Olfactory Function and Olfactory Disorders

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ABSTRACT

The sense of smell is important. This became especially clear to patients with infection-related olfactory loss during the SARS-CoV-2 pandemic. We react, for example, to the body odors of other humans. The sense of smell warns us of danger, and it allows us to perceive flavors when eating and drinking. In essence, this means quality of life. Therefore, anosmia must be taken seriously. Although olfactory receptor neurons are characterized by regenerative capacity, anosmia is relatively common with about 5 % of anosmic people in the general population. Olfactory disorders are classified according to their causes (e. g., infections of the upper respiratory tract, traumatic brain injury, chronic rhinosinusitis, age) with the resulting different therapeutic options and prognoses. Thorough history taking is therefore important. A wide variety of tools are available for diagnosis, ranging from short screening tests and detailed multidimensional test procedures to electrophysiological and imaging methods. Thus, quantitative olfactory disorders are easily assessable and traceable. For qualitative olfactory disorders such as parosmia, however, no objectifying diagnostic procedures are currently available. Therapeutic options for olfactory disorders are limited. Nevertheless, there are effective options consisting of olfactory training as well as various additive drug therapies. The consultation and the competent discussion with the patients are of major importance.

Contents

1. Introduction

Smelling is important. This became especially clear during the SARS-CoV-2 pandemic. Many people are now aware of what it is like to go through life without a sense of smell.

2. Definitions

In the context of quantitative olfactory disorders, there is a change of olfactory intensity (hyposmia or anosmia), whereas in qualitative olfactory disorders, the quality of odors is altered (parosmia) or there is odor perception in the absence of an olfactory stimulus (phantosmia) (▶ **Table 1**). In parosmia or phantosmia typically unpleasant sensations are perceived. Qualitative changes are often found in combination with quantitative changes, but also as solitary olfactory disorders. Parosmias and phantosmias may occur together, and parosmias may also precede prolonged phantosmias. Thus, transitions and intermediate forms are possible in quantitative and qualitative olfactory disorders [1].

In addition, multiple chemosensory sensitivity (MCS, also known as idiopathic environmental intolerance) can be found. MCS is a syndrome in which affected individuals react with a variety of symptoms such as heart palpitations, fainting spells, or asthmatic symptoms to exposure to a wide range of chemicals or fragrances. MCS is classified as a psychosomatic disease and treated accordingly [2, 3].

▶ **Table 1** Classification of olfactory disorders.

Term	Description
Normosmia	Normal olfaction
Quantitative olfactory disorders	
Hyposmia (rarely also “microsmia”)	Reduced olfaction
Functional anosmia	Reduced or non-existing olfaction that is not useful in everyday life
Anosmia	Complete absence of olfaction
Specific anosmia (or “partial anosmia”)	Reduced perception of a certain odorant even if olfaction in general is present (normal physiological property without clinical relevance [445])
Hyperosmia	Increased perception of scents [188]
Qualitative olfactory disorders	
Parosmia (rarely also “cacosmia”, “euosmia”, or “troposmia”)	Qualitatively distorted odor perception
Phantosmia	Perception of odors in absence of an odor source

3. Epidemiology of olfactory disorders

The prevalence of olfactory impairment in the general population has been dynamic since the outbreak of SARS-CoV-2 [COVID-19] pandemic. For both COVID-19-related and non-COVID-19-related olfactory impairment, epidemiologic estimates vary widely depending on demographic samples, definition of impairment, and study method [4].

3.1 Self ratings

The 1994 National Health Interview Survey (NHIS) assessed chemosensory disorders in 42,000 randomly selected households in the United States of America [5]. It was estimated that 1.4 % of the US adult population would have olfactory disorders that persisted at least three months. This prevalence increased with age, with approximately 40 % of participants over 65 years reporting olfactory problems [5]. Other trials such as the Korea National Health and Nutrition Examination Survey (KNHANES) reported in 2009 that ol-

factory dysfunction was present in 4.5 to 6.3 % of over 10,000 participants [6, 7]. The US National Health and Nutrition Examination Survey (NHANES) estimated the incidence of olfactory dysfunction to be 10.6 and 23 %, respectively, in approximately 3,500 participants [8, 9]. Other studies present estimates ranging from 2.4 % to 9.4 % [10–12] (but see also [13]).

3.2 Psychophysical tests

The epidemiology of olfactory disorders has also been studied with psychophysical tests, almost invariably using odor identification tests. In a sample of 1,240 rhinologically healthy patients from Germany, 4.7 % showed anosmia and 15 % hyposmia [14], which was confirmed by a study by Vennemann et al. in 1,312 adults (aged 25 to 75 years, also from Germany) and by Brämerson et al. in Sweden (Vennemann: anosmia in 3.6 %, hyposmia in 18 %; Brämerson: anosmia in 5.8 %, hyposmia in 15.3 %) [15–17] (see also [18]). Consistently, these and other studies revealed an increased prevalence of olfactory disorders with higher age (e. g., [19–27]).

The OLFACAT survey of 9,348 participants examined the detection and identification of 4 self-administered microencapsulated odorants. The prevalence of olfactory impairment ranged from 19.4 % to 48.8 % [28]. In the Beaver Dam trial including 2,491 adults aged 53–97 years, the mean overall prevalence amounted to 24.5 % and increased to 62.5 % in subjects older than 80 years [29].

A recent meta-analysis summarized data from 25 studies with a total of 175,073 participants (mean age of 63 years, 56 % male) [30]. The overall population-based prevalence of olfactory disorders was 22.2 %. Prevalence was significantly higher when psychophysical measurement tools were used, in contrast to reports based on self-ratings (28.8 % and 9.5 %, respectively).

4. Anatomy and physiology of olfaction

Humans are able to perceive millions of different odors [31, 32]. In simplified terms, the recognition of odor molecules is based on interaction with specific receptors on olfactory sensory cells, circuity in the olfactory bulb (OB), and projection to central olfactory networks [33].

Traditionally, the main olfactory epithelium is thought to be confined to the olfactory cleft in the roof of the nasal cavity. However, it is not entirely clear what the extent of the olfactory epithelium is in the nasal cavity, as mature and functional olfactory receptor neurons (ORN), particularly in younger individuals [34, 35], have been found at the base of the middle turbinate [36–40]. These ORN have cilia that project into the mucus and are lined with olfactory receptors [33]. The olfactory receptors are transmembrane proteins that activate a specific G-coupled protein in response to binding to an odorant molecule. Upon this activation, the subunit of the G-protein activates an adenylate cyclase, thus increasing the concentration of cyclic adenosine monophosphate (cAMP) in the cell. The increase of cAMP in turn leads to an opening of cation channels, allowing calcium, among other things, to flow into the neuron. The cation flow causes depolarization of the membrane and initiation of an action potential, which is transmitted along the axons to the OB [41, 42].

Characterization of the olfactory receptor gene families has revealed approximately 400 active olfactory receptor genes in humans [43–45]. Among them, each mature ORN expresses only one olfactory receptor at a time [46, 47]. The perception of millions of odorants is enabled by complex combinatorial coding. Most odor molecules activate multiple receptors, and receptors in turn can be activated by many different odor molecules. Each odorant activates a specific combination of olfactory receptors, which in turn can act as agonists and antagonists [48–51]. This combinatorial effect from the activation or inhibition of olfactory receptors allows comparatively few receptors to recognize a very large number of odor molecules. In addition, other types of chemoreceptors have been identified that are likely to be involved in human chemoreception [52–54].

