Running Title:
Olfactory Position Paper

TYPE OF ARTICLE:
OTHER (Position paper)

Position Paper on Olfactory Dysfunction

Hummel T[1], Whitcroft KL[1-3], Andrews P[2 4], Altundag A[5], Cinghi C[6], Costanzo RM[7], Damm M[8], Frasnelli J[9,10], Gudziol H[11], Gupta N[12], Haehner A[1], Holbrook E[13], Hong SC[14], Hornung D[15], Hüttenbrink KB[16], Kamel R[17], Kobayashi M[18], Konstantinidis I[19], Landis BN[20,21], Leopold DA[22], Macchi A[23], Miwa T[24], Moesges R[25], Mullol J[26], Mueller CA[27], Ottaviano G[28], Passali GC[29], Philpott C[30,31], Pinto JM[32], Ramakrishnan VJ[33], Rombaux P[34], Roth Y[35], Schlosser RA[36], Shu B[37], Soler G[38], Stjärne P[39], Stuck BA[40], Vodicka J[41], Welge-Luessen A[42]

Author Affiliations:

1. Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany
2. UCL Ear Institute, Faculty of Brain Sciences, University College London, London, UK
3. Centre for the Study of the Senses, Institute of Philosophy, School of Advanced Studies, University of London, London, UK
4. Royal National Throat Nose & Ear Hospital, London, UK
5. Department of Otorhinolaryngoglogy, Istanbul Surgery Hospital, Istanbul, Turkey
6. Department of Otolaryngology; Eskisehir Osmangazi University, Istanbul, Turkey
7. Smell and Taste Disorders Center, Department of Otolaryngology Head and Neck Surgery, VCU School of Medicine, Richmond, VA, USA
8. Department of Otorhinolaryngology, Head and Neck Surgery, University of Cologne Medical Center, Cologne, Germany
9. Research Chair in Chemosensory Neuroanatomy, Department of Anatomy, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada
10. Centre for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada
11. Department of Otorhinolaryngology, University of Jena, Jena, Germany
12. Department of Otorhinolaryngology, University College of Medical Sciences and GTB Hospital, Delhi, India
13. Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA
14. Department of Otorhinolaryngology, Konkuk University Medical Center, Hwayang-dong, Gwangjin-gu, Seoul, South Korea
15. Dept. of Biology, St. Lawrence University, Canton, NY, USA
16. Department of Otorhinolaryngology, University of Cologne, Cologne, Germany
17. Department of Otorhinolaryngology, Cairo University, Cairo, Egypt

18. Department of Otorhinolaryngology-Head and Neck Surgery, Mie University Graduate School of Medicine, Mie, Japan
19. Smell and Taste Clinic, Second Academic Otorhinolaryngology Department, Papageorgiou Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
20. Department for ENT, Head and Neck Surgery, Bern University Hospital, Bern, Switzerland
21. Rhinology-Olfactology Unit, Department of Otorhinolaryngology-Head and Neck Surgery, University Hospital of Geneva Medical School, Geneva, Switzerland
22. Division of Otorhinolaryngology-Head and Neck Surgery, Department of Surgery, University of Vermont Medical Center, Burlington, Vermont, USA
23. ENT Clinic, University of Insubria, ASST, sette laghi, Varese, Italy
24. Department of Otorhinolaryngology, Kanazawa Medical University, Uchinada, Kahoku, Ishikawa, Japan
25. Institute of Medical Statistics, Informatics and Epidemiology, University Hospital of Cologne, Cologne, Germany
26. Rhinology Unit & Smell Clínic, IDIBAPS, University of Barcelona, Barcelona, Catalonia, Spain
27. Department of Otorhinolaryngology, Medical University of Vienna, Vienna, Austria
28. Department of Neurosciences DNS, Otolaryngology Section, University, Padua, Italy
29. Head and Neck section, Department of Aging, Neurosciences, Head and Neck and Orthopedic; Catholic University of Sacred heart, "A. Gemelli" Hospital Foundation, Rome, Italy
30. Norwich Medical School, University of East Anglia, Norwich, UK
31. The Smell & Taste Clinic, James Paget University Hospital, Gorleston, UK
32. Section of Otolaryngology-Head and Neck Surgery, The University of Chicago Medicine and Biological Sciences, Chicago, Ill, USA
33. Departments of Otolaryngology and Neurosurgery, University of Colorado, Aurora, CO, USA
34. Université Catholique de Louvain, Institute of Neurosciences, Unit of Otorhinolaryngology, Brussels, Belgium
35. The Institute for Nose and Sinus Therapy and Clinical Investigations, Department of Otolaryngology - Head & Neck Surgery, Edith Wolfson Medical Center, Tel Aviv University Sackler Faculty of Medicine, Holon, Israel
36. Department of Otolaryngology – Head and Neck Surgery, Medical Univeristy of South Carolina, Charleston, SC, USA
37. Department of Otolaryngology, Taipei Veterans General Hospital, National Yang-Ming University School of Medicine Faculty of Medicine, Taipei, Taiwan
38. Division of Otorhinolaryngology, Area of Smell and Taste, Hospital de Clínicas, University of Buenos Aires, Buenos Aires City, Argentina
39. Section of Rhinology, Department of Otorhinolaryngology, Karolinska University Hospital and Karolinska Institutet, Stockhollm, Sweden
40. Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Essen, University Duisburg-Essen, Germany
41. Department of Otorhinolaryngology and Head and Neck Surgery, Hospital Pardubice, Faculty of Health Studies, University of Pardubice, Pardubice, Czech Republic
42. University Hospital Basel - Otorhinolaryngology, Basel, Switzerland

Author Email Addresses:
thummel@mail.zih.tu-dresden.de
k.whitcroft@gmail.com
aaltundagkbb@yahoo.com
antje.haehner@uniklinikum-dresden.de
jordan_orl@hotmail.com
Basile.Landis@hcuge.ch
JMULLOL@clinic.cat
C.Philpott@uea.ac.uk
philippe.rombaux@uclouvain.be
Antje.Welge-Luessen@usb.ch
johannes.a.frasnelli@uqtr.ca
studiodottormacchi@virgilio.it
schlossr@musc.edu
ccingi@gmail.com
orl@wolfson.health.gov.il
dhornung@stlawu.edu
miwataka@kanazawa-med.ac.jp
karl-bernd.huettenbrink@uk-koeln.de
par.stjarne@karolinska.se
Donald.Leopold@uvmhealth.org
write2drneelima@yahoo.com
giancarlo.ottaviano@unipd.it
boris.stuck@uk-essen.de
giulio.passali@rm.unicatt.it
michael.damm@uni-koeln.de
dragracielasoler@yahoo.com.ar
jan_vodicka@hotmail.com
peterandrews@entpeterandrews.co.uk
Vijay.Ramakrishnan@ucdenver.edu
chihhung003@gmail.com
jpinto@surgery.bsd.uchicago.edu
rhinologyrhk@gmail.com
christian.a.mueller@meduniwien.ac.at
ralph@moesges.de
m-koba@doc.medic.mie-u.ac.jp
Hilmar.Gudziol@med.uni-jena.de
richard.costanzo@vcuhealth.org
Eric_Holbrook@meei.harvard.edu
20050692@kuh.ac.kr

Corresponding Author: Thomas Hummel, M.D.; Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany; phone +49-351-458-4189; thummel@mail.zih.tu-dresden.de

Statement: All authors agree on the sections entitled “recommendations”.

Key Words (MeSH headings): Smell, Olfaction Disorders, Therapeutics, Investigative Techniques

SUMMARY:

Background:

Olfactory dysfunction is an increasingly recognised condition, associated with reduced quality of life and major health outcomes such as neurodegeneration and death. However, translational research in this field is limited by heterogeneity in methodological approach, including definitions of impairment, improvement and appropriate assessment techniques. Accordingly, effective treatments are limited. In an effort to encourage high quality and comparable work in this field, among others, we propose the following ideas and recommendations. Whilst full recommendations are outlined in the main document, key points include:

- Patients with suspected olfactory loss should undergo a full examination of the head and neck, including rigid nasal endoscopy.
- Subjective olfactory assessment should not be undertaken in isolation, given its poor reliability.
- Psychophysical assessment tools used in clinical and research settings should include reliable and validated tests of odour threshold, and/or one of odour identification or discrimination.
- Comprehensive chemosensory assessment should include gustatory screening.
- Smell training can be helpful in patients with olfactory loss of several aetiologies.

Conclusions:

We hope the current manuscript will encourage clinicians and researchers to adopt a common language, and in so doing, increase the methodological quality, consistency and generalisability of work in this field.

Word Count: 198

Table of Contents

Introduction

Olfactory dysfunction is an increasingly recognised condition. However, the sense of smell remains relatively poorly researched and is often neglected by the medical community: in 2007 a UK-based survey found that whilst 97% of consultant otorhinolaryngologists managed olfactory dysfunction, 55% did not formally test for chemosensory impairment, and of those who did, only 12% did so routinely [1].

This putative neglect may be due to the perceived subtle effects of olfactory dysfunction and frustration at the apparent lack of treatment options. However, there is increasing evidence that olfactory impairment can affect quality of life, through environmental and social anxiety, food and weight disturbances and depression [2–7]. Moreover, a growing body of evidence connects olfaction to major health outcomes, including neurodegenerative disease and death [8,9]. It is therefore important that olfactory dysfunction is both investigated and treated where possible, particularly amongst ENT specialists. This is reflected in the recent inclusion of olfactory impairment as part of the ENT-UK 'GENERATE' national agenda for research [10], as well as continued emphasis within the United States National Institutes of Health/National Institute on Deafness and Other Communication Disorders strategic plan [11].

At present, the literature on olfaction is limited by heterogeneity in methodological approach. This heterogeneity is reflected in varying definitions of impairment and improvement, lack of consensus regarding appropriate testing methods and wide variations in epidemiological estimates. Therefore, we propose the following definitions and ideas in an effort to improve this evidence base, and in so doing improve patient care. At the same time, we are aware that this cannot be a complete approach unifying all people working in this field of research, but rather a starting point for future development.

Definitions

Olfactory dysfunction can be classified as either quantitative, involving alteration in the strength but not quality of odours, or qualitative, in which the quality of odours is changed. Qualitative disorders, such as parosmia, often involve negatively perceived changes in quality of smell. Very often, qualitative changes are found in combination with quantitative changes, whereas it is much less frequent to find qualitative changes alone. With regards to qualitative changes, parosmia and phantosmia often occur together. Definitions of terms used to describe olfactory function and dysfunction are listed in Table 1.

[Table 1]

*There is some disagreement in the literature regarding terminology. Whilst 'parosmia' is generally used to indicate a qualitative olfactory distortion in the presence of a stimulus, it has on occasion been used to describe more general olfactory dysfunction (including quantitative loss) [(14)]. 'Dysosmia' has been used by some to describe any distortion in olfaction, which would therefore include both quantitative and qualitative changes [(14,15)]. However, others have used this term with reference to qualitative dysfunction in the presence of an odourant stimulus only, thus making it synonymous with parosmia [(16)]. Whilst the term 'cacosmia' is generally accepted as a 'negatively perceived olfactory distortion', some consider this either a form of parosmia (stimulus present) [(16)], phantosmia (stimulus absent) [(14)], or both [(15)]. Euosmia is used to describe pleasant qualitative olfactory distortion in the presence of a stimulus and can therefore be considered a subtype of parosmia [(17)]. Troposmia is generally considered to be synonymous with parosmia [(14)].

Multiple chemical sensitivity (MCS; also known as 'Idiopathic Environmental Intolerance') is a condition in which patients describe a range of subjective symptoms following low-level exposure to various chemicals. Due to the range of organ systems affected, and disparity of offending substances, it has been suggested that MCS is not an organic clinical entity, but rather a predominantly psychological condition. This view has been supported by studies demonstrating no significant difference in patient response to 'active' substances versus placebo [(18,19)]. For this reason, MCS has not been considered further in this position paper.

Recommendations:

- We recommend use of the terms highlighted in bold in the above table, with their associated definitions.

Epidemiology of Olfactory Dysfunction

Though olfactory dysfunction is increasingly recognised, the true prevalence and incidence is unclear. Estimates vary significantly according to sample demographics, definitions of impairment and assessment technique. The latter is particularly important, and the existing literature will therefore be classified according to assessment technique in the following sections [for a comprehensive review, please see ref [(20)]].

Subjective reporting

Using subjective 'self-reporting', early household survey-based studies demonstrated conservative prevalence estimates. The 1994 Disability Supplement to the National Health Interview Survey (NHIS) addressed chemosensory impairment in a randomly selected cohort of 42,000 households (and thereby approximately 80,000 adults over 18) in the United States [(21)]. Using adjusted national estimates, the authors concluded that 2.7 million persons (1.4% of the US adult population) had experienced a problem with their sense of smell that had lasted longer than three months. This prevalence increased markedly with age, with approximately 40% of persons over the age of 65 reporting smell problems [(21)].

