The Human Sense of Olfaction

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Abstract

The sense of olfaction is important not only for the detection of potential dangers such as fire or spoilt food, but also for the quality of life of human beings. In this article, we review the characteristics of the sense of smell and give a short overview about possible olfactory dysfunctions and their therapy.

Keywords
- olfaction
- smell
- olfactory disorders
- characteristics

The human sense of smell is, in many aspects, different from other senses. In the following paragraphs, we would like to review the main characteristics of this extraordinary sense and illustrate what happens if it is impaired.

The Sense of Olfaction is Crucial for the Detection of Potential Dangers, Social Information, and Nutritional Information

Human beings rely on their sense of smell for the detection of potential harms such as fire, smoke, toxic chemicals, and also spoiled food.[1] Research showed that patients with reduced olfactory function often have problems with cooking (73%) or loss of appetite (56%). Odors play a major role in evaluating food's edibility; hence, patients with olfactory disorders may eat rotten (50%) or burnt (30%) food, which may result in food poisoning.[2] On the other hand, olfaction is important for the enjoyment of food, as it is assumed that approximately 80% of the flavor information of a tasty meal is transmitted through olfaction.[3] This can be explained by olfactory information of food being released during the mastication process in the oral cavity and reaching the olfactory receptor neurons in the nose through the retronasal passage. So it is not surprising that olfactory dysfunction can also lead to a change in the dietary habits of the affected patient, as they are trying to compensate their problem by using sweeteners, salt, or irritants/spices to their meals to improve the taste by gustation and trigeminal information. Possible consequences might be either weight gain[4] or weight loss[5] caused by reduced appetite. Patients often confound olfactory-mediated sensations with gustatory-mediated sensations. Therefore, it is not surprising that patients report to suffer from a decreased taste sensitivity, when they actually show reduced olfactory function and the gustatory function—objectively tested—is normal.[6] Self-ratings of olfactory and/or gustatory function are commonly inaccurate,[7–10] which highlights the necessity to objectify olfactory and gustatory function, also to differentiate between retronasal olfactory function and gustatory function.

Odors are closely linked to positive or negative emotions; when an odor is perceived, this association is retrieved from memory.[11] Odors evoke memories, remind of beloved persons and thoughts. Accordingly, people with smell loss may feel socially isolated and insecure. Other issues may relate to personal hygiene, as they are unable to perceive their own smell.[2] Their quality of life is often impaired and patients are more likely to develop psychic problems, such as symptoms of depression (one-fourth to one-third of patients with smell disorders; for a thorough review of the literature, see article by Croy et al[12]). Interestingly, quality of life is even more affected in patients suffering from phantosmia/parosmia.[13]

Self-Ratings of Olfactory Function are Notoriously Inaccurate—That is Why Olfactory Function Needs to be Measured

Self-ratings of olfactory function are notoriously inaccurate.[7–10] Therefore, it is important, especially for medicolegal

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cases, to measure olfactory function preoperatively. In Germany, the "Working Group Olfaction and Gustation" of the German Academy of Otorhinolaryngology, Head and Neck Surgery, recommends subjective olfactometry by Sniffin' Sticks, which is one of the most frequently used methods for psychophysical assessment of olfactory function.[14] Other psychophysical methods for the sense of smell are the University of Pennsylvania Smell Identification test (UPSIT) [15] and the Connecticut Chemosensorial Clinical research Center (CCCRC) test,[16] which are the most frequently used tests for olfaction outside Europe.

Assessment of Olfactory Function

Olfactory function is divided into orthonasal and retronasal olfactory function. Orthonasal olfaction means that odorants are carried toward the olfactory epithelium via the inhalation air stream through the anterior nose, whereas retronasal olfaction describes the arrival of olfactory information, which has been released during the mastication process of food, reaching the olfactory cleft via the nasopharynx.