The axons of the ORN run in bundles (olfactory fila) through the foramina of the lamina cribrosa to the OB. The OB is the first relay in the olfactory system and is located immediately above (dorsal) the lamina cribrosa and below (ventral) the orbitofrontal cortex. Within the OB, olfactory axons form their first synapse with bulbar glomerular cells. ORN are first-order excitatory sensory neurons that extend directly from the mucosa of the olfactory cleft into the brain. The ORN are exposed to the external environment, including pathogens and toxins, which can cause damage and even be lethal. Possibly, as a compensatory protective response to such damage, ORN possess the potential for neurogenesis. In this process, ORN are regenerated from the globose cells of the olfactory epithelium [55]. The turnover time in humans is not known but has been estimated to be 2–4 months [56, 57]. Olfactory neurogenesis is facilitated by glia-like olfactory sheath cells, which can be found in both olfactory epithelium and OB.

The second-order output neurons of the OB are the mitral and tufted cells. After signal integration, these neurons extend their axons along the lateral olfactory tract toward the structures of the primary olfactory cortex. These structures include the piriform cortex, the periamygdaloid cortex, the anterior cortical nucleus, and the entorhinal cortex. Further odor processing occurs in “secondary” and “tertiary” brain areas, including structures such as the hippocampus, parahippocampus, insula, and orbitofrontal cortex [58, 59].

Another important aspect of odor perception relates to the influence of nasal somatosensory sensations. For example, these sensations include the cooling sensation of menthol or the tingling sensation of CO_2 in carbonated beverages. These sensations are mediated in the nose by the first and second trigeminal branches [60, 61]. Trigeminal and olfactory functions are closely interconnected and interdependent [62–65]. In addition, trigeminal activation is crucial for the perception of nasal airflow, which has been used, for example, to explain the sensation of a blocked nose in the absence of an anatomical correlate [66–69].

5. Causes of olfactory disorders

Olfactory disorders are classified according to the site of the lesion or their cause (▶ **Table 2**). However, the sites of lesion in olfactory disorders are not clearly assignable. For example, in olfactory disorders caused by trauma, the periphery or the CNS may be damaged (e. g., rupture of the olfactory fila, contusion of the OB or orbi-

▶ **Table 2** Main causes of olfactory disorders with typical characteristics.

Cause	Onset	Prognosis	Parosmias are present	Phantosmias are present
COVID-19 or other infections of the upper airways	Sudden	Often improvement	+++	++
Chronic rhinosinusitis	Gradual	Very good treatment options	–	++
Craniocerebral trauma	Sudden	Possible improvement	+	++
Neurological diseases like Parkinsons' disease, Alzheimer's disease, myastenia gravis	Gradual	Possible improvement	+	++
Drug-related/toxic causes	Variable	Variable, e. g., good after interruption/removal of the noxae	+	++
Congenital anosmia		No therapy available	–	–
Age	Gradual	Possible improvement	–	–
Other causes like iatrogenic damage (e. g. sinonasal and skull base surgery, laryngectomy), tumors, multiple systemic diseases	Variable	Possible improvement	+	++

tofrontal cortex) [70, 71]. For this reason, the classification by cause is typically used.

5.1 COVID-19-related olfactory disorder

The estimated prevalence of COVID-19-associated olfactory disorders (COVID-19-OD) ranges from 5 % to 88 % [72]. One reason for this variability is the method used to assess olfactory dysfunction. Due to the infectious nature of SARS-CoV-2, the estimation of prevalence was based on subjective claims rather than psychophysical examinations, especially for acute illness. Based on subjective data, the prevalence for olfactory loss varied from 39 [73] to 53 % [74]. In this context, self-assessment seems to significantly underestimate olfactory loss, because when including validated test instruments or using psychophysical testing of olfactory function, the pooled prevalence estimate of COVID-19-OD was significantly higher with 87 and 77 %, respectively, than when using non-validated methods or recording subjective information [72, 74].

Compared with other postviral olfactory disorders, COVID-19 more often causes olfactory loss in younger individuals [73, 75], and women seem to be more commonly affected than men [75–77] (however, not in [73, 78]). When interpreting differences in prevalence, attention should be paid to possible selection bias, as the determination of prevalence is linked, among other things, to the assessment of olfactory function within the context of a targeted query or the spontaneous report of possible complaints, e. g., in consultation hours of specialized Smell and Taste clinics. In a meta-analysis of 3,563 patients, Borsetto et al. [79] found a higher prevalence for the development of an olfactory disorder in patients with a mild to moderate course of disease with about 67 % compared to patients with a severe course with 31 % (see also [73]).

In addition, there is a correlation of the prevalence of COVID-19-OD to viral variant [80, 81], which a higher likelihood of COVID-19-OD in the alpha virus variant (50 %) compared to the delta variant (44 %) or omicron variant (17 %), with the omicron variant being the least likely to cause COVID-19-OD, probably due to mutations related to the so-called "spike" glycoprotein [82].

Olfactory loss is sometimes the only symptom of COVID-19 infection [83, 84]. In a systematic review and meta-analysis of 3,563 patients, loss of smell occurred as the first or only symptom in 20 %, it followed other symptoms in the majority of the cases (54 %), and appeared concurrently with other symptoms in 28 % [79] (since it is a meta-analysis of multiple studies, the total does not reach 100 %). Other symptoms associated with COVID-19 include cough, sore throat, dyspnea, fever, myalgia, rhinorrhea, and nasal obstruction. At the onset of the pandemic, rhinorrhea or nasal obstruction occurred less frequently compared with non-COVID-19-associated postviral olfactory disorders [85, 86].

COVID-19-OD begins suddenly, a few days after SARS-CoV-2 infection. At the onset of the COVID pandemic, a subjectively reported "sudden loss of smell" could detect disease with COVID-19 with a specificity of 97 %, a sensitivity of 65 %, a positive predictive value of 63 %, and a negative predictive value of 97 %, excluding patients with nasal obstruction [85]. In the later omicron variant, nasal obstruction and rhinorrhea were more frequently described with mostly intact olfaction [82].

At the onset of the COVID-19 pandemic, quantitative olfactory disorders in terms of hyposmia and anosmia were prominent [87]. In this context, the described olfactory disorders affect olfactory threshold, odor discrimination, and odor identification [78]. In the course of the disease, qualitative olfactory disorders have been increasingly reported [88, 89].

Based on self-ratings, a majority of COVID-19-OD show significant improvement or complete recovery within 1–2 weeks [90, 91]. Based on subjective assessments and psychophysical examinations, Boscolo-Rizzo et al. [92] reported significant improvement in COVID-19 smell disorders after 4 weeks with improvement reaching a kind of plateau after about 8 weeks. Six months after COVID-19 infection, 77 % of the 110 patients rated their initial olfactory dysfunction as completely restored, while 20 % described improvement, and 3 % reported deterioration. In context of psychophysical testing 6 months after infection, the majority (59 %) of the patients were diagnosed with hypersensitivity or anosmia

by means of an olfactory identification test, despite the subjective absence of olfactory dysfunction. Over a longer observation period of 2 years, 88 % reported complete recovery of their symptoms [95].

Depending on the olfactory test performed and due to the existing selection problem, different data on the course result. In psychophysical testing, reports of persistent olfactory dysfunction vary from 7 % after 3 months (self-performed olfactory test) [93], to 15 % after 3 months or 5 % after 6 months (Sniffin' Sticks identification test) [94], to 21 % after 3 to 6 months (Sniffin' Sticks threshold, discrimination, and identification) [78]. In psychophysical testing, 77 % of the 102 patients were diagnosed with hyp- or anosmia after a mean of 7 months [96]. Tognetti et al. [97] also found persistent olfactory dysfunction 18 months after COVID-19 infection in 37 % of 100 patients, 60 % of whom were not subjectively aware of it. Even for a longer observation period, the proportion of patients with a psychophysically detectable olfactory disorder was significantly higher than in the subjective assessment of olfaction. This indicates that recovery after COVID-19-OD is slower than subjectively perceived.