Newer survey-based studies have reported higher, though still fairly conservative estimates. In 2013, results were published from the 2009 Korea National Health and Nutrition Examination Survey (KNHANES). In this study, olfactory dysfunction was estimated at 4.5%, with prevalence increasing with age [(22)]. The US based National Health and Nutrition Examination Survey (NHANES) also included a chemosensory component. Two studies analysing the prevalence of self-reported olfactory impairment have been published from this data. The first of these was by Bhattacharyya and Kepnes in 2015 [(23)]. Using results gathered from 3,549 adults between 2011 and 2012, they estimated that 10.6% ± 1.0% of the US population had experienced a smell disturbance in the last 12 months. Of these, 50.2% ± 1.8% reported their problem to be 'always there'; 45.2% ± 2.2% reported that their problem 'comes and goes'; and 4.5% ± 0.9% reported that their problem was 'only present with a cold'. Again, prevalence increased with age (odds ratio 1.15, 95% confidence interval 1.00–1.31). Sex did not affect prevalence. In 2016, Rawal and colleagues also published results from the 2011-2012 NHANES project, though from a slightly larger cohort of 3,603 adults [(24)]. They reported a higher prevalence of subjective olfactory dysfunction at 23%. However in this case, impairment was defined 'since age 25', rather than in the preceding 12 months, as was used by Bhattacharyya and Kepnes.

Within the context of epidemiological research primarily investigating the prevalence of chronic rhinosinusitis, work from the Global Allergy and Asthma European Network

(GA^{2}LEN) has demonstrated self-reported smell loss in 7.6% of 57,128 respondents from across Europe [25]. Within the United States, Hirsch and colleagues demonstrated a prevalence of 9.4% subjective smell loss in their source population [26]. This was based on results from their postal survey of 7,847 people (the aim of which was to determine prevalence of patient reported chronic rhinosinusitis).

Psychophysical testing

Previous studies have suggested that olfactory self-rating may be unreliable [27]. Therefore, in order to increase the accuracy of epidemiological estimates, more objective assessment is required in the form of psychophysical testing for odour identification, discrimination or threshold. Odour identification tests may be culturally specific and should therefore be validated for the target population (for more detail, see 'psychophysical testing' in 'olfactory assessment' section).

In Germany, Landis and colleagues assessed olfactory function in 1,240 non-rhinological patients (mean age 41.7 years) presenting to an otorhinolaryngology outpatient clinic. Using the odour identification component of the "Sniffin' Sticks" test battery, they demonstrated functional anosmia in 4.7% and hyposmia in 15% of those tested [28]. Later, in 2008, Vennemann and colleagues performed odour identification testing in a random sample of 1,312 adults (aged 25-75), as part of the Dortmund Health Study. Based on their 12-item screening test an estimated prevalence of 21.6% had impaired olfaction (score of <10), with 3.6% of these being classified as functionally anosmic (score of ≤ 6) [29]. This prevalence increased with age and cigarette smoking.

The Skövde population-based study used the Scandinavian Odor Identification Test (SOIT) in addition to subjective patient reported measures to determine the rate of olfactory dysfunction in Sweden. Their original study population was 1,387 participants (aged ≥ 20 years), following which additional adolescent participants were added to produce a sample of 1,713. In their original study, the prevalence of self-reported 'worse-than-normal' olfactory function was 15.3% [30]. The prevalence of dysfunction based on the SOIT was higher at 19.1%, with 13.3% qualifying as 'hyposmic' (defined as a SOIT score of 10-12) and 5.8% 'anosmic' (SOIT score of ≤ 9) [31]. In their later study, the prevalence of parosmia was found to be 3.9% [32]. Another Swedish study, based on data from the Betula project, demonstrated a negative correlation between age and olfactory function, as determined through testing with a modified SOIT in 1,906 subjects [33].

In Spain, the OLFACAT (Olfaction in Catalonia) survey assessed detection, recognition and identification of 4 self-administered microencapsulated odourants. Responses were obtained from 9,348 persons and normal olfactory function was assigned where the respondent was able to detect, recognise and correctly identify all four odourants. 'Hyposmia' was assigned where a person was unable to correctly detect, recognise or identify one or more odour and 'anosmia' where they were unable to correctly detect, recognise or identify any odours. According to this classification, the prevalence of smell dysfunction in this cohort was 19.4% for detection (0.3% anosmia, 19.1% hyposmia), 43.5% for recognition (0.2% anosmia, 43.3% hyposmia) and 48.8% for identification (0.8% anosmia, 48% hyposmia). This study was potentially limited by the questionnaire distribution method, which was through a local newspaper, and which may therefore have targeted persons mainly of middle/higher socio-economic and educational status [(34)].

Several epidemiological studies utilising psychophysical testing methods have been reported from the United States of America. In 2002, results were published from the Epidemiology of Hearing Loss Study. Olfaction was tested in 2,491 older adults (aged 53-97) living in Beaver Dam, Wisconsin, using the San Diego Odor Identification Test (SDOIT) and subjective patient reporting. Using the former method, overall mean prevalence of olfactory dysfunction (defined as a SDOIT score of <6 out of 8) was 24.5%, rising to 62.5% for subjects over 80 years. Self-reported olfactory dysfunction was less common, at only 9.5%, with the ability to accurately self-assess olfactory function decreasing with age [(35)].

The National Social Life, Health and Aging Project (NSHAP) assessed olfaction in a nationally representative sample of older adults in the United States during two waves. Odour identification was tested in wave one, whilst both identification and threshold scores were tested in wave two. During the former, severe olfactory dysfunction was demonstrated in 2.7% of 3,005 adults aged 57 to 85 years [(36)]. During wave two, olfactory function was shown to deteriorate significantly with advancing age, in a cohort of 2,212 subjects aged 62 to 90 years [(37)]. Of note, this is the only epidemiological study where tests were not only performed for screening tests based on odour identification, but also for odour thresholds.

Prevalence of olfactory dysfunction has also been reported from the US based Honolulu-Asia Aging Study (HAAS) [(38)] and the Memory and Aging Project (MAP) [(39)]. Using the Cross-Cultural Smell Identification Test, the HAAS study demonstrated impaired odour identification in around three quarters of adult men over 71 years. Using the same psychophysical test, the MAP study reported a prevalence of 55.3% in their cohort of mean age 80.6 years.

Devanand and colleagues reported data from the Washington Heights/Inwood Columbia Aging Project cohort, in which odour identification was tested in 1,169 older adults (mean age 80 years) [40]. Using the University of Pennsylvania Smell Identification Test, the average identification score across the entire cohort was 25.18 ± 7.26, therefore falling at the border between 'severe microsmia' and 'microsmia'. During their follow up period, this study went on to demonstrate a statistically significant, independent association between olfactory dysfunction (particularly anosmia) and increased risk of mortality.

Finally, the Blue Mountains Eye Study assessed olfactory function in 1,636 older adults (aged 60 and over) in Australia. Using the SDOIT, the authors demonstrated olfactory impairment in 27% of their cohort. In addition to demonstrating deterioration in olfactory function with age, the authors demonstrated a negative correlation with body mass index, clinically supporting the concept that olfaction enhances appetite and food enjoyment [41].

Conclusion:

- 'Functional anosmia has a prevalence of approximately 5% of the general population. Normal aging significantly contributes to this disease burden.

Anatomy and Physiology of Olfaction

Except in rare circumstances, the perception of odour requires a functional peripheral sensory organ and central pathways.

Approximately 6-30 million bipolar receptor cells, or olfactory sensory neurons (OSN), can be found in the olfactory neuroepithelium of young adult humans, whose axons collectively constitute the olfactory nerve (cranial nerve 1) [42]. The cell bodies of these bipolar cells are found within the nasal olfactory epithelium. Though traditionally thought to be limited to the olfactory cleft, there is uncertainty about the extent of the olfactory neuroepithelium within the nasal cavity, especially in younger people [43], but mature and functional OSN can be found in humans at the insertion of the middle turbinate [44–48].

Olfactory sensory neurons extend multiple dendritic cilia into an overlying olfactory mucus layer, so creating a large surface area for odourant binding. Basally, OSN extend axons in bundles (olfactory fila) through the foramina of the cribriform plate towards the olfactory bulb. The olfactory bulb is the first relay in the olfactory system and is found immediately superior (dorsal) to the cribriform plate and inferior (ventral) to the orbitofrontal cortex. Within the olfactory bulb, OSN axons form their first synapse with bulbar glomerular cells. It is therefore interesting that OSN are first order excitatory sensory neurons, which extend directly from the mucosa of the olfactory cleft into the brain. OSN are also interesting in that they are capable of regeneration from the basal cells found within the olfactory neuroepithelium although the turn-over time in humans is unclear [49].

Olfactory ensheathing cells (OEC) are supporting glial cells, which are present in the peripheral and central olfactory systems (neuroepithelium and olfactory bulb respectively). OECs play a facilitative role in the regeneration of OSNs and may putatively be used in future treatment of nerve lesions [50,51]. The superior turbinate has been demonstrated to be a safe area to harvest olfactory mucosa for OEC cell culture [52] and interestingly there is limited evidence that OEC yield rates are higher in young compared to old patients or in patients with less compared to those with more nasal inflammation [53].

The second order output neurons from the olfactory bulb are the mitral and tufted cells. Following signal integration, these neurons extend their axons along the lateral olfactory tract towards the structures of the primary olfactory cortex. These structures include: the anterior olfactory nucleus, the piriform cortex, the periamygdaloid cortex, the anterior cortical nucleus of the amygdala and the rostral entorhinal cortex. Odour processing may also involve ‘secondary’ and ‘tertiary’ brain areas, including structures such as the hippocampus, parahippocampal gyrus, insular cortex, and orbitofrontal cortex [54].

In order to initiate olfactory processing, odourants must first reach the olfactory neuroepithelium. Here, they become dissolved in the mucus layer and bind with olfactory receptors (OR), which are found on the dendritic cilia of the OSN. Olfactory receptors are G-coupled receptors and binding of the odourant ligand leads to downstream signalling cascades involving activation of adenylyl cyclase and subsequent opening of cAMP-dependent cation channels [55]. Resultant action potential generation is then propagated to the structures outlined above. Human gene studies have demonstrated up to 400 active OR genes, though humans are able to detect thousands of distinct odours ([56,57] but see also: ref [58]). This is made possible through complex combinatorial encoding, whereby each odourant ligand is recognised by varying combinations of OR [59–61]. In addition, other types of chemoreceptors have been identified which are likely to be involved in human chemoreception [62–64].

Finally, it is important to remember that the sensation of smell is also influenced by the somatosensory and chemesthetic sensations of the nose: for example the cooling sensation of menthol or the prickle of carbon dioxide from carbonated drinks. These sensations are mediated in the nose by the trigeminal nerve [65], and there is increasing evidence that trigeminal and olfactory functions are closely linked and potentially interdependent [66–69]. In addition, trigeminal activation is crucial to the perception of nasal airflow [70].

Conclusion:

- OSN are interesting in that they are capable of regeneration from the basal cells found within the olfactory neuroepithelium.

Causes and Classification of Olfactory Loss

Previous attempts have been made to classify olfactory dysfunction according to the location of presumed pathology, in a similar way to classification used in the auditory system. In this way, definitions have included those as in Table 2, below:

[Table 2]

However, anatomical classification in this way may be restrictive. The above categories are not mutually exclusive and their use as such may lead to incomplete appreciation of the underlying pathophysiology. This is particularly evident with regards to several conditions known to cause olfactory dysfunction.

Chronic rhinosinusitis (CRS) is a common inflammatory condition affecting the mucosa of the nose and one or more of the paranasal sinuses. It has several distinct phenotypic subtypes including CRS with or without polyps. It has been suggested that hyposmia and anosmia associated with CRS is caused by mechanical obstruction of odourant transmission to the olfactory cleft due to mucosal oedema or polyps [71]. Accordingly, opacification of the olfactory cleft on CT has been correlated with olfactory function [72]. Alone, this would make CRS a conductive olfactory dysfunction. However, the link between eosinophilia and olfactory dysfunction has been well demonstrated [73–76], and increasing evidence from both animal models and human research has suggested that inflammation within the neuroepithelium can lead to temporary, reversible interference with odourant binding/olfactory perception [77,78]. Furthermore, long term inflammation is believed to cause neuroepithelial remodelling and replacement with respiratory type epithelium [79,80]. Additionally, olfactory bulb volumes are decreased in patients with CRS [81]. Indeed, Gudziol and colleagues have shown that olfactory bulb volume can increase significantly after treatment in patients with CRS, compared with controls [82]. Therefore, it would appear that olfactory dysfunction due to CRS is likely a combination of both conductive, sensorineural and even central components in established disease. This argues against the anatomical classification of olfactory disorders.

Similar anatomical overlap might be described in posttraumatic olfactory loss. The causative pathology in these cases has traditionally been described as severing of the olfactory nerve filaments as they cross the cribriform plate to reach olfactory bulb [83]. However, the temporal course in such patients often does not fit with such dramatic and complete damage, but rather with delayed central damage, for example through cortical oedema [84]. In addition, the degree of posttraumatic olfactory loss can be correlated with central lesions, demonstrated with magnetic resonance imaging of the brain [84]. In this way, the anatomical site of the lesion

might either be sensorineural, central or both. One should also bear in mind that facial lesions obtained during head injury may cause obstruction of airflow to the olfactory cleft, thereby contributing a conductive element to any olfactory dysfunction.