Assessment of Orthonasal Olfactory Function

In Europe, the most widely used test for the assessment of orthonasal olfactory function is the Sniffin' Sticks test.[14,17] This standardized, re-usable, validated test is based on odor-filled felt-tip pens. The extended Sniffin' Sticks test[17] consists of three parts: odor threshold, odor discrimination, and odor identification. The threshold task is suggested to reflect more the function of the olfactory periphery, while the suprathreshold tests (discrimination and identification) are more related to cognitive function.[18–20] The Sniffin' Sticks test should be performed in a well-ventilated, quiet room, in the order threshold → discrimination → identification test, as it has been shown that olfactory performance can be influenced otherwise, which might lead to distorted test results.[21,22]

Within the threshold subtest, 48 pens are arranged in 16 triplets with different concentrations of either *n*-butanol or phenyl ethyl alcohol (PEA). In each triplet, only one pen contains the odor (*n*-butanol or PEA) and two pens contain the solvent. The pens are presented under the nostrils of the subject and the odor-containing pen needs to be identified. The starting point of this test procedure is reached when the subject identifies the target odor twice in a row. The measurement is continued in a staircase manner, with a lower concentration being presented until it has no longer been identified correctly, then the staircase is reversed and a higher odor concentration is presented until it is correctly identified twice in a row. This procedure is repeated until seven turning points of concentration have been presented. The mean threshold value is built from the mean of the last four out of seven reversals. The administration of the odor threshold task takes approximately 15 minutes.

The second Sniffin' Sticks task is the discrimination test, also consisting of 16 pen triplets, where two pens contain the same odor and one a different one. This different scent needs to be identified in a three alternative forced choice procedure. The assessment of odor discrimination takes approximately 10 minutes.

The last part is the odor identification test, where 16 pens are presented, each containing a different odor, which needs to be identified from a list of four descriptors in a forced choice procedure.[23] In clinical routine, for example, preoperatively, often only the odor identification part of the Sniffin' Sticks is used as a screening test for olfactory function. To measure the odor, identification takes approximately 10 minutes.

Normative sex and age-related data for the extended 16-item Sniffin' Sticks test have been published.[24]

Outside of Europe, the UPSIT[25] and CCCRC tests[26] are rather used. The UPSIT is a widely used odor identification test based on the four alternatives in forced choice technique. Odors are microencapsulated on paper and released by scratching its surface ("scratch and sniff" method). The test includes five "trigeminal"-stimulating odorants to identify malingering. In terms of scoring, each correctly identified odor is 1 point, with the score ranging from 0 to 40, with a higher score indicating a better olfactory function. Normative data for this test are available.[25] It takes approximately 10 to 20 minutes to administer the UPSIT.

The CCCRC[26] test consists of a cued odor identification test plus a butanol threshold test, which is based on the method of ascending limits. For threshold assessment, odors are presented in squeeze bottles with different *n*-butanol concentrations, beginning with the lowest concentration. The subject needs to identify the odor-containing bottle out of two (two-alternative forced choice format). If incorrect, participants receive a new pair of bottles with a higher *n*-butanol concentration. If correct, the participant receives a new blank and a new bottle with the same concentration of *n*-butanol. Testing ends when five correct choices were made in a row. The concentration at which this occurs marks the odor threshold of the participant. Possible scores range from 0 to 7 points.

The odor identification test of the CCCRC comprises seven odorants and one "trigeminal" stimulant that are presented in salt dispensers or glass bottles. Possible scores range from 0 to 7 items correctly identified. The average scores of the threshold and identification test build a composite score, with 6 points or more indicating normosmia, a score between 2 and 5 points hyposmia, and a score below 2 points anosmia.[26]

Assessment of Retronasal Olfactory Function

To measure retronasal olfactory function, "taste powders" are available,[27] where 20 powders of different tastes are placed into the oral cavity and needed to be identified by the subject out of a list of four items (four-alternative-forced choice). The administration of this test takes approximately 10 to 15 minutes. Another possibility to measure retronasal olfactory function is the candy smell test,[28] where 23 unique aromas contained in sorbitol hard candies are presented to the test subject. The candy is placed onto the tongue, and while it is dissolved, the flavor is released and needs to be identified in a four alternative choice procedure.[28] The performance of the candy smell test takes approximately 20 minutes.