An analysis of the diagnosis code "post-acute COVID-19 syndrome" (long-COVID) for the second quarter of 2021 was carried out by the health insurance funds in Germany to record the symptoms in a patient group and a control group referring mainly to the wild-type and alpha variant. An olfactory and/or gustatory disorder was described in 3.2 % of the approximately 160,000 long-COVID patients and in 0.2 % of the 320,000 control subjects [13]. Thus, although the reporting of olfactory and gustatory dysfunction is significantly higher within the long-COVID group, it should actually be significantly higher when the general prevalence of measurable olfactory dysfunction is included with 20 % and 5 % anosmia, respectively [15]. In summary, the problem in determining the prevalence of COVID-19-OD is that initially, due to infectivity, many patients will not be tested psychophysically. In addition, many patients are unaware of their olfactory loss during the course of the disease.

Parosmia occurred in 64 % of the patients during the course of the study and started mainly within the first month after COVID-19. For the patients with parosmia, compared to self-ratings better olfactory function was found when using psychophysical testing [89]. Parosmia is therefore discussed as a possible prognostically favorable parameter for an improvement in olfactory function, as this could also be demonstrated for non-COVID-19-related postinfectious olfactory disorders [98, 99].

Despite the SARS-CoV-2 pandemic lasting more than two years, the pathogenesis of olfactory loss has not been fully elucidated. According to current knowledge, the single-stranded RNA virus SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) on human supporting cells of the olfactory mucosa, mediated by transmembrane protease serine subtype 2 (TMPRSS2). In this way, ORN are indirectly damaged, but this may result in more permanent damage if ORN are lost [100, 101]. Downregulation of ORN olfactory signaling genes is thought to be one of the mechanisms of damage [102]. Furthermore, there is an inflammatory change with an invasion of leukocytes into the olfactory mucosa [103, 104]. In addition, a central component of olfactory dysfunction is discussed [105], which is mainly explained by microvascular disturbances [106] and is not linked to viral detection in the brain as initially suspected, which was previously successful in hamsters [103], but not in humans [106].

5.2 Non-COVID-19-related postinfectious olfactory disorder (postviral olfactory disorder)

In addition to SARS-CoV-2, upper respiratory tract infections with other viruses (e. g., parainfluenza, HIV) are a common cause of olfactory disorders [107, 108]. Olfactory disorders can also be caused by bacteria, fungi, or for example microfilariae [109–111]. Women are more frequently affected than men, typically at an age beyond 50 years [112]. The latter may be due to the age-related decreased regenerative capacity of the olfactory system and accumulation of previous lesions [113]. Onset is sudden, and although many patients describe an unusually severe infection, some are unaware of the precipitating infection or the olfactory loss is not apparent until weeks after the infection. Parosmia often occurs during recovery [114]. Postinfectious olfactory loss improves more frequently than is the case with other causes [108]. Reden and colleagues showed improvement in psychophysical test scores of about one third of 262 patients with postviral olfactory impairment (duration ≥ 18 months) over a 14-month follow-up period [115], with higher [116] or lower estimates found in the literature [117, 118]. Important in interpreting the studies is how long the olfactory loss had been present at study entry – the longer the olfactory loss, the lower the prospect of recovery.

Pathophysiologically, either damage to the olfactory mucosa or to the central nervous processing system underlies the postinfectious olfactory disorders [119, 120]. Histological studies in patients with postinfectious olfactory disorders show neuroepithelial remodeling and replacement of olfactory cells by respiratory epithelium or occasionally metaplastic squamous epithelium [112, 121]. The number of ORN is reduced, they are inhomogeneously distributed, and their morphology may be altered (e. g., decrease in volume, reduction or shortening of dendrites) [112]. In addition, OB volumes are reduced in relation to the olfactory deficit and during the course of the disease [122].

5.3 Olfactory disorders as sequela of sinonasal disease

Rhinosinusitis is the main cause of olfactory loss, along with age [110, 123]. This can be either acute (lasting less than 12 weeks, with complete recovery) or chronic rhinosinusitis lasting 12 weeks or longer. There are a variety of phenotypic subtypes, while patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) are most affected by olfactory loss, followed by patients with chronic rhinosinusitis without nasal polyps (CRSsNP), non-allergic rhinitis, atrophic rhinitis, and allergic rhinitis [124]. According to the European Position Paper on Rhinosinusitis and Nasal Polyps and the American Academy of Otolaryngology – Head and Neck Surgery Guidelines as well as the AWMF guidelines on rhinosinusitis, olfactory dysfunction is a cardinal symptom of the disease [125–127]. The prevalence of CRS is 11 % in the general European population [11].

Olfactory dysfunction due to CRS is caused by a combination of factors. These include impaired access of odorants to ORN because of nasal obstruction, mucosal edema, increased mucous secretion, and polyposis, as well as inflammation-related disruption of the

binding of odorants to receptors [128, 129], structural remodeling of the olfactory epithelium [112], and finally functional and/or structural remodeling of the OB and primary and secondary olfactory cortex [130–133]. Olfactory dysfunction associated with sinonasal diseases occurs gradually over months and years and varies over time [134, 135]. They can rarely improve without treatment, and parosmias tend not to be present [114, 136, 137].

5.4 Posttraumatic olfactory disorders

Traumatic brain injury is a major cause of permanent olfactory impairment. Various mechanisms are underlying, including septal fractures with mechanical obstruction of the nasal airway, direct neuroepithelial injury, edema or changes in mucus properties [138], shearing of the fila olfactoria as they are passing through the lamina cribrosa [70, 139] (but see also [140]), cerebral contusions, and intracerebral hemorrhage with subsequent gliosis [141–143].

Trauma-induced olfactory loss usually occurs suddenly but is often noticed until weeks and months after the accident, for example, upon return to the home environment after a prolonged hospital or rehab stay. This delayed onset of olfactory dysfunction could also reflect delayed central nervous damage. The more severe the traumatic brain injury, the more likely the loss of smell [142]. However, even very mild trauma can lead to olfactory loss [144]. In posttraumatic olfactory disorders, phantosmias are found comparatively often, and parosmias less frequently [114, 145, 146]. Regeneration rates in posttraumatic olfactory disorders are significantly lower than in postinfectious olfactory disorders. Nevertheless, recovery occurs over time in about 30 % of the cases, depending on the severity of the injury [108, 115, 147–150].

5.5 Olfactory disorders associated with neurological diseases

Olfactory disorders are an accompanying symptom of many neurological diseases, and neurodegenerative diseases in particular are associated with olfactory disorders. They are found in more than 90 % of patients with idiopathic Parkinson's syndrome (IPS) [151] and are considered as supportive diagnostic criterion in the clinical diagnosis of IPS [152]. In view of the fact that olfactory disorders sometimes precede motor symptoms by more than 10 years [153, 154], the majority of IPS patients already exhibit marked hyposmia or anosmia at the time of diagnosis. Therefore, at least in some patients with idiopathic olfactory loss and other risk factors (e. g., positive family history), an onset of IPS must be considered and neurologically evaluated [153]. To a lesser extent, olfactory disorders occur in atypical Parkinson's disease, whereas, for example, restless legs syndrome or an essential tremor show an almost unrestricted olfactory ability [155]. Severe olfactory dysfunction is also found in Lewy body dementia, frontotemporal dementia, and Alzheimer's disease (AD) [155]. Olfactory dysfunction in AD is also an early symptom of the disease and can already be detected in patients with mild cognitive impairment, with limitations in olfactory identification being a powerful predictor of conversion to dementia [156]. Olfactory deficits of varying severity are also observed in Huntington's disease, heredo-ataxia, and motor neuron disease [155], and myasthenia gravis [157]. Patients with multiple sclerosis [158], many non-degenerative syndromes, such as temporal lobe epilepsy [159], acute depressive episodes [160], and schizophrenia [161] also often are associated with olfactory disorders.