In order to bypass these limitations in classification, chemosensory research has evolved to describe olfactory dysfunction according to putative underlying aetiology. Whilst an extensive number of underlying aetiological conditions have been linked to olfactory dysfunction, the main causes are as follows:

- Olfactory dysfunction secondary to sinonasal disease
- Post-infectious olfactory dysfunction
- Posttraumatic olfactory dysfunction
- Olfactory dysfunction associated with neurological disease
- Olfactory dysfunction associated with exposure to drugs/toxins
- Congenital olfactory dysfunction
- Olfactory dysfunction associated with aging
- Other possible causes: iatrogenic damage (sinonasal and skull base surgery, laryngectomy), tumours, multiple systemic co-morbidities
- Idiopathic olfactory dysfunction

The following section will briefly describe the current pathophysiological evidence for the above classifications.

Olfactory dysfunction secondary to sinonasal disease

Rhinosinusitis is the main cause of olfactory loss due to sinonasal disease. This may be either acute (lasting less than 12 weeks, with complete resolution of symptoms) or chronic rhinosinusitis (lasting 12 weeks or longer). A variety of phenotypic subtypes exist, with olfaction being most affected by chronic rhinosinusitis with nasal polyposis (CRSwNP), followed by chronic rhinosinusitis without polyps (CRSsNP), non-allergic rhinitis, atrophic rhinitis and allergic rhinitis [(85)]. According to the European Position Paper on Rhinosinusitis and Nasal Polyps, as well as the American Academy of Otolaryngology-Head and Neck Surgery Guidelines, quantitative olfactory dysfunction (in the form of hyposmia or anosmia) is one of the key diagnostic symptoms [(86,87)].

As outlined in the above section, olfactory dysfunction due to CRS is likely caused by a combination of factors. These include: obstructed transmission of odourants to the olfactory

neuroepithelium caused by oedema, discharge ± polyps; short term reversible ligand-OR inflammatory-mediated binding dysfunction [77,78]; longer term neuroepithelium remodelling [80] and finally olfactory bulb remodelling. [81,82]

Olfactory dysfunction associated with sinonasal disease tends to occur gradually, and fluctuates over time [88]. It infrequently improves without treatment and is not commonly associated with parosmias [89–91].

Given the high prevalence of CRS within the general population (10.9% in Europe [25]), it is likely that sinonasal diseases constitute the most frequent cause of olfactory dysfunction [92,93]. However, such patients are often managed by their general practitioner or general ENT surgeons, and are therefore less commonly encountered in specialist smell and taste clinics.

Post-infectious olfactory dysfunction

Upper respiratory tract infections are a frequent cause of olfactory dysfunction. Indeed, post-infectious loss is one of the most common presentations seen in specialist clinics [94,95]. Typically, women are affected more frequently than men, and are middle aged or older at presentation [80]. The latter may be due to the reduced regenerative ability of the olfactory system with advancing age and the accumulation of previous insults [96]. Onset is usually sudden, and though patients may describe an unusually severe infection, some may be unaware of the causative episode. Such cases may therefore be incorrectly labelled as idiopathic. Often, patients are affected by parosmia and there is little fluctuation in olfactory ability over time [89]. Whilst post-infectious olfactory impairment can be permanent, this is often not the case. Indeed, it has been suggested that post-infectious olfactory loss improves more frequently than in other common aetiological subgroups [94]. In their 2006 prospective cohort study, Reden and colleagues demonstrated an improvement in the psychophysical test scores of approximately one third of 262 patients with post-infectious olfactory dysfunction over an observation period of 14 months [97]. Whilst higher estimates of recovery have been quoted elsewhere in the literature [98], care should be taken in interpreting data based on patient self-reporting [99], or where patient numbers are limited [100].

A variety of pathogens may cause post-infectious olfactory dysfunction, including viruses, bacteria, fungi, or rare organisms such as microfilaria [16]. The most common of these are viruses, of which a wide variety have been linked with olfactory dysfunction, including those causing the common cold, influenza and HIV [101,102]. However, the terminology post-infectious should be used preferentially to post-viral olfactory dysfunction in order to acknowledge the various causative pathogens within this group.

The pathophysiology of post-infectious olfactory loss remains poorly delineated, but is thought to involve either damage to the olfactory neuroepithelium or central olfactory processing pathways (mediated via direct transmission of pathogens to the brain through the olfactory nerve) [103,104] . With regards to the former, histological analysis in patients with post-infectious olfactory loss shows neuroepithelial remodelling and replacement with respiratory type epithelium or occasionally metaplastic squamous epithelium [80,105]. The number of OSN cells is reduced, they are found in patchy distribution and their morphology may be altered: for example they may be shrunken in size with dendrites that do not reach the mucosal layer. The associated number of receptors is also reduced [80]. Furthermore, olfactory bulb volumes are reduced in patients with post-infectious loss and correlate with residual olfactory function [106,107]. This likely reflects bulb plasticity, partly in response to reduced afferent input from the OSN of the neuroepithelium.

Posttraumatic olfactory dysfunction

Olfactory dysfunction secondary to traumatic injury is a major cause of permanent olfactory impairment, and can be ascribed to one or more mechanisms. First, injuries affecting the nose may result in mechanical obstruction of odourants to the olfactory neuroepithelium, through distorting nasal bone or septal fractures, direct neuroepithelial injury, blood clots, oedema or alteration in mucous characteristics [108]. The second mechanism involves transection, or shearing of the olfactory fila as they traverse the cribriform plate [83]. Such transection may occur with more severe coup/contra-coup type injuries, or with fractures of the midface/anterior skull base, with possible subsequent scarring that may limit axonal regeneration and targeting [109,110]. Finally, contusions, intraparenchymal haemorrhage or resultant gliosis may lead to dysfunction of the central structures involved in olfactory processing [84,111]. For example, localised contusion of the olfactory bulbs following injury has been previously documented [112]. However, posttraumatic olfactory loss can occur without any visible signs of trauma on imaging studies [84].

Patients with posttraumatic olfactory dysfunction may describe sudden onset loss following their injury, however, presentation may also be delayed. Such delay may be in line with the patient first noticing their impairment when back in their usual environment. Alternatively, delayed presentation may reflect an underlying pathology that does not involve olfactory fila transection, but possibly central damage exacted through progressive mechanisms (e.g. oedema). Following onset, fluctuation in function is infrequent and patients are often affected by phantosmia (and to a lesser degree, by parosmia) [89,113,114]. Evidence from several studies suggests that recovery is less frequent than in post-infectious loss and whilst prognosis is

often poor, recovery may occur in approximately 30% of cases over time depending on the severity of the insult [94,97,115–118].

Olfactory dysfunction associated with neurological disease

Over recent years, the link between olfactory dysfunction and neurological disease has been increasingly recognised. Whilst such dysfunction has been associated with epilepsy [119,120], myasthenia gravis [121] and stroke [122] it is most commonly seen in neurodegenerative conditions such as Parkinson's disease and Alzheimer's disease [123–125]. Indeed, evidence suggests that olfactory dysfunction in Parkinson's disease (PD) is more common than the resting tremor and predates motor symptoms by many years [38,126–128].

Functional imaging studies have demonstrated reduced activity of the hippocampus and amygdala in response to odourous stimuli in patients with PD compared with healthy controls [129]. Histological studies have shown deposition of pathological Lewy bodies and neurites within the central olfactory system, including the olfactory bulb and tract, as well as decreased neuronal populations within the anterior olfactory nucleus [123,130]. However, the significance of such changes with regards to the wider neuropathology of PD remains to be fully elucidated. Whilst it has been suggested that the olfactory neuroepithelium may offer an attractive target for diagnostic biopsies, several studies have shown no significant difference in immunohistochemical markers (including different synuclein subtypes) of olfactory epithelium in PD patients versus controls [131,132]. In addition, work by Huisman and colleagues indicates that there are an increased number of (inhibitory) dopaminergic neurons in the olfactory bulb which may explain, at least to some degree, hyposmia in PD patients [133] (but see also [134]).

Patients with olfactory dysfunction secondary to PD commonly describe a gradual onset, and may be initially unaware of their deficit. Such patients do not often report parosmia and are unlikely to see any improvement over time [89]. Olfactory dysfunction is not affected by treatment with anti-PD medications [135].

Olfactory dysfunction associated with exposure to toxins or medications

Chronic exposure to toxins can result in olfactory dysfunction. Pathogenic agents include heavy metals such as cadmium and manganese, pesticides, herbicides and solvents. Chemotherapeutic agents and other medications should also be considered in this group. The pathological correlates of olfactory dysfunction associated with toxin exposure may involve either peripheral neuroepithelial or central damage, the latter being facilitated through transport of toxins via the olfactory nerve [16].

Table 3 shows an abbreviated list of agents and medications that have been reported to affect olfaction. Although many medications have been reported to affect olfaction, carefully controlled data for the effects of such drugs on olfaction is limited.

[Table 3]

Congenital olfactory dysfunction

Certain genetic conditions are known to be associated with congenital dysfunction, most notably the developmental endocrine disorder Kallmann syndrome (hypogonadotropic hypogonadism). Typically, the diagnosis is made at an age between 12 and 16 years. The condition is associated with hypoplastic/aplastic olfactory bulbs and olfactory sulci, and OSN of varying number and maturity [80,144–146]. Such patients usually have functional anosmia, or severe hyposmia from birth. Recent work has also demonstrated olfactory, but not gustatory dysfunction in Turner's syndrome [147], and the Bardet Biedl Syndrome [148].

As MRI scanning becomes more common, non-syndromic hypoplasia/aplasia of the olfactory bulb is increasingly recognised. As such, the most frequent cause of congenital or 'developmental' anosmia is now thought to be isolated, non-syndromic, idiopathic congenital anosmia with no known genetic cause [149]. To make this diagnosis, the normal olfactory bulb structure should be hypoplastic or absent and the olfactory sulcus should be shortened (the sulcus is seen just above the olfactory bulb on coronal scanning) [150] , though there are exceptions to that rule (see [151]). Following diagnosis, patients should undergo genetic, endocrinological and paediatric (if appropriate) evaluation in order to delineate the complete phenotype of the congenital dysfunction.

Olfactory dysfunction associated with normal aging

As evidenced through epidemiological studies, olfactory function decreases with age. One such study demonstrated olfactory impairment in 62.5% of persons over 80 [35]. Furthermore, logistic regression analysis of data from the NSHAP study (described above) has demonstrated that olfactory dysfunction is a predictor of 5-year mortality, after controlling for confounding factors [8,9,152]. The link between olfactory dysfunction and mortality has also been shown in other studies (please see epidemiology section for more details) [40,153].

Previous work has suggested that olfactory loss with age is not homogeneous across smells: sensitivity towards unpleasant odours are usually preserved longer than pleasant ones, perhaps due to the formers' role in environmental navigation and defence [154].

The potential causes of olfactory impairment with advancing age are multiple and varied. A number of generic physiological changes occur within the nose of the aged that may affect olfaction, including parasympathetic/sympathetic dysregulation, reduced mucosal blood flow, fibrosis of the cribriform foramina and possibly also age-related mucociliary dysfunction. Moreover, age related changes in the olfactory neuroepithelium, olfactory bulbs and central olfactory system also occur [155]. Changes in the neuroepithelium and olfactory bulb may be in part due to the reduced regenerative capacity of the OSN [96]. In the absence of efficient OSN regeneration, damage from previous insults (e.g. upper respiratory tract infections and exposure to toxins) may accumulate to form permanent damage. The reduced olfactory bulb volumes seen with advancing age may be partially due to reduced afferent input (and consequent trophic effects) in line with OSN damage [82,156,157].

Other disorders associated with olfactory dysfunction

Other disorders associated with olfactory dysfunction may include intranasal or intracranial neoplasms, nasal surgery (e.g., septoplasty [158]), endocrine disorders (such as Addison's Disease, Turner's Syndrome or hypothyroidism), metabolic disorders such as diabetes mellitus, hypertension, vitamin B_{12} deficiency, dysfunction as a complication of surgery (for example anterior skull base operations) [16,159,160] or surgery resulting in decreased airflow to the olfactory cleft [161]. Psychiatric conditions [162,163] and migraine [13,164] have also been linked to dysfunction as has radiotherapy [165] or alcohol dependence [166–168].

The role of smoking/nicotine in olfactory loss remains controversial. Several previous studies have demonstrated a dose-dependent, negative effect of smoking on olfactory function [29,169,170]. The underlying pathophysiology of this loss has been suggested to involve increased apoptosis of OSN [171] and/or replacement of the olfactory neuroepithelium with squamous metaplasia [172]. However, other work has shown either negligible [173], or indeed protective effects [34] of smoking on olfaction. Work in rats has shown increased odour memory following treatment with nicotine agonists [174], and it has been postulated that this may contribute to the aforementioned protective effects [34]. Smoking also likely causes nasal inflammation, providing another mechanism for olfactory dysfunction. Therefore, although it seems to be clear that smoking causes olfactory dysfunction in certain cases, at least for some aspects more research is needed.

Idiopathic olfactory dysfunction

Where an exhaustive assessment has revealed no clear underlying aetiology, olfactory dysfunction may be classified as idiopathic. Studies suggest that up to 16% of patients

screened at smell and taste centres fall into this category [175]. However, care should be employed when making this diagnosis, as some such cases may be due to asymptomatic upper respiratory infections, or in older patients early neurodegeneration. With respect to the latter, a multidisciplinary approach should be considered [176]. Further studies are needed in this area.

Clinical Assessment

The initial clinical assessment of the olfactory patient is of vital importance: from the history alone a diagnosis can usually be made. Accurate diagnosis is required not just to guide management but also to give prognostic information. This is particularly important in medico-legal cases.

