38. Cortical Olfactory Processing

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The act of smelling is a fundamental perceptual process mediated by the evolutionary very old olfactory system. Smells influence human behavior strongly related to survival, such as food consumption, hazard avoidance, sexuality, and reproduction. Hence, olfactory stimuli are of high ecological importance and are processed in phylogenetically old brain areas. This anatomical deviation leads to changes in the cortical organization of networks responsible for olfactory processing in comparison to other sensory systems that can be perfectly examined with the help of neuroimaging methods.

Within this chapter insights about the anatomy of the peripheral and central olfactory structures will be provided and physiological processes that are the basis for olfactory perception will be explained. The way of the olfactory information processing – starting with the molecules that are sniffed and bind to the receptors in the olfactory epithelium, to information transmission to the olfactory bulb and onward to olfactory cortical areas – will be traced. Alongside this, the reader will be informed about the clinical implications of the sense of smell.

38.1 Sniffing of Odors

To sniff or to draw air into the nose is the physiological precondition of olfactory perception. A sniff is defined as a reflex elicited by chemicals – either irritants or odors. This olfactomotor activity causes a certain level of turbulence in the nostrils responsible for the transport of odors to the olfactory epithelium located in the upper part of the nasal cavity. A sniff is traditionally viewed as a simple transport mechanism carrying the odors to the receptors; however, it can also be considered the earliest stage of olfaction as compared to eye movement in vision [38.1]. Sniffing does not only influence olfactory intensity but also odor identity or quality perception, and sniffing patterns can be quite divergent between individuals, and depending on task [38.2, 3]. Odorant molecules depending on their shape have a distinct sorption rate on the mucosa and high sorption rate odorants are better perceived at high velocities and vice versa [38.4–6]. This is of special interest since the human nose underlies a nasal cycle during which the mucosa alternates between congestion and decongestion from one nostril to the other leading to low and high velocities of the sniffed air [38.7]. In other words, at a given time we find low velocity and a better uptake of low sorption rate odorants in the congested nostril and vice versa in the decongested nostril. Consequently, a different olfactory percept is conveyed through each nostril at a given time [38.5].

Natural sniffing provides optimal chemosensory perception [38.8] and sniff magnitude is largely related to olfactory pleasantness – humans sniff less intense in response to an unpleasant as compared to a pleasant odorant [38.8, 9]. Additionally, breathing patterns during olfactory perception and olfactory imagery are similar [38.10] and even imagery of pleasant odors evoked larger sniffs in comparison to unpleasant odors [38.11–13]. Sniff magnitude is not only of interest with regard to common odors but also due to chemosensory emotional cues. Evidence stares that sniff magnitude increases when smelling fear sweat and decreases after smelling disgust sweat. This phenomenon is interpreted as sensory acquisition and rejection behavior [38.14].

As stated earlier, sniffing is needed for the conscious perception of odorants; however, the adjustment of sniff response also appears during unconscious odor perception. Therefore, the measurement of sniff response offers a great opportunity to examine processing of consciously undetected stimuli [38.15] and renders possible an implicit measure, for example, during sleep [38.16].

Another interesting aspect of sniffing behavior is that humans unconsciously mimic olfactory acquisition behavior of their conspecifics: *Arzi* et al. used the movie *Perfume* to show that the observers sniffed as soon as the characters in the movie started sniffing. This mirror sniffing effect was strongest when subjects heard the sniff but did not see the object emanating a smell. Mirror sniffing is interpreted as a form of mimicry, contagious behavior, such as laughing or yawning or a form of orienting response [38.17].

Regarding the activation of brain areas, sniffing of odorless air alone leads to an activation in the olfactory bulb [38.18] as well as in piriform and orbitofrontal cortices [38.19, 20]. Probably, this activation of typical olfactory brain areas is related to the airflow in the nostrils and provides important hints for the computation of olfactory information. In other words, the sniff prepares the olfactory cortical network for incoming chemosensory information. Further, the hippocampus and the cerebellum are considered the neural control centers of olfactomotor response. The hippocampus receives olfactory information from the entorhinal cortex and projects to respiratory centers [38.1, 21]. Activation of the cerebellum during olfactory perception is interpreted as a feedback mechanism adjusting breathing volume according to odorant concentration [38.22].