Objective assessment of olfactory function can be performed by an "olfactometer." With this instrument, odorous stimuli are presented within a continuous airstream without producing mechanical or thermal sensations.[29] The answer (neuronal activation) to these stimuli, olfactory event-related potentials (oERP), can be obtained from outside of the scalp via electroencephalogram (EEG) data, which is recorded from six electrodes using the international 10 to 20 systems.[30] However, the measurement of olfactory function via an olfactometer is time and money consuming and thus performed mostly in special centers as expert activities, for medicolegal reports, or at scientific studies.

The Olfactory System has the Ability to Regenerate

The olfactory system underlies a continuous equilibrium of apoptosis and neurogenesis. Olfactory stem cells, the so-called basal cells mature and replace dead neurons. There are goblet cells, as well as Bowman and mucous glands producing the mucus, and sustentacular or sustaining cells as well as microvillar cells supporting the architecture of the olfactory epithelium, which thus differs from the respiratory epithelium of the remaining intranasal and sinusoidal space (►**Fig. 1**).

The olfactory bulb (OB) plays a key role in the processing of olfactory information. OB volume, measured by magnetic resonance imaging (MRI), is therefore of interest as a morphological approach to chemosensory function, both in healthy subjects and in patients with olfactory disorders. The OB volume changes according to different types of olfactory disorders, such as sinunasal, posttraumatic, or postviral olfactory loss,[31–33] suggesting that peripheral olfactory input influences the OB volume. Similarly, reduced olfactory input, for example, after laryngectomy[34] or in nasal obstruction,[35] results in reduced OB volume. Olfactory training modulates OB volume in normosmic subjects as well.[36] However, the mechanisms of the olfactory plasticity is still a matter of discussion (for review, see the study by Huart et al;[37] for review of the question of neural regeneration at the level of the OB, see studies by Curtis et al, Lötsch et al, Sanai et al, Jessberger, and Bergmann et al[38–42]).

Adaptation/Habituation/Desensitization in Olfaction

Referring to adaptation describes the decreased perceived intensity and increased detection threshold of a special odor after it has been constantly or repetitively been exposed to the subject.[43] This phenomenon effects the facilitation of the perception of new or changing olfactory stimuli. It is processed on a peripheral and a cortical level. The decrease in responsiveness on a behavioral level is often described as *habituation*, and the decrease in responsiveness at a neuronal level is described as *adaptation*. Thus, the term *desensitization* needs to be distinguished, which is often used as the reduction in neural response in the context of constant stimulation,[44] whereas adaptation is used for a decrease in neural response occurring during repetitive stimulation. The extent of adaptation depends on several factors such as the odor itself, the duration of adaptation, and similarity of the initial odor and that used for stimulation.[45] Interestingly, adaptation is also dependent on the subjectively rated relevance the odor has for the affected subject, with a lower extent of adaptation for odor rated as more important for the person.