In many synucleinopathies like IPS and in AD, neuropathological changes with typical protein deposits in the olfactory mucosa, OB, and olfactory tract, as well as in the primary and secondary olfactory cortex, have been described [162]. The diagnostic usefulness of these neuropathological changes is unclear so far, since, for example, in vivo biopsies of the olfactory epithelium show no significant immunohistochemical differences between IPS and patients with olfactory disorders of other origin [163].

5.6 Olfactory disorders related to age

Age-related olfactory loss is the most common cause of olfactory dysfunction. Approximately 50 % of 65- to 80-year-old subjects and 62–80 % of those over 80 years suffer from hyposmia [164]. Olfactory loss in higher age is considered as a positive predictor of 5-year mortality [165, 166], proving to be a stronger risk factor compared with most chronic diseases [165]. There is a clearer association with mortality for olfactory impairment than for hearing or visual impairment [166] and a pronounced association with neurodegenerative diseases [167].

The possible causes of olfactory disorders with higher age are manifold, although replacement of olfactory by respiratory epithelium with reduced regenerative capacity of the ORN, increasing fibrosis of the foramina of the lamina cribrosa, and loss of volume of the BO are considered typical and possibly causative changes [34, 168].

5.7 Idiopathic olfactory disorders

An idiopathic olfactory disorder is present when a thorough diagnosis does not reveal a clear cause. Up to 16 % of patients examined in special centers fall into this category [169]. The diagnosis of "idiopathic olfactory disorder" is complex and difficult, as some of the cases could be due to, for example, asymptomatic upper respiratory tract infections, age-related olfactory dysfunction, or presymptomatic CRS [170, 171].

5.8 Drug- or toxin-induced olfactory disorders

Chronic exposure to toxins can cause olfactory disorders. Causes may include metals, such as cadmium and manganese, pesticides, herbicides, and solvents. Chemotherapeutic agents and other drugs can also lead to olfactory disorders, mediated by peripheral, neuroepithelial, or central lesions [172].

5.9 Congenital olfactory disorders

With an incidence of about 1:8000, congenital anosmias are found, often as isolated congenital anosmias, less frequently in the context of a genetic disorders (e. g., Kallmann syndrome – hypogonadotropic hypogonadism; Turner syndrome [173]; Bardet-Biedl syndrome [174]). Typically, the diagnosis is made between the ages of 12 and 16 years. Characteristic of congenital anosmia are hypoplastic/aplastic OB and flattened olfactory sulcus (< 8 mm) [112, 175–178]. However, cases of congenital anosmia in developed OB have also been reported in mutation of the CNGA2 gene [179]. On the other hand, a normal sense of smell in the absence or very much reduced OB also seems possible [180, 181]. In cases of suspected Kallmann syndrome or other syndromic constellati-

ons, patients should undergo genetic, endocrinological, and pediatric examinations.

5.10 Other causes of olfactory disorders

Olfactory dysfunction can be caused by a number of different diseases, e. g., intranasal or intracranial neoplasms, nasal surgery (for example, septoplasty [182]), endocrine diseases (for example, Addison's disease, hypothyroidism, diabetes mellitus), hypertension, vitamin B12 deficiency, dysfunction as a complication of surgery (for example, anterior skull base surgery) [109, 183, 184], or nasal surgery and tracheostomies (e. g., during laryngectomy) that change nasal airflow [185], psychiatric disorders [186, 187], migraine [188, 189], radiation therapy [190], or alcohol abuse [191, 192].

The role of smoking/nicotine abuse in olfactory loss is controversially discussed [193–195]. Several studies have shown a dose-dependent, negative effect of smoking on olfactory function [16, 196, 197]. Increased apoptosis of ORN [198] and/or replacement of olfactory epithelium by squamous metaplasia [199] could be at the base of these changes.

6. Qualitative olfactory disorders

Parosmia and phantosmia are qualitative olfactory disorder: parosmia is the distorted perception of a smell in the presence of an odor; phantosmia is an olfactory perception without an odor being present.

6.1 Parosmia

Perception of an odor is considered a parosmia if the subjective expectations and the actual experience of an odor quality do not match. In general, parosmias are unpleasant ("burnt, fecal, putrid, musty"), although distortions that are pleasant in principle ("euosmia") have also been described [200, 201]. Parosmia has been reported in 4–10 % of the population and in 7–56 % of patients with olfactory dysfunction [87, 202–205]. The high degree of variance is explained by the nature of the detection of parosmia and by the differences in the study populations, and also indicates the subjectivity of the symptomatology and its presentation.

Parosmia occurs most frequently in patients with postviral olfactory disorders, but also in olfactory disorders of other causes [205, 206]. Parosmias usually present with an interval of weeks or months after the onset of the olfactory disorder [87, 88, 97, 206], in association with recovery of olfactory function. Parosmias occur in hyposmia and anosmia but also in normosmia [205]. Moreover, they are more likely to occur in younger women and may be a positive prognostic sign [98, 99, 206] (but see also [205]). The psychosocial impact of parosmia can be severe [206–209].

There are several hypotheses regarding the origin of parosmia. The "miswiring" hypothesis of parosmia [210] assumes that parosmias are due to incorrect or incomplete encoding of scents, which again may be based on different mechanisms: 1) incorrect assignment of ORN axons to glomeruli in the OB; 2) changes in ORN receptor expression; and 3) incomplete ORN regeneration leading to changes or gaps in pattern generation [102, 139, 145, 146, 211–215]. The "central" hypothesis assumes central nervous misprocessing or misconnection based on the following observations: 1) small OB in patients with parosmia; 2) reduced volume of grey matter in the olfactory cortex; and 3) altered activation patterns in cerebral scent processing [122, 216–219].

Parosmias are more likely to be triggered by certain odor groups, such as pyrazines, thiols, or furans, than by others [220]. Typically, the thresholds for perception of these odorants are low. Coffee, chocolate, meat, onion, garlic, egg, and mint/toothpaste are commonly cited as triggering fragrances [221, 222].

The diagnosis of parosmia is based on subjective statements of patients [223]. Short questionnaires help in the diagnosis [224], similarly to the classification according to the frequency and intensity of parosmic perceptions and the impairment caused by the parosmia [225]. Psychophysical instruments have been suggested (Sniffin' Sticks Parosmia Test – "SSParoT" [226]), but probably need further modification [227].

6.2 Phantosmia

Phantosmias are odor perceptions in the absence of an odor source; they are typically described as unpleasant ("burnt/smoky, rotten, fecal, chemical") [228, 229]. Phantosmia is experienced by approximately 1–31 % of the general population [14, 202, 230] and up to 16 % of patients with olfactory disorder [204–206, 229], often together with parosmia [204]. Patients with phantosmia are often functionally anosmic (43 %) [205], tend to be middle-aged, and frequently have a post-traumatic olfactory disorder. However, phantosmia also occurs in patients with other causes of olfactory disorders [205, 206], and olfactory hallucinations are reported in neurological and psychiatric disorders [240], for example in temporal lobe epilepsy or as auras in migraine [231, 232].