Since sniffing is necessary for odor perception, neurological or psychiatric disorders that are accompanied with smell dysfunction might be related to impairments of sniffing [38.1]. Sniffing deficiencies that are at least partly related to olfactory impairment have been proven for patients suffering from Parkinson's disease [38.23]. Additionally, children with autism spectrum disorder showed an altered sniff response in comparison to typically developing children and did not adjust sniff magnitude with regards to odor pleasantness [38.24]. The measurement of sniff response can thus be considered as novel diagnostic tool and biomarker for several neurological and psychiatric diseases. To go one step further, sniffing is also a helpful tool in emergency medicine: sniffing enables communication and environmental control in severely disabled people. In an elegant study, *Plotkin* and colleagues [38.25] established that sniffing provides a control interface to write text and drive an electric wheelchair in patients suffering from locked-in syndrome.

38.2 Olfactory Epithelium

The molecules that are sniffed, reach the olfactory epithelium situated in the upper part of the nasal cavity. The olfactory epithelium lines the mucosa right below the cribriform plate and the mucosa of the superior turbinate and houses the olfactory receptors, G-protein coupled receptors [38.26]. Humans possess approximately 340–400 different functional olfactory receptor genes coding for olfactory receptors [38.27–29]. Odor molecules retain different functional groups activating different receptors. In other words, the olfactory receptors are units that detect molecular features of the odorants [38.30]. One study provides a first hint for a topographical organization of the olfactory receptors in the epithelium based on pleasantness of the odors that activate the receptor [38.31].

Olfactory receptor cells are bipolar cells; their apical end is situated in the nasal mucosa where the odorants bind to the receptors. This causes an action potential that travels along the long axon of the receptor cell (fila olfactoria, that are grouped into the olfactory nerve – cranial nerve I) through the lamina cribrosa directly into the olfactory bulb [38.26]. Please see Chap. 27 for more details on odorant sensing.

By means of a combinatorial code, it is possible that thousands of different odor molecules are recognized with a relatively low number of receptors [38.32]. In scientific literature of the last decades it is assumed that humans can perceive about 10 000 different odors. Recently, psychophysical testing was used for an estimation of the actual number of discriminable smells. In contrast to the existing literature, the authors approximate that humans can discriminate more than one trillion different substances by their smell [38.33] and hence provide evidence that the olfactory system outperforms other sensory systems with regards to the number of physically different perceivable stimuli.

Although humans can distinguish such a great number of smells, they perform surprisingly bad at naming familiar olfactory impressions [38.34]. The interactions between language and olfactory perception are complex (see also Chap. 53).On the one hand, it is more difficult to assign words to an olfactory experience than to any other sensory experience. It is supposed that this shortcoming is based on the early development of the olfactory system in relation to the relatively late development of the language system during evolution [38.35]. On the other hand, olfactory stimuli can be processed without any linguistic involvement – smelling an odor without identifying it can lead to episodic memory recall and a strong emotional response. Controversially, in case a word and an odor are presented concomitantly and thereby linked to each other, words and verbal context are more powerful modulators of olfactory information than stimuli of any other sensory modality [38.36]. More recent studies established that the odor-language integration network consists of the orbitofrontal cortex and the anterior temporal lobe/temporal pole for odor object coding and semantic integration and the inferior frontal gyrus for olfactory naming and verbalization [38.37–39]. Another area that might be of importance for olfactory identification processes is the olfactory bulb. In a voxel-based morphometry study, olfactory bulb volume of the subjects predicted behavioral performance in an olfactory identification test – the larger the olfactory bulb the better are humans in identifying the odor [38.40]. Within the network of the brain areas described earlier, smells are linked to their name and odor identification takes place.

38.3 Olfactory Bulb

The olfactory bulb is considered the first relay station in the olfactory system. In the glomeruli of the olfactory bulb, olfactory information is transmitted from the primary neuron, the olfactory receptor cell to a secondary neuron, the mitral cell. Glomeruli respond to a range of different odorants that share a particular pattern of molecular characteristics. Further, glomeruli that receive input related to a similar molecular range group together and form molecular-feature clusters in the bulb [38.30]. Thus, odorant-specific activation of receptors is translated into an odorant-typical spatial activation pattern in the olfactory bulb [38.41, 42]. At this stage, we find a high level of convergence from thousands of neurons onto a few glomeruli.