When assessing patients with chemosensory impairment, one should bear in mind the close association of smell and taste [177]. Where a patient complains of reduced or dysfunctional taste, often they are in fact suffering from olfactory impairment and describing consequent impact on flavour perception [95]. For example, the patient may be complaining of retronasal olfactory dysfunction but unaware that they are also experiencing orthonasal impairment.

History

Thorough history taking should include:

Specific impairment

Is the patient describing a problem with their sense of smell, taste with respect to flavour or taste with respect to basic gustatory attributes (sweet/salty/bitter/sour/umami)? Is their dysfunction quantitative, qualitative or both? If they are experiencing qualitative dysfunction, is this parosmia (stimulus present; parosmia absent when nares closed) or phantosmia (stimulus absent) or could there in fact be an internal stimulus, e.g., from the sinuses. If they are experiencing quantitative dysfunction, is this affecting all odours, or only specific odours, and how severe is their dysfunction in terms of frequency (i.e. daily or less) and intensity (i.e. functional anosmia or hyposmia)? What treatment have they had for their dysfunction to date, and has this been successful?

Onset

Sudden onset loss is more common in post-infectious or posttraumatic olfactory dysfunction, although in posttraumatic olfactory loss often there is a gap of days and weeks between the trauma and recognition of the deficit. Gradual onset is more often seen in sinonasal disease, neurodegenerative causes and aging.

Duration

Dysfunction since childhood is likely to indicate congenital anosmia (and pertinent questions regarding other syndromic attributes should be considered). Longer duration of dysfunction may be a poor prognostic sign, particularly in cases of chronic rhinosinusitis and posttraumatic olfactory dysfunction.

Fluctuation

Olfactory function fluctuates most markedly in cases due to inflammatory disease (CRS or allergy).

Other nasal symptoms

Common symptoms of sinonasal disease (e.g. CRS, allergy) should be assessed, including nasal obstruction, rhinorrhoea, postnasal drip, facial pain, sneezing and itching.

Specific impairments and quality of life

Does the patient rely on their sense of smell professionally (e.g. chef, sommelier)? Is their dysfunction causing problems with interpersonal communication (particularly of note in mothers) or nutrition (including quantified weight change)? Does the patient describe anxiety or depression as a result of their dysfunction? If the patient is suffering from significant psychological effects, referral for appropriate assessment and management should be considered as appropriate. Does the patient live alone? If so, have they experienced any home accidents (e.g. fires, gas leaks etc.)? Such patients should be counselled regarding smoke and gas alarms and adherence to 'use-by' dates on foods.

Past medical history

Direct questioning should include previous head injuries, upper respiratory tract infections, nasal or neurosurgery and any other chronic diseases that might affect olfaction. Specific questions regarding symptoms of undiagnosed neurodegenerative disease should be considered in older patients where there is clinical suspicion. Such patients should be referred to neurological services as appropriate [(178)].

Medications

Current and previous medication history (including chemotherapies) should be obtained as well as compliance. The latter may be important where medications are required for control of chronic conditions (such as L-thyroxine in hypothyroidism). Where a patient has previously been treated with corticosteroids with improvement in smell, it is likely that they are suffering from sinonasal disease.

Allergies

Allergies to medications, seasonal, perennial and occupational environmental allergens should be assessed as well as treatment for these.

Smoking and alcohol

Current smoking and drinking may be associated with both reduced olfaction and taste.

Toxins and occupational exposure

Exposure to toxins known to cause olfactory dysfunction should be assessed. Additionally, exposure to substances that increase the risk of malignancy should be considered (e.g. soft and hardwood dusts and sinonasal/nasopharyngeal carcinoma).

Family history

Family history of olfactory dysfunction may aid in a diagnosis of congenital dysfunction. In older patients, a family history of neurodegenerative diseases should be assessed (including PD and Alzheimer's disease).

Recommendations:

- Thorough clinical histories should be sought from all patients.

Clinical Examination

Examination should include a full ENT examination. In addition to anterior rhinoscopy, nasal endoscopy is desirable, ideally with a 0° Hopkin's rod lens endoscope (4mm diameter or smaller) to start. A 30° endoscope may then be used to facilitate visualisation of the olfactory cleft, which is found in the superior nasal cavity, and bounded by the superior and middle turbinates laterally and superior nasal septum medially [47]. Whilst nasal decongestant may be used [179], it should be noted that topical anaesthetic may cause temporary olfactory dysfunction [180] and should therefore be avoided until after olfactory testing is performed.

Features to note on endoscopy include:

- General nasal anatomy including inferior, middle and superior meati.
- Visibility of olfactory cleft, patency and any abnormalities thereof. Discharge, polyps, oedema, crusting, and scarring may be documented using the recently proposed Olfactory Cleft Endoscopy (OCES) Scale [181]. The use of nasal decongestants may be helpful.

- Signs of acute or chronic rhinosinusitis (including oedema, discharge (mucopurulent or serous), nasal polyps, crusting, scarring). Traditional endoscopic staging of the paranasal sinuses in CRS can be performed using the Lund-Kennedy scoring system [182] (a more recent endoscopic staging system specific to the olfactory cleft in patients with CRS has been developed and correlates with olfactory function [183]).
- Other sinonasal abnormalities such as benign or malignant neoplasms. Where malignancy is suspected a full examination of the mucosal surfaces of the head and neck should be undertaken, so requiring thorough oral, pharyngeal and laryngeal examinations.

Where a neurological aetiology is suspected, a full cranial nerve and peripheral nervous system examination should be undertaken. Tests of memory and cognition should be deferred to the appropriate neurological specialists [184] , although appropriate screening tests may be performed if feasible.

Where an asymptomatic patient requires assessment for medico-legal purposes, for example prior to surgery (e.g. anterior skull base [160]), a full examination of the head and neck should be undertaken, including nasal endoscopy, though neurological examination can be omitted if appropriate.

Recommendations:

- Patients with suspected olfactory loss should undergo a full examination of the head and neck, including rigid nasal endoscopy with small diameter endoscopes.
- Asymptomatic patients requiring assessment for medico-legal purposes should also undergo a full head and neck examination with endoscopy.
- Basic neurological examination should be undertaken where there is suspicion of an underlying neurological aetiology, though formal and detailed neurocognitive testing can be deferred to the appropriate specialists.

Olfactory Testing

The method used for assessing olfactory function and dysfunction is vitally important with respect to accurate diagnosis, outcome reporting and tracking of olfactory changes over time. A limitation of the current literature base is the heterogeneity of assessment techniques used, with consequent effect on definitions of impairment and improvement. As highlighted in the epidemiology section above, this can lead, for example, to large differences in estimated

prevalence rates, and impacts significantly on the generalisability of results, especially where non-standardised and potentially unreliable tests are used.

In general, three different types of olfactory testing can be undertaken:

1. Subjective, patient reported olfactory assessment.
2. Psychophysical olfactory assessment.
3. Olfactory assessment using electrophysiological studies or magnetic resonance imaging.

Subjective Assessment

Subjective testing can be performed using visual analogue scales, Likert questionnaires, or as part of other outcome assessments. For example, the commonly used Sino-Nasal Outcome Test (SNOT-22) is a validated patient reported outcome measure for CRS, which assesses overall disease burden. However, this contains only one question regarding olfactory dysfunction [185]. Olfactory-specific patient reported outcome measures, such as the Questionnaire of Olfactory Disorders (QOD), appear to have a greater ability to differentiate between patients with normosmia versus hyposmia than simple Likert questions analyzed from sinus specific questionnaires such as the SNOT-22 and Rhinosinusitis Disability Index [186].

However, as discussed briefly above, olfactory self-assessment tends to be unreliable and it has been shown that people do not perform well when compared with psychophysical testing [27,73,187–191]. In 2003 a group of healthy individuals were assessed for correlation between subjective, self-reported olfactory ability and composite psychophysical olfactory test scores [27]. This study found that where subjective rating preceded psychophysical testing (using "Sniffin' Sticks"- see below), there was no significant correlation between the two.

Poor self-rating abilities have also been shown in patient populations. An early study by Delank and colleagues showed that 30-40% of CRS patients with impaired olfactory function rated themselves as unimpaired [188]. In a UK based study of 80 patients presenting to a rhinology clinic, only 27.5% accurately reported their olfactory ability [187].

Whilst subjective assessment is useful in characterising the clinical effect of interventions, including the 'minimal clinically important change' [192], given the above issues, these should not be performed in isolation. Rather, when diagnosing olfactory impairment, or assessing the

effects of treatment, patient reported outcomes should be used in conjunction with more objective forms of assessment, as outlined below.

Recommendations:

- In patients reporting olfactory dysfunction olfactory assessment should be undertaken in order to fully determine disease burden and clinical impact of interventions.
- Where possible, validated questionnaires should be used. Where this is not possible, a recognized form of assessment, possibly quantitative and/or anchored, such as a visual analogue scale, should be used.
- Subjective olfactory assessment should not be undertaken in isolation, given its poor accuracy.

Psychophysical Testing

Psychophysical tests provide a more reliable assessment of olfactory function than subjective testing. Similar to an audiogram, during such assessment, an olfactory stimulus is provided and the outcome of the test is dependent on the patient's response. Psychophysical testing therefore requires a cooperative subject who can understand and follow instructions, as well as communicate choices to the clinician/investigator.

Orthonasal psychophysical tools

Through modification of psychophysical test type, different aspects of olfaction can be quantitatively assessed. Broadly, these different aspects can be divided into threshold and suprathreshold olfactory function.

Odour threshold is the concentration of an odourant where 50% of the stimuli are detected and 50% remain undetectable to a subject. Odour threshold in itself does not require specific identification of the odourant stimulus, rather a detection of 'something', usually in comparison to a blank, odourless stimulus. Where comparison is made between odourant and blank stimuli, some degree of short-term, working memory is required. However, this test does not utilize episodic or semantic memory [193] and therefore has a lower cognitive burden.

Suprathreshold olfactory testing involves presentation of odour stimuli of sufficient concentration such that they should be detectable (i.e. above the threshold level) in an

unimpaired person. By varying the odour presented, such tools allow for the testing of odour discrimination and identification abilities. Odour discrimination describes the non-verbal ability to differentiate between different odours. Odour identification involves both recognition of a stimulus and communication of its correct identity (i.e., the ability to name an odour). Unprompted odour identification is difficult [194], hence most psychophysical tests incorporate either visual or written cues [195]. Unlike odour threshold, performance in the suprathreshold tasks of discrimination and identification correlate significantly with a subject's executive function and semantic memory [193]. Furthermore, tests of odour identification require previous exposure to odour stimulus, and may therefore be culturally specific (e.g., the well-known smell of wintergreen in the USA which is almost unknown in Germany). This also includes the idea that olfactory tests should be adapted to children (see below). For this reason, such tests must be validated in a local population and associated normative data collected before use.

The hedonic value of an odour as well as its relative intensity can also be considered forms of suprathreshold olfactory testing. Hedonic assessment of an odour, or how pleasant or unpleasant an odour is, does not require recognition or identification. However, there is a greater emotional component to these ratings and as such, episodic memory may be of greater importance compared with the other aspects of olfaction described above. Relative intensity can be considered a form of threshold testing. Odour detection threshold is not to be confused with odour recognition threshold, which is the concentration of an odour required for recognition or identification. As this test involves identification of the odourant, it combines elements of both suprathreshold and threshold tasks. Hedonic value, intensity ratings and odour recognition thresholds are infrequently used during clinical diagnosis or outcomes assessment.

In addition, there are tests that rely on changes in breathing behavior in relation to olfactory stimulation, e.g., the Sniff Magnitude Test [196] or the recording of respiratory patterns in relation to olfactometric stimulation [197]. The Alcohol Sniff Test [198] uses the distance of the odor source from the nostrils as a measure of olfactory function. Subjects close their eyes and an opened alcohol pad is placed 30 cm below the nose. With each exhalation the odor source is moved 1cm closer until the patient reports smelling alcohol.

The utility of testing for multiple psychophysical components of olfaction (e.g. threshold, discrimination and identification) when assessing olfactory dysfunction is debated. Previous work by Doty has suggested that different psychophysical tests measure a common source of variance, meaning that olfactory impairment and improvement may be effectively assessed

using, for example odour identification alone [199]. However, this theory is contradicted by other work. In 1988 Jones-Gotman and Zatorre described impairment of odour identification but not thresholds after selective cerebral excision [200]. Similarly, odour identification is affected by HIV dementia, whereas odour threshold scores are preserved [201]. Work by Whitcroft and colleagues demonstrated that the pattern of psychophysical test scores obtained in 1,226 subjects, with olfactory loss of varying cause, reflected underlying disease aetiology [202]. In this study, subjects with olfactory loss due to sinonasal disease were particularly impaired in their odour threshold scores, whereas patients with Parkinson's disease were preferentially impaired in suprathreshold olfactory tasks (odour discrimination and identification). Taken together, these studies suggest that olfactory threshold preferentially tests peripheral causes of olfactory loss (for example due to sinonasal disease), whereas the suprathreshold tests of discrimination and identification preferentially assess central or cognitive causes of olfactory dysfunction. Therefore, assessing both odour threshold and suprathreshold tasks adds to the diagnostic value of the psychophysical tool.