Hypotheses for the origin of phantosmias refer to epileptiform, i. e., disordered activity, for example in the area of the BO, orbitofrontal cortex, or gyrus rectus [233–237] or the olfactory mucosa [139, 206, 238, 239], and they can also be elicited by irradiation of the brain.

The diagnosis of phantosmia is based on the information provided by the patients and can be supported by structured questionnaires [224]. Graduation of phantosmia based on the incidence, intensity, and degree of impairment has been proposed in analogy to the assessment of parosmia [225]. Phantosmia often improves spontaneously within 6–12 months [241] (but see also Pellegrino et al. [206]) and tends not to indicate a favorable prognosis [98, 99, 205].

7. Clinical examination

Clinical assessment of patients with olfactory disorders is important, especially with regard to diagnosis, which is the prerequisite for prognostic counseling and therapy [242, 243].

7.1 Medical history, clinical examination

The medical history should include questions like: specific impairment of orthonasal olfaction, retronasal olfaction (fine taste), or tasting (gustatory perception); presence of parosmia or phantosmia; percentage assessment of current olfaction, tasting, and nasal breathing, duration of the olfactory disorder and type of onset (gradual, sudden) as well as concomitant/preceding events (infection, trauma, medication); fluctuations in olfactory perception; previ-

ous diseases, especially sinonasal diseases or previous ENT surgery; occupational exposure (e. g., chefs/people working in professional food processing – approximately 450,000 in Germany!); history of danger due to the lack of perception of warning odors; intake of medication; smoking status; neurodegenerative diseases (e. g., IPS) in first-degree relatives.

The examination should encompass a complete ENT examination, including anterior rhinoscopy and nasal endoscopy with inspection and evaluation of the olfactory cleft, preferably after application of a decongestant nasal spray [244, 245]). A complete olfactory examination of the patient should also include screening of tasting [246].

7.2 Olfactory tests

Olfactory examinations can be divided into three groups: 1) subjective patient reports/self-ratings; 2) psychophysical tests; 3) electrophysiological measurements and imaging procedures [242].

7.3 Subjective patient reports

Subjective reports can be performed with visual analog scales, questionnaires, or with other patient-oriented measurements. For example, the SNOT-22 is a questionnaire primarily about CRS that assesses general distress, but contains only one question about olfaction [247]. In addition, there are more specific questionnaires regarding olfaction, such as the Questionnaire of Olfactory Disorders (QOD), which better distinguishes between patients with normal and reduced olfaction than simple questions like the one used in the SNOT-22 [207, 248, 249]. For a recent review of olfactory questionnaires and scales, see [171]. However, self-ratings of chemosensory function tend to be unreliable [19, 250–253].

7.4 Psychophysical tests

Psychophysical tests provide a more reliable assessment of olfaction than subjective reports, but of course also depend on the cooperation and the biases and expectations of the person being tested and also on the examiner. Roughly, a distinction can be made between tests in which olfactory thresholds are measured and tests in which olfactory performance is assessed using suprathreshold odor concentrations. Orthonasal olfactory tests are most commonly used.

The olfactory threshold is the lowest concentration of an odorant that one can perceive. As an approximation of the threshold, clinically the concentration at which 50 % of the stimuli are detected is often measured. Olfactory threshold does not require identification of the odor stimulus, but rather the perception of "something", usually in comparison to an odorless stimulus. Test results from threshold studies are therefore usually less dependent on cognitive factors than, for example, results from odor identification and odor discrimination tests [254].

In suprathreshold tests, odors are offered in concentrations that are reliably recognized by people with normal olfactory abilities. Scent identification tests use odors that should be known, but this depends on the subjective experience and also on the linguistic abilities of the person being tested. For example, the scent "wintergreen" is well known in the UK, but rather unknown in Germany. This also means that odor identification tests must be regionally different or can only be used to a limited extent with people from a different cultural background. As a rule, only a few people are able to recognize odors spontaneously, which is why odors are typically offered together with a list of odors words (e. g., pineapple, rose, grass, onion) from which the one that most closely matches the scent must be selected [255]. Odor recognition tests are based on the recognition of 3 to 40 odors. The more odors are tested, the more reliable and reproducible the results are and the better the discrimination between anosmia, hyposmia, and normosmia [256].

In scent discriminations tests, 2 or 3 odors are offered. The task of the examinee is to find out the odor which is different from the other two odors ("forced choice"). The task is largely independent of verbal abilities.

Why are the tests carried out in a forced-choice procedure? Forced-choice procedures are necessary to prevent patients form choosing the option "no odor perception". This option would probably be chosen by many patients, regardless of whether something was actually perceived or not. Only if these patients are asked to focus on the odors by forced-choice, they exploit their actual perceptual abilities – and quite often achieve results that are surprising for the patients themselves. In addition, the forced-choice procedure standardizes the conduction of the test.

Is the assessment of multiple psychophysical components of olfaction, e. g., threshold, discrimination, and identification useful or not? Doty et al. reported that different psychophysical tests measure a common source of variance implying that olfactory loss and improvement can be effectively assessed by odor identification performance alone [257]. However, this opinion is challenged – Jones-Gotman and Zatorre showed a reduction in odor identification, but not thresholds, after selective cerebral excisions [258, 259]. Whitcroft et al. revealed that the patterns of psychophysical test scores of patients with olfactory loss of different origins reflects the underlying disease etiology [114]. In this study, patients with sinonasal olfactory disorders had lower olfactory thresholds, whereas patients with Parkinson's disease had primarily impaired odor discrimination and identification (see also [260]).

These and other trials indicate that the olfactory threshold is more indicative of peripherally related changes in olfaction, e. g., due to sinonasal disease, whereas suprathreshold tests (discrimination and identification of odors) preferentially detect central or cognitive causes of olfactory dysfunction (see also [71]).

Results from different olfactory tests are also pooled to achieve greater accuracy and reproducibility. For example, in the Connecticut Chemosensory Clinical Research Center Test (CCCRCT), olfactory threshold and odor identification are combined [261]. In the Sniffin' Sticks Test, the TDI score is the sum of the results for olfactory threshold (T), discrimination (D), and identification (I).

There are many test procedures to examine olfaction, but by no means have all of them been thoroughly investigated in terms of their reliability and validity. For example, the University of Pennsylvania Smell Identification Test (UPSIT) is a reliable, valid odor identification test based on microencapsulation of odors released by scratching their surface. It is adapted for use in different countries [262–265]. Olfactory testing with the UPSIT does not require monitoring [266–268]. Another widely used psychophysical test is the "Sniffin' Sticks", which is composed of three parts (see above) [269]. The test is based on felt-tip pen-like odor dispensers, is reusable, and is typically administered by an examiner, but parts can

▶ **Table 3** Selection of the most frequently applied psychophysical olfactory tests.

Psychophysical test	Assessed olfactory function
Extensive orthonasal olfactory tests	
"Sniffin' Sticks" (original version) [269]	Threshold, discrimination, identification
Connecticut Chemosensory Clinical Research Center Test [261]	Threshold, identification
T & T Olfactometer [446]	Threshold, identification
University of Pennsylvania Smell Identification Test [262]	Identification
Barcelona Smell Test (BAST-24) [447]	Odor perception, identification, olfactory memory
Orthonasal short tests	
Smell diskettes [448]	Identification
Pocket Smell Test [282]	Identification
"Sniffin' Sticks" (3, 5, o 12 odor samples) [281, 283, 449]	Identification
Brief Smell Identification Test (B-SIT; 12-item Cross-Cultural Smell Identification Test) [280]	Identification
Retronasal tests	
Candy Smell Test (23 samples) [290]	Identification
Taste powders (20 samples) [289]	Identification

also be used by the patients alone. Reliability and validity have also been confirmed for the Sniffin' Sticks, and minimal clinically significant difference has been investigated [270].