The olfactory bulb also contains periglomerular neurons and interneurons transmitting inhibitory signals to neighboring glomeruli, as well as to the contralateral olfactory bulb. Those cells also receive retrograde inhibitory signals from higher order brain areas. The functional importance of those cells is to enhance the contrast between olfactory stimuli and background noise resulting in an increase of discriminability and sensitivity of the system.

Until recently, the olfactory bulb was largely underestimated regarding its function and importance. Nowadays, it is recognized that the olfactory bulb fulfills tasks comparable to that of other primary sensory cortices. In the olfactory bulb, the signal is condensed and amplified and a basal cognitive processing already takes place. Although traditionally the piriform cortex (pirC) has been termed as primary olfactory cortex, due to the discovery of the sophisticated functions of the pirC (see in the following) this concept does not hold true. Thus, the olfactory bulb serves as primary olfactory cortex encoding the chemical features of odorants and organizing them in a spatial pattern [38.43–46].

One of the anatomical deviations of the olfactory system is that olfactory information can be transmitted to cortical areas without a thalamic relay [38.47]. Thereby smells have the capability to bypass attentional gating processes. The olfactory bulb can hitherto also be considered the olfactory thalamus [38.48]. This is reasoned since the olfactory bulb has a bottleneck and relevance filter function regarding information processing before the cortex, comparable to the function of the thalamus in processing of other sensory stimuli.

38.4 Central Olfactory Pathways and Networks

From the olfactory bulb, the information about the chemical structure of an odorant is transmitted via the lateral olfactory tract to a set of small structures: the pirC, the entorhinal cortex, the amygdala and periamygdaloid cortex, the olfactory tubercle, and the anterior olfactory nucleus. An overview about the olfactory pathways and network can be found in Fig. 38.1.

The pirC is one of the key nodes in the cortical olfactory system. In a recent meta-analysis of olfactory brain imaging data the pirC revealed the highest activation consistency across all included functional imaging studies (Fig. 38.2) [38.50]. The pirC is anatomically divided into two parts that are responsible for different tasks. The anterior or frontal part of the pirC is

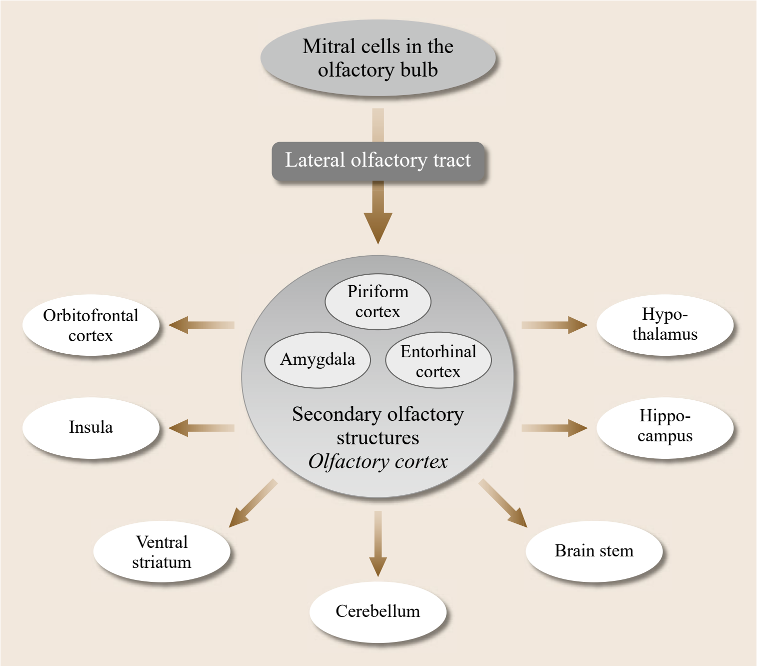

Fig. 38.1 Brain areas involved in olfactory processing (after [38.49])

related to an initial neural representation of an odorant and encoding of its molecular features [38.51], whereas the posterior or temporal part of the pirC is responsible for a holistic odor object formation, hedonic quality coding, and categorization [38.52, 53]. In the pirC the perceptual quality of an odor is shaped by attention [38.54], expectancy [38.55–57], learning [38.58], recognition and memory [38.59], as well as valence-dependent responses [38.60]. The pirC can consequently be considered association cortex connecting olfactory perception with behavioral, cognitive and contextual information [38.43, 46].