Furthermore, the accuracy of psychophysical tools has been shown to increase when composite scores are used. In a study of 2,178 participants of mixed olfactory ability, the diagnostic sensitivity of the individual tests odour threshold (T), discrimination (D) and identification (I) as compared with composite 'TDI' scores, were 64%, 56%, and 47% respectively [203]. These sensitivities increased where paired test scores were used, but did not reach the diagnostic sensitivity of the full composite 'TDI' score. Using principle component analysis, this study further demonstrated that olfactory threshold scores individually explained more of the observed variance than odour discrimination or identification. However, these tests require additional effort and take some time to be administered, so logistical issues may limit their use.

A variety of orthonasal, psychophysical olfactory tests have been developed for clinical and research use. Some of these tests assess just one aspect of olfaction, whilst other assess multiple components [204,205]. For example, the well known 'University of Pennsylvania Smell Identification Test' (UPSIT) is a reliable, standardized microencapsulated odour identification test, which has been adapted and validated for use in a number of different countries, as well as in children [206–209]. The UPSIT does not require clinician supervision and is therefore very convenient. Accordingly, it is frequently used in the clinical setting, as well as in research [210–212]. The "Sniffin' Sticks" are another popular psychophysical test battery, the classical version of which tests odour threshold (T) and discrimination (D) in addition to identification (I) [214]. This tool utilises reusable odourant 'pens' which are presented to the subject by an examiner. A three-alternate forced choice paradigm is employed for odour threshold and

discrimination, whilst odour identification is tested using four-alternate forced choice written/visual cues. Composite 'TDI' scores from the individual subtests are used in diagnosis, and higher scores indicate better olfactory function. Again, this assessment tool is reliable, has been validated in different countries, and normative data are available for children [215–218]. Accordingly, "Sniffin' Sticks" are used extensively in research [128,219,220]. Other olfactory tests allow for the assessment of some, but not all components of olfaction. For example, the Connecticut Chemosensory Clinical Research Center Test assesses odour threshold and identification [221].

As mentioned previously, odour identification tests are culturally specific. Certain odours may not be familiar to those outside the country where the specific test had been developed. For this reason, normative data should ideally be collected from local populations [e.g., 213] or alternatively local versions developed. [e.g., 206,207].

Table 4 provides a list of psychophysical olfactory tests which have been used in research and/or clinical settings.

[Table 4]

Given the diagnostic utility of assessing multiple aspects of olfaction as described above, in combination with the apparent individual value of threshold testing, we suggest that psychophysical tools used in the comprehensive assessment of olfaction should ideally incorporate threshold testing as well as a test of suprathreshold function, for example identification.

Recommendations:

- Psychophysical assessment tools used in clinical and research settings should include tests of odour threshold, and/or one of odour identification or discrimination. Ideally, however, testing should include two or three of these subcomponents.
- Psychophysical assessment tools should be reliable and validated for the target population.

Olfactory testing in children

Measuring olfactory ability in children can be challenging since attention span can be limited and, for example, pairing of odor names with the smells may be age and location dependent [222]. However, olfactory tests have been successfully used in children as young as five, with successful completion of the test increasing with age. As an alternative, for very young and/or

noncompliant children, the 'Smell Wheel' has been used successfully in children as young as four [223]. The smell wheel is an 11-odour game-like test in which odors are identified using words and pictures. A pediatric version of "Sniffin' Sticks" (a 14 odour identification test) is also available [224].

Recommendation

- When testing olfaction in children, the test should fit the motivation of the child and be culturally appropriate.

Use of psychophysical tools to diagnose olfactory impairment

When using psychophysical tools to define olfactory impairment and improvement, it is important that reference is made to normative data collected for that test. Hyposmia can be separated from normosmia using the 10th percentile of normal test scores gathered from a population of young, healthy subjects [209,214]. Typically, normosmia is related to young healthy people. In contrast, functional anosmia is defined on the basis of the empirical distribution of scores obtained by anosmic people [215][225].

In a clinical setting, psychophysical testing is most commonly performed birhinally, where results represent the better of the two sides [27,226]. However, increasing evidence suggests that lateralised olfactory testing may serve both diagnostic and prognostic utility.

In 2007, Gudziol *et al.* reported results of monorhinal olfactory testing in 479 healthy controls, 765 patients with CRS and 53 patients with sinonasal or olfactory bulb neoplasms [227]. Using a 12-item screening version of the Sniffin' Sticks odour identification test, they found lateralised differences in function of 3 or more points occurred in 15% of controls, 26% of patients with CRS and 32% of those with neoplasms. In 2010, Welge-Lussen and colleagues performed a similar study in 518 patients with olfactory dysfunction of mixed cause [228]. Using the full Sniffin' Stick test battery they demonstrated significant lateralised differences of between 12.5 and 57.1%, depending on cause, the largest side differences being in patients with neoplasms. This study went on to demonstrate that lateralised differences in threshold score correlated significantly with lateralised differences in discrimination, identification and composite TDI scores. Work from Huart and colleagues demonstrated asymmetrical olfactory function (using the "Sniffin' Stick" test battery) in patients with mild cognitive impairment, which could be used to efficiently differentiate these patients from those with post-infectious impairment or age-matched controls [229]. Imaging studies have additionally shown correlation between monorhinal test scores and ipsilateral olfactory bulb

volume [230]. With regards to prognosis, follow-up work by Gudziol *et al.* showed that patients with lateralised olfactory differences were more likely to develop bilateral dysfunction than those without side differences [231].

Should lateralized olfactory testing be considered, even in a time-pressured clinical setting, psychophysical testing could begin with monorhinal odour threshold testing. Where there is no significant difference in threshold score (for Sniffin' Sticks, <2.5 points) between the right and left sides, testing can continue birhinally. However, where a lateralised difference is present, full monorhinal testing should be performed.

Recommendations:

- Definitions of olfactory impairment should only be made with reference to normative values for the psychophysical test being used.
- Psychophysical testing should ideally begin with monorhinal testing, if feasible. Where there is no significant difference in lateralised scores, testing may continue bihrinally.

Use of psychophysical tools to define clinically relevant change in olfactory function

The final consideration when using psychophysical tools to characterise olfactory function is the minimum test score change required to indicate clinical improvement or deterioration. This is particularly important when reporting the results of longitudinal prognostic studies and when assessing interventions: whilst there may be a statistically significant improvement in olfactory test scores following some form of treatment, this will not necessarily reflect an improvement in subjective disease burden, unless the change is of sufficient magnitude to be clinically relevant (i.e. has reached the minimal clinically important difference) [232] [117].

Recommendations:

- When reporting changes in psychophysical test scores, improvement or deterioration in olfactory function should be defined according to established clinical correlates for that test.

Psychophysical tests used in screening

In a clinical context, olfactory screening tests are often required for identification of potential impairment in asymptomatic subjects (for example during pre-operative assessment for medico-legal reasons). Where screening is required, validated tools have been developed which allow for rapid differentiation between normosmia and impaired olfactory function. Such tests include the 12 item Cross-Cultural Smell Identification Test [233] or the 12-item

identification adaptation of the "Sniffin' Sticks" test [234]. Where abnormalities are identified through screening, patients should then undergo full olfactory testing. Olfactory screening using dedicated psychophysical tools is felt to be preferable to subjective assessment alone, as self-reported symptom questionnaires are not as sensitive or specific as screening odour identification testing, particularly for mild hyposmia [235].

Recommendations:

- Screening for abnormal olfactory function in asymptomatic patients should be undertaken using validated psychophysical tools.
- Patients with abnormal screening results should undergo full olfactory testing.

Gustatory testing

Gustatory dysfunction occurs less frequently than olfactory impairment. The ability to distinguish subtleties of food flavor relies heavily on retronasal olfaction, including features unique to the human oropharynx and inspiratory airflow [236]. Accordingly, when patients complain of "abnormal taste", they are usually suffering from retronasal olfactory dysfunction [95]. Retronasal olfaction can be tested by asking patients to identify flavoured powders. Such tests are useful where there is diagnostic uncertainty. For example, it has been demonstrated that in cases of sudden onset olfactory dysfunction, such as posttraumatic loss, both orthonasal and retronasal functions decline concurrently. However, more progressive dysfunction, such as is seen in sinonasal disease, may preferentially affect the orthonasal route whilst retronasal olfaction may be preserved [237,238]

As part of a full olfactory assessment, screening of gustatory function should be undertaken. This can be achieved using liquids applied to the tongue for sweet, salty, sour or bitter (umami is not commonly screened for as it is poorly identified) [239]. Where any abnormalities are identified, full gustatory testing should be undertaken using validated tests with normative data [240–246].

Recommendations:

- Comprehensive chemosensory assessment should include gustatory screening for sweet, salty, sour and bitter tastes.
- Full gustatory testing should be performed where abnormalities are identified on screening. Ideally, this should include discrimination between retronasal olfaction (flavours) and gustatory (taste) abnormalities.

Electrophysiology and Functional Imaging

Whilst subjective and psychophysical tools are sufficient for most clinical and research based testing, olfaction can also be assessed in a less subjective way using electrophysiological and imaging studies.

Electrophysiological studies include electroencephalography (EEG) and electro-olfactography (EOG - the recording of generator potential via an electrode in contact with the olfactory neuroepithelium) [247–251]. As EEG and EOG are both event-related, delivery of a known concentration of odorant must be precisely controlled using an olfactometer, which therefore limits the use of such testing for clinical purposes [252]. Instead, EEG is useful in medico-legal assessment as well as in patients who might not be able to comply with psychophysical testing. EOG testing is limited to the research setting.

Functional imaging allows for the identification of brain activity in response to odourous stimuli, and includes positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) [253]. Both techniques utilise changes in cerebral blood flow in order to map brain activity changes in response to stimuli [254]. However, the use of radioactive isotopes for PET makes this a less attractive technique, and fMRI has become more common. The use of olfactory functional imaging is again typically limited to the research setting.

Recommendations:

- Whilst electrophysiological and imaging studies are often reserved for research purposes, EEG based olfactory testing can be useful for medico-legal purposes.

Other Investigations

Where olfactory dysfunction has been established, but no cause identified, or further information is needed, structural MRI scanning may be helpful (although there is an unresolved argument, e.g.: [255] and [256]). In doing so, the olfactory apparatus (olfactory neuroepithelium, the olfactory bulb and higher pathways) can be assessed, intracranial neoplasms (benign or malignant) excluded, undetected neoplasms in the nasal cavity or paranasal sinuses and asymptomatic chronic inflammation of the paranasal sinuses excluded, and traumatic brain injury characterised. It is of note that in head trauma the degree of olfactory loss can be predicted from brain lesion patterns [84].

MRI scanning additionally allows for calculation of olfactory bulb volume, as well as olfactory sulcus depth. These structures are affected in a number of conditions, namely: post-infectious olfactory loss, neurodegenerative diseases, exposure to toxins and congenital olfactory dysfunction [145,149].

Adjusted for age and gender, the olfactory bulb volume can be considered as normal, hypoplastic or aplastic. If the olfactory bulb volume is taken at the 10th percentile of the distribution, one can consider that an abnormal OB volume for a man <45 years is less than 58mm^3 and for a man >45 years is less than 46mm^3. A large number of studies have demonstrated that olfactory bulb volume is correlated to decreased olfactory perception in many disparate diseases (for review see: [257]).

In patients with CRS, traditional CT staging focused upon the paranasal sinuses correlates weakly with olfactory function, however, it appears that volumetric techniques to assess opacification of the olfactory cleft may provide additional information regarding olfactory function in certain subsets of patients [183].

Treatment of olfactory dysfunction

Despite considerable efforts within both the clinical and research communities, long-term, effective treatments for olfactory dysfunction largely remain elusive. In the following sections

we will outline the more common, or more successful interventions currently available and their evidence base.

Medications

Currently, medication is the mainstay of treatment in olfactory dysfunction, with 89% of clinicians in a previous European survey preferring topical steroids irrespective of aetiology [92] (Table 5).

Corticosteroids

With regards to olfactory loss secondary to chronic rhinosinusitis ± nasal polyposis, evidence exists to support use of both topical and systemic steroids [220,258–262]. Indeed, extensive guidelines exist for the management of CRS, in which initial medical treatment with corticosteroids is recommended [86,87,263–269]. We would refer you to these guidelines for management of such patients. With regards to non-CRS-related causes of olfactory dysfunction, the literature base is less robust, and it is difficult to draw firm conclusions regarding the utility of steroids in such patients.

In 2012, Schriever *et al.* published results from a retrospective analysis of psychophysical olfactory scores before and after treatment with 14 days of systemic methylprednisolone. Patients with olfactory dysfunction of any cause were included, though the majority (52%) had olfactory loss secondary to sinonasal disease. Overall, 26.6% of patients improved by more than 6 points on TDI testing (the minimal clinically important difference). However, a control group was not included in this study and the validity of findings should be confirmed using a prospective, controlled study [270].

Jiang *et al.* assessed threshold scores following administration of high dose systemic prednisolone, in patients with posttraumatic olfactory loss [271]. Improved olfaction was seen in 16.4% of the study population. However, this modest improvement is difficult to interpret given that the study did not include a control group.

Systemic steroids have also been combined with other agents, namely Zinc, vitamin B and Ginkgo biloba [272–274]. These studies suggest a possible additive benefit for the former two, though the additional benefit from Ginkgo biloba did not reach statistical significance.

In addition to anti-inflammatory effects, animal studies suggest that corticosteroids may lead to the modification of olfactory gene expression [275].