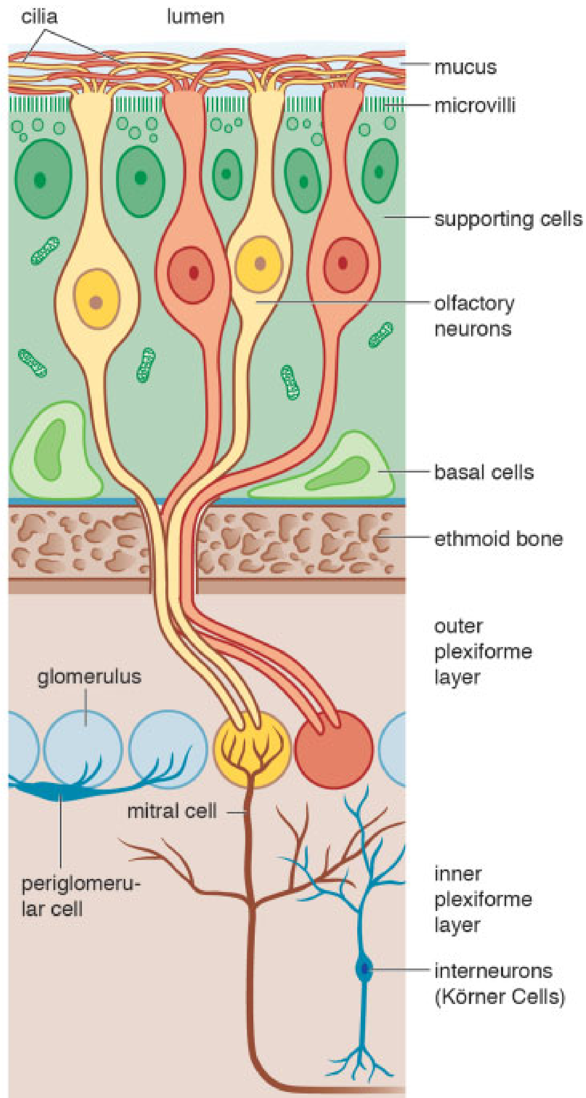

Fig. 1 Olfactory epithelium.

Odors, Emotion, and Memory

The olfactory path is a part of the palaeocortex, the oldest part of the brain, triggering emotions and accounting for memory (►**Fig. 2**).

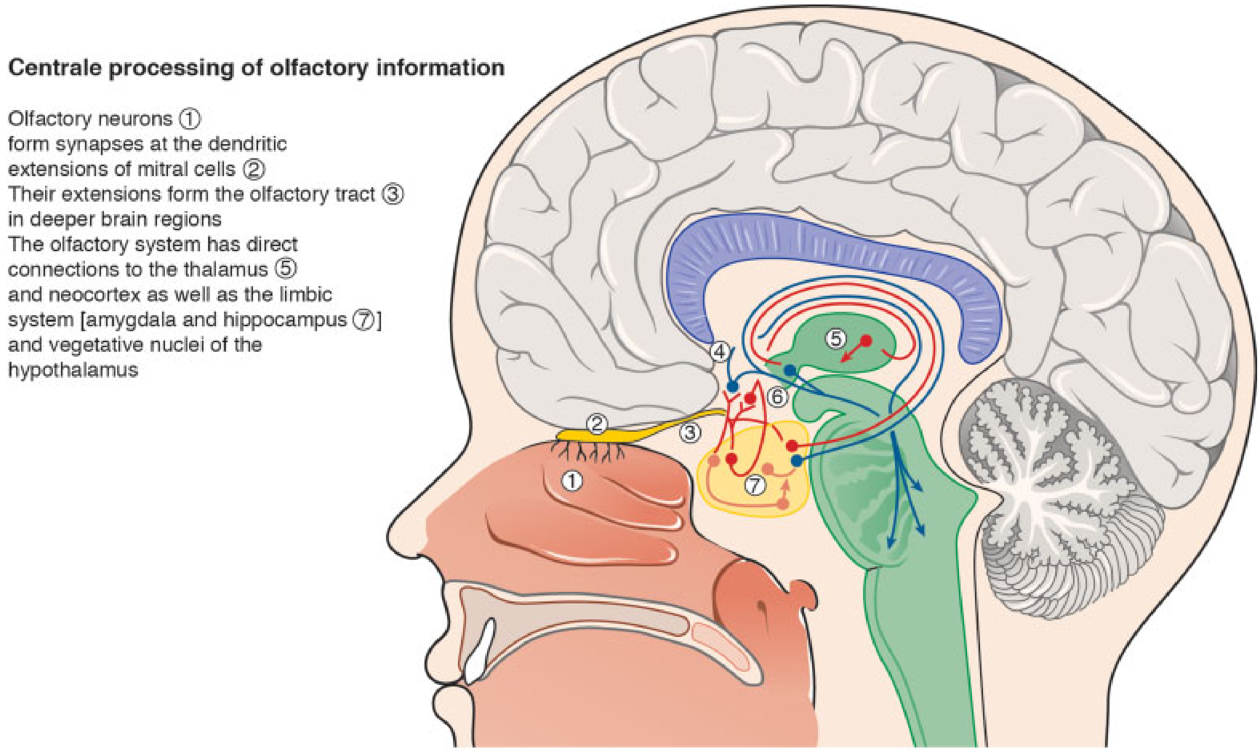

Fig. 2 Central processing of olfactory information.