In addition, there are tests based on changes in breathing behavior during odor perception [271]. These techniques allow a very precise assessment of olfactory ability (e. g., [272]), but they are not widely used.

A special case of olfactory testing is the examination of children. Here, special olfactory tests have been developed that are adapted to the relatively limited verbal abilities of children and their limited experience with odors. Psychophysical olfactory testing is more or less reliable in children as of the age of 4 years [273, 274].

▶ **Table 3** provides a list of psychophysical tests that have been used in clinical settings.

When using psychophysical tests to define olfactory disorders and changes in olfactory function, the availability of normative values is important. Hyposmia is differentiated from normosmia based on the 10th percentile of test scores of young healthy subjects [262, 269]. In contrast, anosmia is defined based on the empirical distribution of olfactory test scores of anosmic people [275].

In a clinical setting, psychophysical tests are usually performed birhinally without prior application of a decongestant nasal spray [250, 276]. However, several papers show that lateralized olfactory tests have both diagnostic and prognostic value [277–279].

7.5 Short psychophysical tests

In clinical routine, screening tests are often used for cursory examination of olfaction, e. g., in the preoperative assessment of olfaction (▶ **Table 3**). Odor identification tests are typically used [280, 281], some of which are based on only 3 or 5 odors [282, 283]. They are easy to understand and require little time (▶ **Table 3**). However, they make it difficult to document changes because of their low resolution. If abnormalities are detected during screening, they should be further elucidated with a valid, complete olfactory test.

In addition, tests that can be performed in the home environment, using domestic odors, have also been introduced in recent years [284–287]. It remains to be seen whether these tests will be widely used.

7.6 Retronasal olfactory tests

Flavor perception, retronasal smelling, depends on olfactory function. Tasting, i. e. gustatory sensitivity and retronasal smelling are often not separated, i. e. many patients complain about the loss of "taste" although actually retronasal smell is affected [209]. In addition to these confusions, it is not uncommon for patients to state that orthonasal olfaction is severely impaired but retronasal olfaction is intact [288]. Such dissociations can be found in protracted olfactory loss, e. g. in sinonasal olfactory disorders or in age-related olfactory loss. Simple retronasal olfactory detection tests are available for clinical testing [289–291].

7.7 Electrophysiological examinations and functional imaging

Electrophysiological examinations encompass the measurement of odor-induced changes in the electroencephalogram (EEG), i. e. the olfactory event-correlated potentials and also the changes in the stimulus-dependent EEG [292, 293]. They are less dependent on patients' expectations and cooperation than psychophysical measurements. Because of the need for precise stimulus presentation, computerized olfactometers are a technical prerequisite, which limits the widespread use of the method [294].

Functional imaging allows visualization of brain activity in response to olfactory stimuli and includes for example, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Both techniques are ultimately based on odor-induced changes in cerebral blood flow [295]. The use of radioactive isotopes makes PET less attractive, and olfactory fMRI has low reliability, which significantly limits its clinical value in individual diagnostics [296].

7.8 MRI examinations of the nose and the brain

MRI can be used to assess the nose and its sinuses, the BO as well as primary and secondary olfactory cortex, and to rule out intracranial space-occupying lesions. In trauma-induced olfactory disorders, the degree of olfactory loss can be predicted based on the brain lesion pattern [141]. Imaging and measurement of the OB and olfactory sulcus are significant in the diagnosis of congenital anosmia [177, 178], and OB volume provides prognostic information in patients with olfactory loss [292].

8. Treatment of quantitative olfactory disorders

Olfactory disorders are treated according to their cause. For the treatment of olfactory disorders associated with CRS, topical or systemic application of steroids is the main focus, in addition to treatment options including surgery or monoclonal antibodies [297–299]. Precise and comprehensive guidelines exist for the treatment of CRS and are referred to in these references [125–127, 300–306]. In contrast, treatment options for olfactory disorders of other origins are limited [164, 307, 308]; however, there are also several options.

8.1 Consultation for olfactory disorders

Consultation for olfactory disorders is particularly important with regard to the avoidance of hazards, e. g., regarding the handling of food or the installation of smoke detectors and gas warning devices. Detailed information is available from the Working Group on Olfaction and Gustation of the German Society of Otorhinolaryngology, Head and Neck Surgery, https://rebrand.ly/nvru0xc., or, for example, from patient support groups like https://www.abscent.org

8.2 Systemic corticosteroids

Several studies have dealt with the use of systemic corticosteroids for treatment of postviral olfactory dysfunction and have come to negative [309, 310], but also positive results (e. g. [311–315]). However, in some of these studies, the control group was missing, e. g. in Ikeda et al. and also in Fukazawa. Since spontaneous recovery is common, especially in patients with postviral olfactory disorders, these studies appear difficult to interpret. The investigations of Vaira et al. and Le Bon et al. were each performed on small groups (n < 10 per treatment arm).

Various studies showed improvement in posttraumatic olfactory disorders with the use of systemic steroids, but without concomitant study of a control group [316–318]. Although the spontaneous recovery rate in posttraumatic olfactory loss is lower than in postviral olfactory disorders, this still limits the interpretation of the results. Jiang et al. [319] reported that oral prednisolone per se did not result in significant improvement compared with an untreated control group.

8.3 Topical corticosteroids

Topical steroids have been used to reduce inflammation in various studies, but often in groups with different causes of olfactory disorders. Often the nasal spray is used with the regular nozzle which makes it unlikely that the injected spray would reach the olfactory cleft [320–322].

A double-blind, randomized controlled trial by Blomqvist et al. showed no significant difference in olfactory threshold after 6 months of treatment with intranasal fluticasone spray, placebo spray, or no treatment (n = 20, n = 10, and n = 10, respectively) [323]. Heilmann et al. [324] also found no effect of treatment with mometasone nasal spray in a retrospective review. In contrast, Fleiner et al. [325] found a significant improvement in a group of patients with olfactory disorders treated with topical steroids and olfactory training (see below). Similarly, Kim et al. [326] showed improvement with the combined use of systemic and topical steroids compared with the use of topical steroids alone in a relatively large group of patients (491 in total) with various causes of olfactory disorders.

Regarding COVID-19-OD, in a controlled study Hintschich and colleagues [327] showed no advantage in terms of the TDI score for the treatment of mometasone nasal spray (application to the olfactory cleft with extra-long applicator) together with olfactory training versus olfactory training alone. Kasiri and colleagues conducted a double-blind randomized controlled trial in patients with COVID-19-OD comparing intranasal mometasone furoate spray/smell training (n = 39) with intranasal sodium chloride/smell training (n = 38) [328]. After 4 weeks of treatment, there was no statistically significant difference in the change in odor identification test scores between the groups. Similarly, in another randomized controlled trial of 100 patients with COVID-19-OD, 50 of whom were treated with olfactory training and 50 were treated with olfactory training and an intranasal mometasone spray [329], there was no significant difference between the two groups. However, participants rated their olfactory ability using visual analog scales only. In contrast to previous studies, a randomized controlled trial [330] comparing olfactory training and intranasal irrigation with budesonide (n = 66) with olfactory training and intranasal NaCl irrigation (n = 67) in patients with olfactory disorders of various origins showed a greater clinical improvement in odor identification scores for patients in the budesonide group (44 %) compared to the NaCl group (27 %) after 6 months.