When considering use of systemic corticosteroids, the risk of side effects must be taken into account [276–278]. At present, evidence-based guidelines regarding the acceptable frequency of systemic corticosteroid use do not exist. It therefore falls to the individual clinician to exercise the appropriate prudence, particularly in cases of non-CRS related olfactory loss, where the evidence supporting steroid use is poor.

Recommendations:

- Systemic and/or topical steroids should be prescribed in patients with olfactory dysfunction secondary to CRS and other inflammatory conditions according to existing guidelines.
- There is limited evidence to support use of steroids for other causes of olfactory dysfunction.
- The risk of potential side effects should be taken into account when prescribing systemic corticosteroids.

Phosphodiesterase inhibitors

Phosphodiesterase inhibitors are theorised to improve olfactory function through preventing degradation of intracellular cAMP (see anatomy and physiology section). Two studies in 2009 demonstrated improved olfactory function following phosphodiesterase inhibitor administration. The first of these was a prospective study which assessed "Sniffin' Sticks" scores before and after administration of pentoxifylline (which was in this case being given for otological conditions) [279]. The authors demonstrated a significant improvement in odour threshold levels, in keeping with a theorised improvement in peripheral olfactory function. However, a mixture of normosmic and impaired patients were included in this study and there was heterogeneity in the route of pentoxifylline administration. The second study by Henkin and colleagues utilised an unblinded controlled trial design to assess the effect of oral theophylline on olfactory function in hyposmic patients with reduced nasal/saliva cAMP/cGMP levels [280]. Whilst this study also demonstrated improved olfactory function with treatment, the patient population (i.e. those with low cAMP/cGMP levels) and study design (an increasing dose of theophylline was given where response was deemed suboptimal – a design which may have neglected spontaneous recovery) limits the generalisability of the results.

Disappointing results have been demonstrated following double-blind administration of sildenafil (a cGMP type 5 phosphodiesterase inhibitor) and caffeine [282,283]. Finally,

application of topical theophylline to supravital mouse olfactory epithelium, did not lead to enhancement of associated EOG recordings [284].

Recommendations:

- Currently there is insufficient evidence to support use of phosphodiesterase inhibitors in the treatment of olfactory dysfunction.

Intranasal calcium buffers

Free calcium within the nasal mucus layer plays a role in negative feedback inhibition of the intracellular olfactory signalling cascade [285,286]. It is therefore theorised that sequestration of such free calcium, using buffer solutions such as sodium citrate, may lead to amplification of the olfactory signal and consequent improvement in olfactory function.

In 2005 Panagiotopoulos and colleagues reported improved odour identification scores in hyposmic patients treated with intranasal sodium citrate [287]. Whilst subgroup analysis according to aetiology was not undertaken in this study, it is worth noting that the majority of these patients had post-infectious hyposmia. Using a single-blind, placebo-controlled study design, Whitcroft *et al.* also demonstrated an improvement in the odour identification scores of patients with post-infectious hyposmia, following administration of intranasal sodium citrate [288]. A further, prospective and internally controlled study in post-infectious patients showed significantly improved composite threshold and identification scores after sodium citrate treatment [289]. Additional basic and clinical research into the utility of intranasal calcium sequestration in post-infectious olfactory loss should be undertaken.

[Table 5]

Olfactory training

Olfactory training involves repeated daily exposure of a subject to a range of odourants. In 2009, Hummel and colleagues prospectively investigated the utility of such training in a group of patients with olfactory loss due to post-infectious, posttraumatic or idiopathic aetiologies [300]. Forty of these patients underwent twice-daily smell training using 4 odourants: phenylethylalcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves). Compared with baseline psychophysical olfactory test scores (using "Sniffin' Sticks"), the training group significantly improved at 12 weeks, whereas the non-training group did not. This study was replicated by Haehner *et al.* in 70 patients with

Parkinson's disease [301]. Again, psychophysical test scores significantly improved only in the training group (n=35).

A more recent study from Geißler *et al.*[302] demonstrated improved psychophysical test scores following prolonged training (32 weeks), however, these results are limited by lack of a comparative control group. A randomised, controlled, multicentre study led by Damm *et al.* in 144 patients also recently showed that olfactory training with high odour concentrations resulted in greater improvement than very low odour concentrations [303] indicating that olfactory training in fact is not related to sniffing but to olfactory stimulation; this study was also the first "quasi placebo" controlled study demonstrating the efficacy of olfactory training. Altundag and colleagues also showed improved olfactory function following training for 9 months (using 4 different odours every 3 months), with greater benefit being seen following longer training duration [304]. Whilst each of the latter three studies addressed patients with post-infectious olfactory loss, Konstantinidis and colleagues have shown good results following training in patients with posttraumatic dysfunction [305]. Few studies, however, have addressed the effect of training in patients with sinonasal disease [306] (for a list of studies see Table 6; for a meta-analysis on studies on olfactory training see [281]).

The exact underlying pathophysiological mechanism for improvement following smell training is unknown. However, it is postulated to involve increased regenerative capacity of olfactory neurons as a result of repeated odourant exposure [307].

[Table 6]

Given the low associated cost and high safety of olfactory training, it is an attractive treatment modality, which can be employed with relative impunity.

Recommendations:

- Smell training can be recommended in patients with olfactory loss of several aetiologies (this treatment requires further evaluation in patients with sinonasal disease).

<u>Surgery</u>

Surgical intervention is largely reserved for treatment of patients with CRS ± polyps. Again, as for treatment with steroids, extensive guidelines exist for the use of surgery in such patients. Furthermore, two recent Cochrane reviews have been published regarding the utility of surgery in these patients, though olfaction is not extensively discussed as an outcome

[313,314]. A review of 20 studies published since 1991 shows that olfaction generally improves following functional endoscopic sinus surgery [73,188,210,219,220,258,260,315–327]. A recent study examining olfactory outcomes after surgery for CRS utilised the QOD-NS questionnaire and 40-item SIT, demonstrating the greatest improvement was seen in patients with the most preoperative disease on CT scans [186]. There is some difficulty, however, in comparing these studies, as marked heterogeneity exists in the methodology used. For example, 5 studies utilised only subjective measures of olfactory function, 4 utilised only odour identification and 7 only odour threshold testing (Table 8).

The utility of surgery in addressing olfactory dysfunction due to causes other than CRS is less well established. In a follow up study, Schriever and colleagues demonstrated that nasal septoplasty had no beneficial effects on olfaction as measured at one year [326], though other studies have demonstrated benefit [187]. The effect of septorhinoplasty on olfaction has not yet been sufficiently demonstrated, though some reports suggest that it may lead to improved function [328,329]. In addition, surgery other than nasal surgery, e.g. gastric bypass does not seem to improve olfactory function [330], though there is controversy in the literature [331].

As mentioned above, without an obvious odour present, patients with phantosmia report experiencing a very unpleasant smell, often described as ‘rotten meat’, ‘chemical’ or ‘burnt’ (in some cases preceding a seizure or migraine; in others the smell is present persistently throughout the day). For patients with neurological conditions, the condition often dissipates with treatment. However for those without an obvious co-existing condition there is no universally accepted treatment. Surgical removal of the olfactory epithelium has been tried in a few patients [14,332]. This procedure has not been validated and is high risk and should therefore be attempted only as a very last resort and only at an experienced, major medical centre. Topical application of cocaine hydrochloride can offer temporary relief [333]. In some patients phantosmia will spontaneously decline over time.

[Table 7]

Recommendations:

- Functional endoscopic surgery for olfactory loss caused by the CRS disease spectrum should be undertaken in line with existing guidelines [86].
- There is presently insufficient evidence to support other surgery types for olfactory dysfunction, though further characterisation of the effects of functional septorhinoplasty is required.

Conclusions

In the preceding sections we have provided an overview of current evidence and recommendations for the definition, investigation and management of olfactory dysfunction. We hope that these guidelines will encourage clinicians and researchers to adopt a common

language, and in so doing, increase the methodological quality, consistency and generalisability of work in this field.

ACKNOWLEDGEMENTS:

None.

AUTHORSHIP CONTRIBUTION:

Hummel T	Conceptual design. Supervision of project. Administrative support.
Whitcroft KL	Conceptual design. Writing of manuscript. Integration of co-author comments.
Andrews P	Review of content and agreement with final recommendations.
Altundag A	Review of content and agreement with final recommendations.
Cinghi C	Review of content and agreement with final recommendations.
Costanzo RM	Review of content and agreement with final recommendations.
Damm M	Review of content and agreement with final recommendations.
Frasnelli J	Review of content and agreement with final recommendations.
Gudziol H	Review of content and agreement with final recommendations.
Gupta N	Review of content and agreement with final recommendations.
Haehner A	Review of content and agreement with final recommendations.
Holbrook E	Review of content and agreement with final recommendations.
Hong SC	Review of content and agreement with final recommendations.
Hornung D	Review of content and agreement with final recommendations.
Hüttenbrink KB	Review of content and agreement with final recommendations.
Kamel R	Review of content and agreement with final recommendations.
Kobayashi M	Review of content and agreement with final recommendations.
Konstantinidis I	Review of content and agreement with final recommendations.
Landis BN	Review of content and agreement with final recommendations.
Leopold DA	Review of content and agreement with final recommendations.
Macchi A	Review of content and agreement with final recommendations.
Miwa T	Review of content and agreement with final recommendations.
Moesges R	Review of content and agreement with final recommendations.
Mullol J	Review of content and agreement with final recommendations.
Mueller CA	Review of content and agreement with final recommendations.
Ottaviano G	Review of content and agreement with final recommendations.

Passali GC	Review of content and agreement with final recommendations.
Philpott C	Review of content and agreement with final recommendations.
Pinto JM	Review of content and agreement with final recommendations.
Ramakrishnan VJ	Review of content and agreement with final recommendations.
Rombaux P	Review of content and agreement with final recommendations.
Roth Y	Review of content and agreement with final recommendations.
Schlosser RA	Review of content and agreement with final recommendations.
Shu B	Review of content and agreement with final recommendations.
Soler G	Review of content and agreement with final recommendations.
Stjärne P	Review of content and agreement with final recommendations.
Stuck BA	Review of content and agreement with final recommendations.
Vodicka J	Review of content and agreement with final recommendations.
Welge-Luessen A	Review of content and agreement with final recommendations.

CONFLICT OF INTEREST:

None.

REFERENCES:

1. McNeill E, Ramakrishnan Y, Carrie S. Diagnosis and management of olfactory disorders: Survey of UK-based consultants and literature review. *J Laryngol Otol*. 2007;121(8):713-720. doi:10.1017/S0022215107006615.
2. Croy I, Hummel T. Olfaction as a marker for depression. *J Neurol*. 2016;Epub ahead. doi:10.1007/s00415-016-8227-8.
3. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life-an updated review. *Chem Senses*. 2014;39(3):185-194. doi:10.1093/chemse/bjt072.
4. Kohli P, Soler ZM, Nguyen SA, Muus JS, Schlosser RJ. The Association Between Olfaction and Depression: A Systematic Review. *Chem Senses*. 2016;41:479-486. doi:10.1093/chemse/bjw061.
5. Miwa T, Furukawa M, Tsukatani T, Costanzo RM, DiNardo LJ, Reiter ER. Impact of olfactory impairment on quality of life and disability. *Arch Otolaryngol Head Neck Surg*. 2001;127(5):497-503. doi:10.1001/archotol.127.5.497.
6. Philpott CM, Boak D. The impact of olfactory disorders in the United kingdom. *Chem Senses*. 2014;39(8):711-718. doi:10.1093/chemse/bju043.
7. Ahn S, Shin HW, Mahmood U, et al. Chronic anosmia induces depressive behavior and reduced anxiety via dysregulation of glucocorticoid receptor and corticotropin-releasing hormone in a mouse model. *Rhinology*. 2016;54(1):80-87. doi:10.4193/Rhin15.209.
8. Schubert CR, Fischer ME, Pinto AA, et al. Sensory Impairments and Risk of Mortality in Older Adults. *J Gerontol A Biol Sci Med Sci*. 2016;0(0):1-6. doi:10.1093/gerona/glw036.
9. Schubert CR, Cruickshanks KJ, Fischer ME, et al. Carotid intima media thickness, atherosclerosis, and 5-year decline in odor identification: The beaver dam offspring study. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2014;70(7):879-884. doi:10.1093/gerona/glu158.
10. Bohm N, Marshall M, Fulop N, Lund V, Schilder A. The Research Agenda for ENT , Hearing and Balance Care A UK Partnership of Patients , Professionals and the Public. ENT-UK. https://www.entuk.org/generate. Published 2015.
11. Health NI of. National Institute on Deafness and Other Communication Disorders (NIDCD). US Department of Health and Human Services. https://www.nih.gov/about-nih/what-we-do/nih-almanac/national-institute-deafness-other-communication-disorders-nidcd. Published 2016.
12. Croy I, Olgun S, Mueller L, et al. Peripheral adaptive filtering in human olfaction?

Three studies on prevalence and effects of olfactory training in specific anosmia in more than 1600 participants. *Cortex*. 2015;73:180-187. doi:10.1016/j.cortex.2015.08.018.