The olfactory bulb and pirC send projections to the entorhinal cortex that renders the gateway to the hippocampus responsible for memory processes [38.61]. From rodent studies, it is suggested that the entorhinal cortex projects back to the pirC and the olfactory bulb and thereby serves as a *powerful top-down modulator of olfactory cortical function and odor perception* [38.62]. The entorhinal cortex, especially the transentorhinal region is one of the first brain areas showing a neuropathology in patients suffering from Alzheimer's disease [38.63, 64] and is thus responsible for early olfactory deficits seen in Alzheimer's disease patients. For further insights about disrupted olfactory perception please refer to Chap. 31.

The amygdala and periamygdaloid cortex receive input from the olfactory bulb and the pirC and are responsible for a cognitive evaluation of olfactory input. In a recent meta-analysis about predictors of amygdala activation it was established that olfactory and gustatory stimulation had the highest amygdala activation probability in comparison to other sensory modalities [38.65]. Traditionally, the amygdala was considered the neural substrate for odor pleasantness assignment [38.66, 67]. More recently, evidence arose

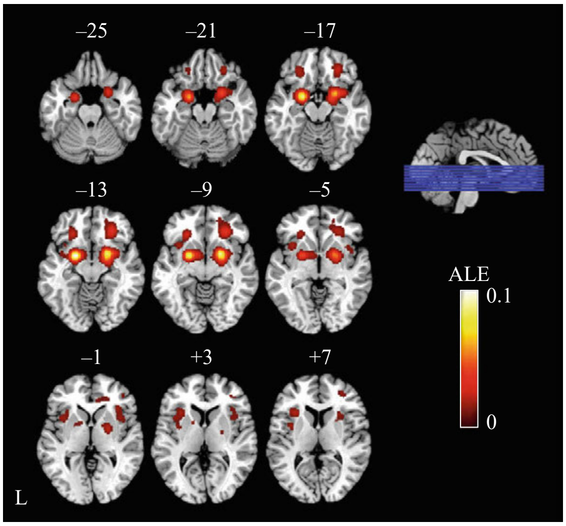

Fig. 38.2 Typical brain activation during olfactory stimulation. Depicted are the results of a meta-analysis of olfactory brain activation in 45 functional imaging studies. Bilateral activation of the pirC, the OFC, as well as anterior insula can be found (courtesy of Elsevier, after [38.57])

that the amygdala is rather responsible for olfactory intensity coding but only if the odor is considered pleasant or unpleasant. In other words, emotional or behavioral salience encoding takes place in the amygdala [38.68], whereas odor pleasantness or valence is coded in the orbitofrontal cortex [38.69]. Please see Chap. 39 for a detailed review on olfactory valence.During studies using chemosensory stimulation, amygdala response was correlated with response in pirC, orbitofrontal cortex, and insula hinting toward a network of those areas responsible for processing of chemosensation [38.70].

An attempt to describe the temporal pattern of odor perception is the cascade model of olfactory perception by Jonas Olofsson. This model states that odor detection is the first and fastest step followed by a direct odor valence determination. An indirect path links odor detection with odor valence by way of identification of the odor object. The slowest perceptual process is the rating of edibility of the odorant [38.71]. Hence, olfactory perception is based on a hierarchical and partial parallel organization of the olfactory system [38.72].

From this set of smaller brain areas, olfactory information is passed on to brain areas that are not specific for olfactory processing but rather convey cognitive processes related to the perception of odors: the orbitofrontal cortex (OFC), the insula, hippocampus, thalamus, hypothalamus, ventral striatum, cingulate cortex, and the cerebellum.