Overall, the evidence regarding positive effects with the use of corticosteroids for non-sinonasal olfactory dysfunction is low [331] – partly due to the lack of high-quality studies. Despite this situation, systemic and topical steroids are commonly used to treat non-sinonasal olfactory disorders [123, 332].

8.4 Phosphodiesterase inhibitors

Phosphodiesterase inhibitors like theophylline have been reported to improve olfactory function by preventing the breakdown of intracellular cAMO or reducing IL-10 secretion [333, 334].

A prospective trial investigating the Sniffin' Sticks scores before and after pentoxifylline administration [130] revealed a significant improvement in olfactory thresholds. However, normosmic and hyposmic patients were included in this study. Henkin et al. used a non-blinded, controlled study design to investigate the effect of oral theophylline on olfactory function in hyposmic patients [335]. The study showed improvement in olfactory function with incremental doses of theophylline over time, but spontaneous recovery was not considered. In a non-controlled study of the effects of topical theophylline [336] in 10 patients, subjective improvement was seen in 8/10 patients after 4 weeks of treatment. In contrast, using a double-blind, placebo-controlled, randomized design in an analysis of a small group of patients with postviral olfactory dysfunction (n ≤ 12) [337], Lee et al. showed no improvement in odor recognition (UPSIT) for the use of theophylline, but an improvement in odor-related quality of life. Overall, the efficacy of phosphodiesterase inhibitors in olfactory disorders does not seem assessable at present [338–340].

8.5 Intranasal calcium buffer

Free calcium in the nasal mucus layer, among countless significant functions, plays a role in inhibiting negative feedback in the intra-

cellular olfactory signaling cascade [341]. Therefore, it has been suggested that the sequestration of free calcium using buffer solutions such as sodium citrate may lead to an enhancement of the olfactory signal and a consequent improvement in olfactory function.

Panagiotopoulos et al. reported significantly improved odor identification scores in hyposmic patients with a majority of postviral olfactory disorders treated with intranasal sodium citrate [342]. A series of studies also revealed short-term effects of sodium citrate on olfaction [343–345], but there was no significant improvement in olfactory test scores (Sniffin' Sticks) on the treated side when sodium citrate was applied monorhinally for two weeks. In addition, however, there was a significant reduction (82 %) in the proportion of patients reporting phantosmia.

A series of recent blinded studies by Abdelazim et al. [346–348] on sodium gluconate, sodium pyrophosphate, and sodium nitrilotriacetate showed a significant improvement in olfaction in patients with postviral olfactory dysfunction. A confirmation of these results, for example in a multicenter study, would certainly be desirable.

8.6 Vitamin A

Vitamin A comprises a family of fat-soluble retinoids, the oxidation of which leads to the production of the biologically active retinoic acid, which is significant as a transcriptional regulator in tissue development and regeneration [349, 350]. Several studies suggest the role of retinoic acid in olfactory function [351, 352]. Specifically, retinoic acid controls the differentiation of olfactory progenitor cells [353–355].

In humans, Duncan and Briggs reported that high doses (up to 150,000 IU/day) of systemic vitamin A improved olfaction in 48 of 54 patients [356]. In a non-controlled study, significant improvement in odor identification scores (Sniffin' Sticks) was shown after administration of isoretinoin [357]. However, in a double-blind, placebo-controlled, randomized trial in patients with postviral (n = 19) and posttraumatic olfactory disorders (n = 33) with 10,000 IU/day of systemic vitamin A (n = 26) or placebo (n = 26) for 3 months, no significant effects were found [358], possibly due to an insufficient dose.

In a retrospective analysis of the treatment of patients with postviral and posttraumatic olfactory disorders, the topical application of intranasal vitamin A (10,000 IU/day; 8 weeks, 12 weeks of olfactory training; n = 124) led to significant improvement (olfactory training + vitamin A vs. olfactory training alone) [359] (see also [360].

8.7 Olfactory training

Repeated exposure to odorants, e. g. to androstenone, can improve olfactory sensitivity to this odor [361]. This principle underlies olfactory training, in which patients try to improve their sense of smell over a period of about 3 months by repeated and conscious sniffing of a range of odorants [362].

The exact mechanism that might underlie an improvement in olfaction after olfactory training is unknown. It is likely that plasticity of both peripheral [363–366] and central nervous olfactory systems plays a role, at the levels of the OB [367], the primary and secondary olfactory cortex [368], and intracerebral connectivity [369].

The potential benefit of such training was first investigated in a group of 40 patients with olfactory loss due to postviral, posttraumatic, and idiopathic olfactory disorders [370]. The patients performed olfactory training twice daily with 4 odorants: phenylethyl alcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (clove). The training group (n = 40) significantly improved their psychophysical test scores (Sniffin' Sticks) after 12 weeks, while the non-training group (n = 16) did not. This result has since been repeatedly confirmed, although rarely in controlled trials [371, 372].

A randomized controlled multicenter trial [373] of 144 patients showed that olfactory training with high odor concentrations resulted in greater improvement than olfactory training with very low, barely perceptible odor concentrations [373], indicating that olfactory training is actually not related to sniffing but to olfactory stimulation. Furthermore, it was shown that the therapeutic effect was greatest when initiated promptly after olfactory loss. In addition, a greater improvement in olfactory function was demonstrated after performing olfactory training over a longer period of 9 months [374] (using 3 times 4 different odors, when changing the 4 odors every 3 months – so-called "modified olfactory training"). A recent systematic review and meta-analysis of olfactory training specifically for postviral olfactory disorders showed that patients were more likely to achieve clinically relevant improvement with olfactory training than the control group [375, 376].

In relation to posttraumatic olfactory loss, the results of olfactory training are more heterogeneous. Konstantinidis and colleagues showed clinically significant improvement after the implementation of olfactory training in 33 % of 38 patients versus 13 % of 15 controls [377]. Langdon and colleagues [378] conducted a prospective randomized controlled trial in 42 patients with posttraumatic olfactory dysfunction. Compared with the control group, there was a significant improvement in n-butanol thresholds after 12 weeks. However, there were no statistically significant improvements on an odor identification test (BAST-24) or the participants' self-reports. Jiang and colleagues reported on two studies that looked at the effect of olfactory training of patients with posttraumatic olfactory dysfunction. However, in both studies, patients were pretreated with prednisolone and zinc. After 6 months of olfactory training, significant effects were seen at the level of olfactory thresholds, but not on an olfactory identification test (UPSIT-TC) [379, 380].

In general, patients with postviral olfactory disorders respond better to olfactory training than patients with posttraumatic olfactory loss. This may be due to the overall relatively poor prognosis in patients with posttraumatic olfactory disorders.

A benefit of olfactory training has also been demonstrated in patients with neurodegenerative diseases [381]. However, few studies have addressed the effect of training in patients with sinonasal disorders [325] (reviews of [372, 382, 383]).

8.8 Surgical therapy options

Surgical interventions are largely reserved for the treatment of patients with CRSwNP. Similar to steroid therapy, extensive guidelines exist for the use of surgery in such patients. Several reviews of

surgical therapy in patients with sinonasal olfactory disorders are available [306, 384]. A meta-analysis on changes in olfaction with functional endoscopic sinus surgery (FESS) concluded that such surgery for CRS improves "almost all" subjective and psychophysical parameters [385] (but see also [386]). In addition, changes in the volume of olfactory significant brain structures have been shown to be associated with improved olfactory function after FESS [133, 387].

The benefit of surgical treatment strategies for non-sinonasal olfactory disorders is less well established. Schriever et al. showed that septoplasty had no significant or minor effects on olfaction [388], in contrast to other studies [252, 389, 390]. Reports of positive effects of a surgical procedure can also be found for septorhinoplasty [391–395]. In addition, a positive effect has been reported for dilation of the olfactory cleft [396].