13. Blau JN, Solomon F. Smell and other sensory disturbances in migraine. *J Neurol*. 1985;232(5):275-276. doi:10.1007/BF00313864.
14. Leopold D. Distortion of Olfactory Perception: Diagnosis and Treatment. *Chem Senses*. 2002;27(7):611-615. doi:10.1093/chemse/27.7.611.
15. Hong S-C, Holbrook EH, Leopold DA, Hummel T. Distorted olfactory perception: A systematic review. *Acta Otolaryngol*. 2012;132(S1):S27-S31. doi:10.3109/00016489.2012.659759.
16. Murphy C, Doty RL, Duncan HJ. Clinical disorders of olfaction. In: Doty RL, ed. *Handbook of Olfaction and Gustation*. 3rd ed. New York: Marcel Dekker; 2003:461-478.
17. Landis BN, Frasnelli J, Hummel T. Euosmia: a rare form of parosmia. *Acta Otolaryngol*. 2006;126(1):101-103. doi:10.1080/00016480510043954.
18. Bornschein S, Hausteiner C, Römmelt H, Nowak D, Förstl H, Zilker T. Double-blind placebo-controlled provocation study in patients with subjective Multiple Chemical Sensitivity (MCS) and matched control subjects. *Clin Toxicol (Phila)*. 2008;46(5):443-449. doi:10.1080/15563650701742438.
19. Das-Munshi J, Rubin GJ, Wessely S. Multiple chemical sensitivities: A systematic review of provocation studies. *J Allergy Clin Immunol*. 2006;118(6):1257-1264. doi:10.1016/j.jaci.2006.07.046.
20. Yang J, Pinto JM. The Epidemiology of Olfactory Disorders. *Curr Otorhinolaryngol Rep*. 2016;4(2):130-141. doi:10.1007/s40136-016-0120-6.
21. Hoffman HJ, Ishii EK, MacTurk RH. Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the 1994 disability supplement to the National Health Interview Survey (NHIS). *Ann N Y Acad Sci*. 1998;855:716-722. doi:10.1111/j.1749-6632.1998.tb10650.x.
22. Lee WH, Wee JH, Kim D-K, et al. Prevalence of subjective olfactory dysfunction and its risk factors: korean national health and nutrition examination survey. *PLoS One*. 2013;8(5):e62725. doi:10.1371/journal.pone.0062725.
23. Bhattacharyya N, Kepnes LJ. Contemporary assessment of the prevalence of smell and taste problems in adults. *Laryngoscope*. 2015;125(5):1102-1106. doi:10.1002/lary.24999.
24. Rawal S, Hoffman HJ, Bainbridge KE, Huedo-medina TB, Duffy VB. Prevalence and Risk Factors of Self-Reported Smell and Taste Alterations: Results from the 2011-2012 U.S. National Health and Nutritions Survey (NHANES). *Chem Senses*.

2016;41(1):69-72. doi:10.1093/chemse/bjv057.

25. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe - An underestimated disease. A GA 2LEN study. *Allergy Eur J Allergy Clin Immunol*. 2011;66(9):1216-1223. doi:10.1111/j.1398-9995.2011.02646.x.
26. Hirsch AG, Stewart WF, Sundaresan AS, et al. Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample. *Allergy*. 2016;(2). doi:10.1111/all.13042.
27. Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. *Chem Senses*. 2003;28(8):691-694. doi:10.1093/chemse/bjg061.
28. Landis BN, Konnerth CG, Hummel T. A study on the frequency of olfactory dysfunction. *Laryngoscope*. 2004;114(10):1764-1769. doi:10.1097/00005537-200410000-00017.
29. Vennemann MM, Hummel T, Berger K. The association between smoking and smell and taste impairment in the general population. *J Neurol*. 2008;255(8):1121-1126. doi:10.1007/s00415-008-0807-9.
30. Nordin S, Brämerson A, Bende M. Prevalence of self-reported poor odor detection sensitivity: the skövde population-based study. *Acta Otolaryngol*. 2004;124(10):1171-1173. doi:10.1080/00016480410017468.
31. Brämerson A, Johansson L, Ek L, Nordin S, Bende M. Prevalence of olfactory dysfunction: the skövde population-based study. *Laryngoscope*. 2004;114(4):733-737. doi:10.1097/00005537-200404000-00026.
32. Nordin S, Brämerson A, Millqvist E, Bende M. Prevalence of parosmia: The Skövde population-based studies. *Rhinology*. 2007;45(1):50-53.
33. Larsson M, Nilsson LG, Olofsson JK, Nordin S. Demographic and cognitive predictors of cued odor identification: Evidence from a population-based study. *Chem Senses*. 2004;29(6):547-554. doi:10.1093/chemse/bjh059.
34. Mullol J, Alobid I, Mariño-Sánchez F, et al. Furthering the understanding of olfaction, prevalence of loss of smell and risk factors: a population-based survey (OLFACAT study). *BMJ Open*. 2012;2:e001256. doi:10.1136/bmjopen-2012-001256.
35. Murphy C, Schubert CR, Cruickshanks KJ, Klein BEK, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *JAMA*. 2002;288(18):2307-2312. doi:10.1001/jama.288.18.2307.
36. Boesveldt S, Tessler Lindau S, McClintock M, Hummel T, Lundström JN. Gustatory and olfactory dysfunction in older adults: a national probability study. *Rhinology*. 2011;49(3):324-330.
37. Kern DW, Wroblewski KE, Schumm LP, Pinto JM, Chen RC, McClintock MK. Olfactory Function in Wave 2 of the National Social Life, Health, and Aging Project. *Journals Gerontol Ser B Psychol Sci Soc Sci* . 2014;69(Suppl 2):S134-S143.

doi:10.1093/geronb/gbu093.

38. Ross GW, Petrovitch H, Abbott RD, et al. Association of olfactory dysfunction with risk for future Parkinson's disease. *Ann Neurol*. 2008;63(2):167-173. doi:10.1002/ana.21291.
39. Wilson RS, Arnold SE, Tang Y, Bennett DA. Odor identification and decline in different cognitive domains in old age. *Neuroepidemiology*. 2006;26(2):61-67. doi:10.1159/000090250.
40. Devanand DP, Lee S, Manly J, et al. Olfactory identification deficits and increased mortality in the community. *Ann Neurol*. 2015;78(3):401-411. doi:10.1002/ana.24447.
41. Karpa MJ, Gopinath B, Rochtchina E, et al. Prevalence and neurodegenerative or other associations with olfactory impairment in an older community. *J Aging Health*. 2010;22(2):154-168. doi:10.1177/0898264309353066.
42. Jafek BW. Ultrastructure of human nasal mucosa. *Laryngoscope*. 1983;93(12):1576-1599. doi:10.1288/00005537-198312000-00011.
43. Holbrook EH, Wu E, Curry WT, Lin DT, Schwob JE. Immunohistochemical characterization of human olfactory tissue. *Laryngoscope*. 2011;121(8):1687-1701. doi:10.1002/lary.21856.
44. von Brunn A. Beitrage zur mikroskopischen Anatomie menschlichen Nasenhohle . *Arch Mikr Anat*. 1892;39:632-651.
45. Read EA. A contribution to the knowledge of the olfactory apparatus in dog, cat and man. *Am J Anat*. 1908;8(1):17-47. doi:10.1002/aja.1000080103.
46. Lang J. Clinical Anatomy of the Nose, Nasal Cavity and Paranasal Sinuses (3rd ed). In: New York: Thieme Medical Publishers; 1989.
47. Leopold DA, Hummel T, Schwob JE, Hong SC, Knecht M, Kobal G. Anterior distribution of human olfactory epithelium. *Laryngoscope*. 2000;110(3 Pt 1):417-421. doi:10.1097/00005537-200003000-00016.
48. Feron F, Perry C, McGrath J, Mackay-Sim A. New Techniques for Biopsy and Culture of Human Olfactory Epithelial Neurons. *Arch Otolaryngol Head Neck Surg*. 2016;124:861-866.
49. Brann JH, Firestein SJ. A lifetime of neurogenesis in the olfactory system. *Front Neurosci*. 2014;8(8 JUN):1-11. doi:10.3389/fnins.2014.00182.
50. Kachramanoglou C, Li D, Andrews P, et al. Novel strategies in brachial plexus repair after traumatic avulsion. *Br J Neurosurg*. 2011;25(September 2010):16-27. doi:10.3109/02688697.2010.522744.
51. Chen CR, Kachramanoglou C, Li D, Andrews P, Choi D. Anatomy and cellular constituents of the human olfactory mucosa: a review. *J Neurol Surg B Skull Base*. 2014;75(5):293-300. doi:10.1055/s-0033-1361837.

52. Andrews P, Poirrier A, Lund V, Choi D. Safety of human olfactory mucosal biopsy for the purpose of olfactory ensheathing cell harvest and nerve repair: a prospective controlled study in patients undergoing endoscopic sinus surgery. *Rhinology*. 2016;54(2):183-191. doi:10.4193/Rhin15.365.
53. Kachramanoglou C, Law S, Andrews P, Li D, Choi D. Culture of olfactory ensheathing cells for central nerve repair: The limitations and potential of endoscopic olfactory mucosal biopsy. *Neurosurgery*. 2013;72(2):170-178. doi:10.1227/NEU.0b013e31827b99be.
54. Hummel T, Welge-Lüssen A. *Taste and Smell: An Update*. Vol 53.; 2006. doi:10.1017/CBO9781107415324.004.
55. Buck L, Axel R. A novel multigene family may encode odorant receptors: A molecular basis for odor recognition. *Cell*. 1991;65(1):175-187. doi:10.1016/0092-8674(91)90418-X.
56. Gilad Y, Lancet D. Population differences in the human functional olfactory repertoire. *Mol Biol Evol*. 2003;20(3):307-314. doi:10.1093/molbev/msg013.
57. Verbeurgt C, Wilkin F, Tarabichi M, Gregoire F, Dumont JE, Chatelain P. Profiling of olfactory receptor gene expression in whole human olfactory mucosa. *PLoS One*. 2014;9(5):21-26. doi:10.1371/journal.pone.0096333.
58. Dunkel A, Steinhaus M, Kotthoff M, et al. Nature's chemical signatures in human olfaction: A foodborne perspective for future biotechnology. *Angew Chemie - Int Ed*. 2014;53(28):7124-7143. doi:10.1002/anie.201309508.
59. Firestein S. How the olfactory system makes sense of scents. *Nature*. 2001;413(6852):211-218. doi:10.1038/35093026.
60. Axel R. The molecular logic of smell. *Sci Am*. 1995;273(4):154-159. doi:10.1038/scientificamerican1095-154.
61. Holley A, Duchamp A, Revial MF, Juge A. Qualitative and quantitative discrimination in the frog olfactory receptors: analysis from electrophysiological data. *Ann N Y Acad Sci*. 1974;237:102-114. doi:10.1111/j.1749-6632.1974.tb49847.x.
62. Horowitz LF, Saraiva LR, Kuang D, Yoon K, Buck LB. Olfactory receptor patterning in a higher primate. *J Neurosci*. 2014;34(37):12241-12252. doi:10.1523/JNEUROSCI.1779-14.2014.
63. Liberles SD, Buck LB. A second class of chemosensory receptors in the olfactory epithelium. *Nature*. 2006;442(7103):645-650. doi:10.1038/nature05066.
64. Wallrabenstein I, Kuklan J, Weber L, et al. Human Trace Amine-Associated Receptor TAAR5 Can Be Activated by Trimethylamine. *PLoS One*. 2013;8(2). doi:10.1371/journal.pone.0054950.
65. Hummel T, Kaehling C, Grosse F. Automated assessment of intranasal trigeminal

function. *Rhinology*. 2016;54(1):27-31.

66. Hummel T, Iannilli E, Frasnelli J, Boyle J, Gerber J. Central processing of trigeminal activation in humans. *Ann N Y Acad Sci*. 2009;1170:190-195. doi:10.1111/j.1749-6632.2009.03910.x.
67. Daiber P, Genovese F, Schriever VA, Hummel T, M??hrlen F, Frings S. Neuropeptide receptors provide a signalling pathway for trigeminal modulation of olfactory transduction. *Eur J Neurosci*. 2013;37(4):572-582. doi:10.1111/ejn.12066.
68. Doty RL, Brugger WE, Jurs PC, Orndorff MA, Snyder PJ, Lowry LD. Intranasal trigeminal stimulation from odorous volatiles: Psychometric responses from anosmic and normal humans. *Physiol Behav*. 1978;20(2):175-185. doi:10.1016/0031-9384(78)90070-7.
69. Mihara S, Shibamoto T. The role of flavor and fragrance chemicals in TRPA1 (transient receptor potential cation channel, member A1) activity associated with allergies. *Allergy Asthma Clin Immunol*. 2015;11(1):11. doi:10.1186/s13223-015-0074-0.
70. Scheibe M, Schulze S, Mueller CA, Schuster B, Hummel T. Intranasal trigeminal sensitivity: Measurements before and after nasal surgery. *Eur Arch Oto-Rhino-Laryngology*. 2014;271(1):87-92. doi:10.1007/s00405-013-2466-4.
71. Alobid I, Benitez P, Cardelus S, et al. Oral plus nasal corticosteroids improve smell, nasal congestion, and inflammation in sino-nasal polyposis. *Laryngoscope*. 2014;124(1):50-56. doi:10.1002/lary.24330.
72. Vandenhende-Szymanski C, Hochet B, Chevalier D, Mortuaire G. Olfactory cleft opacity and ct score are predictive factors of smell recovery after surgery in nasal polyposis. *Rhinology*. 2015;53(1):29-34. doi:10.4193/Rhino14.160.
73. Pade J, Hummel T. Olfactory function following nasal surgery. *Laryngoscope*. 2008;118(7):1260-1264. doi:10.1097/MLG.0b013e318170b5cb.
74. Klimek L, Klimek L, Eggers G, Eggers G. Olfactory dysfunction in allergic rhinitis is related to nasal eosinophilc inflammation. *J Allergy Clin Immunol*. 1997;100:159-164.
75. Soler ZM, Sauer DA, Mace J, Smith TL. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. *Otolaryngol Neck Surg Off J Am Acad Otolaryngol Neck Surg*. 2009;141(4):454-461. doi:10.1016/j.otohns.2009.06.085.
76. Oka H, Tsuzuki K, Takebayashi H, Kojima Y, Daimon T, Sakagami M. Olfactory changes after endoscopic sinus surgery in patients with chronic rhinosinusitis. *Auris Nasus Larynx*. 2013;40(5):452-457. doi:10.1016/j.anl.2012.12.001.
77. Pozharskaya T, Liang J, Lane AP. Regulation of inflammation-associated olfactory neuronal death and regeneration by the type II tumor necrosis factor receptor. *Int*

Forum Allergy Rhinol. 2013;3(9):740-747. doi:10.1002/alr.21187.