Perception of olfactory stimuli is emotionally influenced. Unpleasant odors typically are perceived faster than pleasant ones and, in addition, lead to an accelerated heart rate.[46] This could also be demonstrated in a study using oERP, where the unpleasant odor (in that study H_2S) produced an earlier response compared with the pleasant odors (in that study peach and rose).[47] The mechanism that unpleasant odors are perceived faster and are linked to negative emotions like disgust[48] is suggested to reflect the warning function of the olfactory system.[47,48] Furthermore, it has been demonstrated that also the familiarity influences the perception of odors,[49] and that there is a positive correlation between the familiarity and the pleasantness of an olfactory stimulus.[50,51]

Odors are closely connected to memories of the past, able to evoke strong emotions. [52] A special perfume, for example, can evoke memories of long forgotten scenes and connected feelings of the past (odor-evoked memories). This association seems to be stronger, the more important those emotions were for the affected person.[52] It is not surprising that the same olfactory stimulus can provoke different responses in different subjects depending on whether the odor was initially linked to a good or a bad event of the subject.

Sex Differences in Olfaction

Differences between women's and men's sense of olfaction have been demonstrated for more than 100 years.[53] Later studies have shown that females score better in several olfactory tests, including detection, discrimination, and identification tasks, compared with males.[54–56] These findings were also observed in adolescents.[57,58] In addition, research concerning trigeminal and oERP found sex differences with women showing higher amplitudes and shorter latencies of the major ERP peaks than men.[59–61] There seem to be especially pronounced sex differences in the late positivity P2 peak of ERP. P2 has been shown to be associated with more cognitive aspects of stimulus processing such as stimulus salience or novelty.[62,63] Furthermore, there were significantly better results of women in lateralization tasks—indicating trigeminal sensitivity—compared with men.[64] It has been suggested that the better olfactory results in women may result from a more efficient central processing of olfactory stimuli.[61,65] Women's better olfactory function might also be influenced by a higher significance of olfaction in daily life of females.[57,66] Moreover, hormonal effects have been suggested to influence sex differences in olfaction.[67]

Olfactory Function Decreases with Increasing Age

Research with a high number (>3,000) of participants could demonstrate that olfactory function decreases significantly in humans older than 55 years,[24,68] the so-called presbyosmia. This is especially true for olfactory thresholds, which decrease more pronouncedly compared to olfactory identification or discrimination tasks.[69] However, age may not be the cause, but just an accompanying variable, as very healthy elderly people may also exhibit normal olfactory function.[70,71] Age-related decrease of olfactory function might also relate to side effects of drugs or an onset of neurodegenerative diseases. Several hypotheses have been proposed for age-related decrease in olfactory function, such as (1) changes in mucus composition, mucociliary movement, and epithelia thickness, which might disturb the transport of the odorant toward the receptor;[72] (2) reduced regeneration capacity of olfactory receptor neurons;[73] (3) changes inside the OB: reduced number, concentration, and size of mitral cells and glomeruli.[74] In healthy subjects, it was demonstrated via MRI that with increasing age and declining olfactory function, the OB volume also decreased.[65,75]