8.9 Platelet-rich plasma

Platelet-rich plasma (PRP) is an autologous concentrate of platelet-rich plasma protein prepared from whole blood. During hemostasis, activated platelets release a variety of growth factors and cytokines. These factors promote angiogenesis, cell proliferation, and cell differentiation, which ultimately contributes to lesion regeneration [397, 398]. Regarding olfaction, intranasal PRP showed improvement in olfactory behavioral tests in a mouse anosmia model [399]. In patients with sinonasal olfactory disorders, Mavrogeni et al. [400] reported positive results after repeated intranasal injection of PRP. Yan et al. also showed significantly improved olfactory performance (Sniffin' Sticks) 3 months after a single intranasal PRP injection [401] (see also [450]). In treatment-resistant patients with anosmia, improvement in the olfactory test was demonstrated after treatment with PRP-soaked sponges (B-SIT) [402].

8.10 Omega-3 fatty acids

Omega-3 fatty acids comprise a group of polyunsaturated fatty acids that are key substrates of fat metabolism. Three types of omega-3 are important for humans: α-linolenic acids (ALA – an essential fatty acid available only through the diet), eicosapentaenoic acid (EPA) and docosahexaenoid acid (DHA). Thus, animals deficient in omega-3 show poorer results in odor discrimination tasks [403]. This is thought to be due to reduced levels of DHAS in the brain and particularly in the BO. Omega-3-rich diets are associated with good performance in odor discrimination tests in humans [404, 405].

In a randomized controlled trial, Yan et al. showed significantly better recovery of olfaction in patients after endoscopic sellar or parasellar tumor resections compared to a control group [406]. A non-blinded prospective study by Hernandez et al. [407] in patients with postviral olfactory dysfunction also suggested a positive effect on olfactory recovery compared to a control group.

8.11 Further treatment options

In addition to the above, numerous other treatment options have been proposed, for example, phenytoyl ethanolamide plus luteolin [408], acupuncture [409], lavender syrup [410], famotidine [411], blocking of the stellate ganglion [412], toki shakayaku san – a mixture of herbal medicines [413, 414], or B vitamins [415].

9. Treatment of qualitative olfactory disorders

9.1 Phantosmia

Phantosmia associated with neurological diseases rarely occurs. It often disappears in the course of treatment of the initial disease. Accordingly, successful use of topiramate, verapamil, nortriptyline, and gabapentin in patients with migraine has been described in case reports [416, 417]. Sodium valproate and phenytoin have also been used successfully in two cases of idiopathic phantosmia [418]. Mirrissey et al. reported successful treatment with haloperidol in patients with idiopathic phantosmia [239].

Topical application of saline solution to the olfactory mucosa can provide temporary relief [223]. Leopold and Hornung showed transient improvement in 6 patients with idiopathic or postviral phantosmia after local anesthesia of the olfactory mucosa (topical application of cocaine) [419]. Initially the treatment resulted in anosmia in all 6 patients; in 4 patients, phantosmia returned simultaneously with olfaction, and in two, there was a delayed onset of phantosmia after return of olfaction. As described above, there was a significant decrease in postviral phantosmia after application of intranasal sodium citrate for 2 weeks [345]. In addition, there was also a decrease in parosmic symptoms, although this did not reach statistical significance.

In cases of severe, prolonged phantosmia, surgical removal of the olfactory epithelium [223, 239, 420] or the OB [236, 237] has been successfully used as a last resort in a few selected patients.

9.2 Parosmia

Because of the typical association of parosmia with quantitative olfactory disorders, they are often treated together with quantitative olfactory disorder rather than separately [324, 345, 421, 422]. Parosmias are thought to resolve with the normalization of olfactory function.

Surgical treatment of long-lasting parosmia was described by Liu et al. – by formation of mucosal adhesions, airflow to the olfactory cleft is reduced, which led to improvement for at least two years in at least a single case with unilateral parosmia [423].

Problematic in the treatment of parosmia and phantosmia, however, is the poor quantifiability and objectifiability of the complaints, which ultimately makes the control of any therapeutic attempt more difficult.

10. Possible new therapy approaches

10.1 Olfaction implants

During smelling, chemical stimuli are converted into electrical signals, which are processed in the brain in complex ways to form olfactory percepts. In analogy to the cochlear implant that is used to restore hearing in congenital or acquired severe hearing loss [424], implants to restore olfactory function are currently being developed.

In humans, the first experiments on electrical stimulation in the area of the olfactory mucosa took place as early as 1886 [425]. Some authors described that olfactory impressions could be trig-

gered by electrical stimuli [426, 427], others were not successful [428, 429]. Activation in the area of the primary olfactory cortex by electrical stimulation was demonstrated by fMRI [429]. In addition, odor sensations could be produced by electrical stimulation of the OB [233, 430]. When studied in patients with epilepsy or IPS, olfactory sensations could be triggered after electrical stimulation using depth electrodes [234, 235, 431–435].

These investigations show that activation of the olfactory system by electrical stimulation is possible and thus olfactory sensations can be elicited. However, the expectations on an olfactory implant are immense. A large number of odors must be detected and odor-specific electrical signals generated for transmission. Constanzo and Coelho filed a first patent back in 2016. Extensive projects are currently underway to develop an olfactory implant, such as the EU-funded ROSE project (restoring odorant detection and recognition in smell deficits) [436].

10.2 Olfactory transplantations

Transplantation of olfactory epithelium or olfactory stem cells represents a therapeutic approach to directly restore damaged olfactory epithelium. First transplantations of olfactory mucosa took place already in 1983 by Morrison and Graziadei in rats. After transplantation of olfactory mucosa into the OB, fourth ventricle, or parietal cortex of rats/mice, regeneration of the ORN was demonstrated [437–439], with a survival rate of 83–85 %.

In mice, both intravenous and local transplantation of labeled bone marrow stem cells was shown to migrate into the olfactory mucosa and partially differentiate into ORN [440, 441]. Improvement in olfactory function has been demonstrated in electrophysiological studies compared to a control group [442]. Kurtenbach et al. transplanted tissue-specific stem cells from the olfactory epithelium in mouse experiments and were able to confirm the development of ORN in the olfactory epithelium with axon sprouting into the OB in histological studies. In addition, behavioral testing and electrophysiological measurements demonstrated restored olfactory function compared with the control group [443].

Transplantation of both, stem cells and olfactory epithelium represent promising therapeutic options, but studies have not yet gone beyond animal experiments. Furthermore, it should be kept in mind that stem cell transplantation is accompanied by chemotherapy and/or radiotherapy, as well as immunosuppression, which in turn is an increased risk of morbidity and mortality [444].

11. Conclusion

Although one can apparently get through life well without a sense of smell, olfaction is significant, among other things for recognizing danger, for our social life, and for eating and drinking. Without the sense of smell, the quality of life is considerably impaired in many, but not in all, people. In this respect, patients with olfactory disorders deserve attention and care. Diagnostic methods are largely standardized and commercially available for a wide variety of questions. In contrast to the detailed diagnostic possibilities, options for the therapy of olfactory disorders are limited. However, this does not mean that there are no options.

Conflict of Interest

T Hummel: Seit 2019 arbeitete ich zusammen mit folgenden Firmen: Smell and Taste Lab, Geneva, Switzerland; Takasago, Paris, France; aspuraclip, Berlin, Germany; Baia Foods, Madrid, Spain; Burghart, Holm, Germany; Primavera, Kempten, Germany. The other authors declare that they have no conflict of interest.

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