*DPC*). The three subdivisions of the piriform cortex are the ventral subdivision of the anterior piriform cortex (*APCv*), the dorsal subdivision of APC (*APCd*), and the posterior piriform cortex (PPC). The olfactory tubercle (*OT*) is part of the ventral striatum. Cortical amygdaloid nuclei include the nucleus of the lateral olfactory tract (*nLOT*), the anterior cortical amygdaloid nucleus (*ACo*), and the posterolateral cortical amygdaloid nucleus (*PLCo*). Lateral entorhinal area (*LEA*) forms the pathway to the hippocampus. Each target area in the neocortex is surrounded by a *solid line*. *VLO* ventrolateral orbital cortex, *LO* lateral orbital cortex, *AIv* ventral agranular insular cortex, *AIp* posterior agranular insular cortex, *PRh* perirhinal cortex

Ikemoto 2003, 2007; Ikemoto et al. 2005; Switzer et al. 1982) and is thought to have a key role in the olfactory cortex–ventral striatum–ventral pallidum–thalamus–frontal cortex loop (see Chap. 8).

In addition to these major afferent pathways, a variety of associational and top-down axonal projections occur across different regions of the central olfactory system. The central olfactory system thus forms large-scale neuronal networks that connect local circuits in the olfactory bulb, olfactory cortex, orbitofrontal cortex, agranular insular cortex, thalamus, hypothalamus, amygdala, hippocampus, and ventral striatum. Olfactory researchers are now struggling to understand the

functional logic of the large-scale networks of the central olfactory system that enables human and animals to translate external odor information to appropriate behavioral outputs.

As described in the previous section, the information processing mode in the large-scale networks of the olfactory system depends heavily on the sniff cycle. Therefore, olfactory researchers are interested in the question of "when" in the sniff cycle the central olfactory system translates the external odor information to behavioral outputs. During the on-line inhalation phase of the sniff, what type of information processing occurs in the large-scale networks of the central olfactory system? During the inhalation phase, how and via which pathways is the odor information transferred in the large-scale networks? In parallel with the transition from inhalation phase to exhalation phase, the information processing mode and the direction of information streams appear to change. It is largely unknown, however, how the large-scale networks of the central olfactory system change the information processing mode at different phases of the sniff cycle. Future research will address these questions, which are particularly important in understanding the workings of the central olfactory system.

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