Specific Anosmia

Specific anosmia characterizes the inability to perceive a particular smell in otherwise normosmic individuals. This phenomenon, also described as partial anosmia or odor blindness, was first mentioned for vanilla more than 100 years ago.[76] It is supposed to represent a peripheral filter function of olfactory processing. The prevalence of specific anosmia in the general population primarily depends on different variables such as the investigated odor and the definition of nonperception. It may even differ between families and between human races.[77] To date, specific anosmias have been shown for approximately 60 odorants[78] and it is very likely that specific anosmias are present for many more odorants. Causes for specific anosmia are, among other factors, changes in secretion and composition of the nasal mucus on the olfactory epithelium and the expression of olfactory receptors. Interestingly, on average only around 26% of the entire olfactory receptor genes are expressed in humans beings.[79] However, olfactory perception is typically based on pattern recognition, as odorants usually bind to more than just one receptor. Consequently, nonexpression of a specific olfactory receptor can be compensated by binding of the odorant to other receptors. In addition, high concentration of the olfactory molecule coactivates the trigeminal system.[78] As a result, a person affected by specific anosmia is not necessarily unable to perceive a specific smell at all, but may have higher detection threshold for this odor compared with others. Interestingly, research could show that the perception of odors, affected by a specific anosmia, can be improved and even normalized through olfactory training.[78]

Prevalence of Olfactory Disorders in the Population

Olfactory disorders can be divided into qualitative (parosmia, phantosmia) and quantitative (anosmia, hyposmia) disorders (see ►**Table 1**). The prevalence of olfactory disorders varies between 19% (≥20 years[80]) and 24% (≥53 years[68]). The highest prevalence has been demonstrated in older males. Commonly, affected patients are unconscious of their decreased olfactory function.[68,81] The prevalence of self-reported olfactory dysfunction varies between 1.4 and 15%.[68,82,83] Quantitative olfactory disorders are more frequent compared with qualitative ones; thus, the prevalence of phantosmia is estimated between 0.8 and 2.1%[84] and that of parosmia is around 4%.[85] The prevalence of congenital anosmia is even lower and is estimated to range from 1:5,000 to 1:10,000.[86]

Olfactory Disorders Influence Taste Perception

It is well known that flavor perception is closely associated with olfaction; it is said that 80% of the information of a meal is mediated by olfactory function. During the mastication of food, flavors are released and transmitted to the olfactory cleft via the nasopharynx (retronasal smell). This retronasal olfaction is especially involved in the appreciation of food's flavor. It is not surprising that smell–taste confusions have been frequently described.[6] Only 5% of the patients presenting in smell and taste clinics actually exhibit isolated taste disorders, and the majority suffers from changes in flavor perception caused by their olfactory dysfunction.[6] In addition, olfactory disorders are accompanied by a decrease in taste function.[87–89]

Patients with olfactory Disorders Should Be Seen by an ENT Specialist

The most common etiologies of a decreased sense of smell comprise postviral upper airway infection and

Table 1 Nomenclature of olfactory dysfunctions

	Olfactory dysfunction	Definition
Quantitative olfactory disorders	Hyposmia	Decreased olfactory sensitivity
	Anosmia: Complete Functional Specific	No olfactory function present with no residual olfactory function Decreased olfactory function including complete anosmia and the situation where some minor olfactory function may be left, which is, however, not useful in daily life anymore Compared with the general population, decreased sensitivity for a specific odor without pathological value
Qualitative olfactory disorders	Parosmia	Distorted perception of an odor in the presence of an odor source
	Phantosmia	Perception of an odor in the absence of an odor source

nasal/sinonasal disease such as chronic rhinosinusitis or allergies (7–56%). This is also probably due to the high frequency of chronic rhinosinusitis in the general population.[90] Less frequent causes include head trauma (8–20%), toxic damage/drug geneses (2–6%), and congenital anosmia (0–4%).[91,92] Diagnosis of patients who complain about decreased olfactory function must include a detailed history (onset, course, nature of the disease, and medication) followed by a physical examination including nasal endoscopy to evaluate the olfactory cleft and the presence of nasal polyps. Referral to a neurologist should follow when neurological/neurodegenerative disease is suspected or in case of idiopathic olfactory loss. Imaging could include CT scan of the nasal sinuses to evaluate a possible rhinosinusitis and/or MRI, when the dysfunction is suspected to be congenital.[93]