Here the OFC is considered a key node in the olfactory system and a crucial center for cognitive odor processing. In the OFC higher order processes shape the odor signal coming from the pirC and create the final conscious smell percept. While olfactory bulb volume predicted olfactory identification of healthy subjects, OFC volume rather predicted threshold scores and olfactory discrimination ability [38.40]. Thus, the OFC mediates processes related to olfactory sensitivity and discrimination tasks. Further, experience-dependent modulation of the signal as well as affective coding (as stated earlier) are computed in the OFC. It is also known, that the OFC is the brain area in which olfactory information is integrated with information from other sensory modalities [38.73] and the language system [38.39]. With regards to food odor perception, the OFC involves mechanisms of reward assignment [38.74]. Hence, the OFC does not exclusively process odor information but rather engages in processes important for human perceptual decision-making and resolving sensory uncertainty.

The insula is traditionally considered primary gustatory cortex [38.75]; however, displays frequent activation as response to odors. It receives input from not only pirC and amygdala, but also from OFC [38.76]. Evidence exists that the anterior insula plays a role in integrating chemosensory information especially with regards to food [38.45] leading to an integrated flavor perception [38.77]. Furthermore, the anterior insula is crucial for the elicitation of avoidance behavior and is thus correlated not only with the perception of negatively valenced olfactory or trigeminal stimuli [38.78] but also negative multisensory stimulus combinations [38.79]. The insula moreover is involved in regulation of autonomic interoception. In the context of a strong connectivity of the insula with pirC, amygdala, and OFC it can be suggested that chemosensation influences interoception and interoceptive processes are regulated within this network [38.70].

The olfactory system is unique in the sense that sensory information passes only two synapses and reaches brain areas involved in emotion and memory processing. The hippocampus conveys memory processing associated with odorants. Smells indeed can elicit very vivid and emotional memories. On a timeline, smells in comparison to pictures or language have the capability to evoke memories of early life – smells remind us of earlier events in comparison to pictures or language [38.80]. For a more detailed description of olfactory memory processes please refer to Chap. 42. The hippocampus further seems to be involved in integration of olfactory with other sensory stimuli [38.73].

As already mentioned, the main direct pathway of olfactory information processing is from the olfactory bulb and pirC to the neocortex; however, an indirect pathway through the mediodorsal thalamus to the neocortex also exists. The mediodorsal thalamic nucleus (MDT) is considered a part of the thalamus responsible for odor processing as it receives afferents from pirC, amygdala, enthorhinal cortex, and projects to the OFC [38.81, 82]. In an elegant study, *Plailly* and colleagues [38.83] demonstrated that attention toward an odor strengthened the connectivity between the MDT and the neocortex (OFC). As described earlier, in olfaction the OB and pirC inherit functions of a primary sensory thalamic control including sensory coding, gain control and state-dependent modulation. Hence, the MDT might rather be seen as a higher order olfactory thalamus [38.82].

The cingulate cortex, especially the anterior cingulate is traditionally involved in odor–taste integration and is therefore considered a part of the flavor network [38.84]. Cingulate cortex belongs to the limbic system and its activation is also frequently found following olfactory stimulation and might therefore be involved in attention processes in relation to odors. Especially the anterior cingulate is responsible for detection of conflicts of attention [38.85].

As stated earlier, the involvement of the cerebellum in olfactory processing was established as a kind of regulation center that adjusts sniff magnitude to concentration of the smell [38.22]. The sniffs of patients with cerebellar lesions were invariant with regard to odor concentration and thus olfactory identification was impaired. The authors suggest an olfactocerebellar pathway that is important for identification of odorants [38.86].

38.5 Conclusion

Taken together, the olfactory system involves three anatomical deviations. First, the main central gate for olfactory input is the olfactory bulb; here we find a topical map of odor representation. Olfactory information does not pass a thalamic relay on its way from receptors to neocortex, which might be the reason for a multitude of unconscious processes involved in olfactory perception. Second, olfactory information is first processed in the paleocortex (olfactory bulb, pirC) and then passed on to the neocortex while sensory information in other modalities is mainly processed in neocortex. Third, the olfactory system is strongly connected to the limbic system resulting in strong emotionally toned responses to odors and robust relation to memory processing. Those characteristics of the olfactory cortical system form the basis for smell perception which renders unique among other sensory perceptions.

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