Presented to an ENT specialist, causal treatment of patients suffering from nasal/sinonasal disease is possible by means of administration of corticosteroids alone or a combination of conservative and surgical treatment such as sinus surgery.[94] Furthermore, patients with non-sinonasal olfactory dysfunction might benefit from olfactory training. In 10 to 30% of patients affected by posttraumatic olfactory loss and in approximately 60% of the patients with postviral olfactory disorders, the sense of smell recovers at least partially over time. This recovery is more likely in young, nonsmoking patients with a high residual olfactory function and initial parosmia. Furthermore, it has been shown that a large OB volume and large amplitudes of ERP to trigeminal stimuli indicate a good prognosis in terms of recovery of the sense of smell.[93]

Olfactory function can also be impaired or improved after rhinosurgery, especially when the olfactory epithelium is affected or nasal airflow is altered postoperatively. It is thus recommended to add olfactory testing to a routine preoperative examination.[95–98]

Olfactory Dysfunction Might Indicate an Early Beginning of Neurodegenerative Disease

Several studies have demonstrated that a decreased olfactory function precedes the onset of the most frequent neurodegenerative diseases: idiopathic Parkinson's disease and Alzheimer's dementia.[93,99–101] For example, in idiopathic Parkinson's disease, approximately 75% of the patients exhibit a decreased sense of smell compared with their age group.[102] Interestingly, in idiopathic Parkinson's disease, the olfactory dysfunction precedes the motor symptoms by approximately 4 to 6 years. Thus, especially patients with idiopathic olfactory dysfunction and depression or rapid eye movement sleep behavior disorders should be considered to be referred to a neurologist to exclude idiopathic Parkinson's disease. One major problem is that the olfactory function decreases slowly and therefore is often unnoticed by affected patients. Also, in patients affected by Alzheimer's dementia, olfactory dysfunction has been shown to precede the cognitive impairment.[103]

Impairment in the sense of smell has been demonstrated also in other neurodegenerative diseases, but usually occurs not as an early sign, but at the same time as the onset of the disease, for example, in Huntington's disease,[104] Friedreich ataxia, and spino-cerebellar ataxia types 2 and 3,[93] and parkinsonian syndromes such as Lewy body dementia.[100] Other neurodegenerative syndromes such as multisystemic atrophy, progressive supranuclear ophthalmoplegia, and corticobasal degeneration do not seem to show an affected sense of smell.[100]

Olfactory Training Can Help Improve Olfactory Function

Investigations demonstrated that exposure to odors leads to improvement of olfactory function. The basis for this phenomenon is the ability of the olfactory system to regenerate. Olfactory training is recommended to be performed twice daily (in the morning and in the evening) for around 10 seconds of each odorant for a duration of 4 to 6 months. Odors suitable for the training are citronellal (lemon), cineol (eucalyptus), phenyl-ethyl-alcohol (PEA; rose), and eugenol (cloves), which represent the odor categories such as floral, fruity, aromatic, and resinous,[105] but other odors can also be used.[106,107] The efficiency of olfactory training can be further increased by an extension of the duration or a change of the trained odorants.[106] The effectiveness of olfactory training was shown for the olfactory sensitivity in healthy subjects.[108,109] Olfactory training has also been shown to be helpful in patients with postinfectious olfactory loss[110,111] or in Parkinson's disease.[112] Results of olfactory training seem to be better the shorter the olfactory disorder is present.

A special case is presbyosmia, the common decrease of olfactory function in elderly. Here, research indicates that repeated odorant exposure helps prevent olfactory deterioration, but does not improve olfactory function.[113] It is assumed that the regenerative ability of the olfactory mucosa decreases with increasing age, as also the number of mature olfactory receptor neurons decreases and cell turnover becomes slower.[114,115] This is called a disbalance of the equilibrium of apoptosis and regrowth of the olfactory cells.[110]

Conclusion

The sense of smell is complex. Its dysfunction can impair the quality of life significantly. Neuroplasticity allows for recovery and improvement of olfactory function. Olfactory screening prior to rhinosurgery is recommended.

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