78. Lane AP, Turner J, May L, Reed R. A Genetic Model of Chronic Rhinosinusitis-Associated Olfactory Inflammation Reveals Reversible Functional Impairment and Dramatic Neuroepithelial Reorganization. *J Neurosci*. 2010;30(6):2324-2329. doi:10.1523/JNEUROSCI.4507-09.2010.
79. Doty RL, Mishra a. Olfaction and its alteration by nasal obstruction, rhinitis, and rhinosinusitis. *Laryngoscope*. 2001;111(3):409-423. doi:10.1097/00005537-200103000-00008.
80. Jafek BW, Murrow B, Michaels R, Restrepo D, Linschoten M. Biopsies of Human Olfactory Epithelium. *Chem Senses*. 2002;27(7):623-628. doi:10.1093/chemse/27.7.623.
81. Rombaux P, Potier H, Bertrand B, Duprez T, Hummel T. Olfactory bulb volume in patients with sinonasal disease. *Am J Rhinol*. 2008;22(6):598-601. doi:10.2500/ajr.2008.22.3237.
82. Gudziol V, Buschhüter D, Abolmaali N, Gerber J, Rombaux P, Hummel T. Increasing olfactory bulb volume due to treatment of chronic rhinosinusitis-a longitudinal study. *Brain*. 2009;132(11):3096-3101. doi:10.1093/brain/awp243.
83. Delank KW, Fechner G. Zur Pathophysiologie der posttraumatischen Riechstörungen. *Laryngol Rhinol Otol*. 1996;75:154-159.
84. Lotsch J, Reither N, Bogdanov V, et al. A brain-lesion pattern based algorithm for the diagnosis of posttraumatic olfactory loss. *Rhinology*. 2015;53(4):365-370. doi:10.4193/Rhino15.010.
85. Rombaux P, Huart C, Levie P, Cingi C, Hummel T. Olfaction in Chronic Rhinosinusitis. *Curr Allergy Asthma Rep*. 2016;16(5):41. doi:10.1007/s11882-016-0617-6.
86. Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl*. 2012;50(23):1-298. http://www.ncbi.nlm.nih.gov/pubmed/22764607.
87. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical Practice Guideline (Update): Adult Sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(2 suppl):S1-S39. doi:10.1177/0194599815572097.
88. Enriquez K, Lehrer E, Mullol J. The optimal evaluation and management of patients with a gradual onset of olfactory loss. *Curr Opin Otolaryngol Head Neck Surg*. 2014;22(1):34-41. doi:10.1097/MOO.0000000000000013.
89. Whitcroft KL, Cuevas M, Haehner A, Hummel T. Patterns of olfactory impairment reflect underlying disease etiology. 2016;0:1-5. doi:10.1002/lary.26229.
90. Seiden A. Olfactory loss secondary to nasal and sinus pathology. In: Taste and smell

disorders. In: Seiden A, ed. *Taste and Smell Disorders*. Thieme Medical Publishers; 1997:52-71.

91. Jafek B, Moran D, Eller P, Rowley J, Jafek T. Steroid-dependent anosmia. *Arch Otolaryngol Head Neck Surg*. 1987;113:547-549.
92. Damm M, Temmel A, Welge-Lussen A, et al. Riechstorungen: Epidemiologie und Therapie in Deutschland, Österreich und der Schweiz. *HNO*. 2004;52(2):112-120. doi:10.1007/s00106-003-0877-z.
93. Philpott C. Smell and taste disorders in the UK: first experience with a specialised small and taste outpatient clinic. *Ann R Coll Surg Engl*. 2014;96:156-159. doi:http://dx.doi.org/10.1308/rcsbull.2014.96.5.156.
94. Temmel AFP, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. Characteristics of olfactory disorders in relation to major causes of olfactory loss. *Arch Otolaryngol Head Neck Surg*. 2002;128(6):635-641. doi:ooa00128 [pii].
95. Deems D, Doty R, Settle R. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg*. 1991;117(5):519-521.
96. Loo AT, Youngentob SL, Kent PF, Schwob JE. The aging olfactory epithelium: Neurogenesis, response to damage, and odorant-induced activity. *Int J Dev Neurosci*. 1996;14(7-8):881-900. doi:10.1016/S0736-5748(96)00046-9.
97. Reden J, Mueller A, Mueller C, et al. Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. *Arch Otolaryngol - Head Neck Surg*. 2006;132(3):265-269.
98. Hendricks A. Olfactory dysfunction. *Rhinology*. 1988;26(4):229-251.
99. Mori J, Aiba T, Sugiura M, et al. Clinical Study of Olfactory Disturbance. *Acta Otolaryngol*. 1998;583:197-201. doi:10.5631/jibirin.104.703.
100. Duncan H, Seiden A. Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection. *Arch Otolaryngol Head Neck Surg*. 1995;121:1183-1187.
101. Philpott C, DeVere R. Post-infectious and post-traumatic olfactory disorders. In: Welge-Lüssen A, Hummel T, eds. *Management of Smell and Taste Disorders: A Practical Guide for Clinicians*. Thieme Medical Publishers; 2013:91-105.
102. Suzuki M, Saito K, Min W-P, et al. Identification of viruses in patients with postviral olfactory dysfunction. *Laryngoscope*. 2007;117(2):272-277. doi:10.1097/01.mlg.0000249922.37381.1e\r00005537-200702000-00016 [pii].
103. Baker H, Genter M. The Olfactory System and the Nasal Mucosa as Portals of Entry of Viruses, Drugs, and Other Exogenous Agents into the Brain. In: Doty RL, ed. *Handbook of Olfaction and Gustation*. 2nd ed. New York: Marcel Dekker; 2003:549-

574.

104. Youngentob SL, Schwob JE, Saha S, Manglapus G, Jubelt B. Functional consequences following infection of the olfactory system by intranasal infusion of the olfactory bulb line variant (OBLV) of mouse hepatitis strain JHM. *Chem Senses*. 2001;26(8):953-963. http://www.ncbi.nlm.nih.gov/pubmed/11595672.
105. Yamagishi M, Fujiwara M, Nakamura H. Olfactory mucosal findings and clinical course in patients with olfactory disorders following upper respiratory viral infection. *Rhinology*. 1994;32(3):113-118.
106. Mueller A, Rodewald A, Reden J, Gerber J, von Kummer R, Hummel T. Reduced olfactory bulb volume in post-traumatic and post-infectious olfactory dysfunction. *Neuroreport*. 2005;16(5):475-478. doi:00001756-200504040-00011 [pii].
107. Buschhüter D, Smitka M, Puschmann S, et al. Correlation between olfactory bulb volume and olfactory function. *Neuroimage*. 2008;42(2):498-502. doi:10.1016/j.neuroimage.2008.05.004.
108. Costanzo RM, DiNardo LJ, Reiter ER. Head injury and olfaction. In: Doty RL, ed. *Handbook of Olfaction and Gustation.* 2nd ed. New York: Marcel Dekker; 2003:629-638.
109. Jafek BW. Post-traumatic Anosmia. *Arch Neurol*. 1989;46(3):300. doi:10.1001/archneur.1989.00520390066018.
110. Holbrook EH, Leopold D a, Schwob JE. Abnormalities of axon growth in human olfactory mucosa. *Laryngoscope*. 2005;115(12):2144-2154. doi:10.1097/01.MLG.0000181493.83661.CE.
111. Schofield PW, Moore TM, Gardner A. Traumatic brain injury and olfaction: A systematic review. *Front Neurol*. 2014;5:1-22. doi:10.3389/fneur.2014.00005.
112. Costanzo RM, Zasler ND. Epidemiology and Pathophysiology of Olfactory and Gustatory Dysfunction in Head Trauma. *J Head Trauma Rehabil*. 1992:15-24. doi:10.1097/00001199-199203000-00005.
113. Yee KK, Costanzo RM. Changes in odor quality discrimination following recovery from olfactory nerve transection. *Chem Senses*. 1998;23(5):513-519. doi:10.1093/chemse/23.5.513.
114. Christensen MD, Holbrook EH, Costanzo RM, Schwob JE. Rhinotopy is disrupted during the re-innervation of the olfactory bulb that follows transection of the olfactory nerve. *Chem Senses*. 2001;26(4):359-369.
115. Fan LY, Kuo CL, Lirng JF, Shu CH. Investigation of prognostic factors for post-traumatic olfactory dysfunction. *J Chinese Med Assoc*. 2015;78(5):299-303. doi:10.1016/j.jcma.2014.11.009.
116. Sumner D. Post-traumatic anosmia. *Brain*. 1964;(87):107-120.

117. Doty R, Yousem D, Pham L, Kreshak A, Geckle R, Lee W. Olfactory dysfunction in patients with head trauma. *Arch Neurol*. 1997;54:1131-1140.
118. Mueller CA, Hummel T. Recovery of olfactory function after nine years of post-traumatic anosmia: a case report. *J Med Case Rep*. 2009;3:9283. doi:10.4076/1752-1947-3-9283.
119. Desai M, Agadi JB, Karthik N, Praveenkumar S, Netto AB. Olfactory abnormalities in temporal lobe epilepsy. *J Clin Neurosci*. 2015;22(10):1614-1618. doi:10.1016/j.jocn.2015.03.035.
120. Hummel T, Henkel S, Negoias S, et al. Olfactory bulb volume in patients with temporal lobe epilepsy. *J Neurol*. 2013;260(4):1004-1008. doi:10.1007/s00415-012-6741-x.
121. Leon-Sarmiento F, Leon-Ariza D, Doty R. Dysfunctional chemosensation in myasthenia gravis: a systematic review. *J Clin Neuromuscul Dis*. 2013;15:1-6.
122. Wehling E, Naess H, Wollschlaeger D, et al. Olfactory dysfunction in chronic stroke patients. *BMC Neurol*. 2015;15:199. doi:10.1186/s12883-015-0463-5.
123. Attems J, Walker L, Jellinger KA. Olfactory bulb involvement in neurodegenerative diseases. *Acta Neuropathol*. 2014;127(4):459-475. doi:10.1007/s00401-014-1261-7.
124. Bahuleyan B, Singh S. Olfactory memory impairment in neurodegenerative diseases. *J Clin Diagnostic Res*. 2012;6(8):1437-1441. doi:10.7860/JCDR/2012/3408.2382.
125. Doty RL. Olfaction in Parkinson's disease and related disorders. *Neurobiol Dis*. 2012;46(3):527-552. doi:10.1016/j.nbd.2011.10.026.
126. Alves G, Forsaa EB, Pedersen KF, Dreetz Gjerstad M, Larsen JP. Epidemiology of Parkinson's disease. *J Neurol*. 2008;255(SUPPL. 5):18-32. doi:10.1007/s00415-008-5004-3.
127. Ponsen MM, Stoffers D, Booij J, Van Eck-Smit BLF, Wolters EC, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. *Ann Neurol*. 2004;56(2):173-181. doi:10.1002/ana.20160.
128. Haehner A, Boesveldt S, Berendse HW, et al. Prevalence of smell loss in Parkinson's disease - A multicenter study. *Park Relat Disord*. 2009;15(7):490-494. doi:10.1016/j.parkreldis.2008.12.005.
129. Westermann B, Wattendorf E, Schwerdtfeger U, et al. Functional imaging of the cerebral olfactory system in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2008;79(1):19-24. doi:10.1136/jnnp.2006.113860.
130. Duda JE. Olfactory system pathology as a model of Lewy neurodegenerative disease. *J Neurol Sci*. 2010;289(1-2):49-54. doi:10.1016/j.jns.2009.08.042.
131. Witt M, Bormann K, Gudziol V, et al. Biopsies of olfactory epithelium in patients with Parkinson's disease. *Mov Disord*. 2009;24(6):906-914. doi:10.1002/mds.22464.

132. Duda JE, Shah U, Arnold SE, Lee VM, Trojanowski JQ. The expression of alpha-, beta-, and gamma-synucleins in olfactory mucosa from patients with and without neurodegenerative diseases. *Exp Neurol*. 1999;160(2):515-522. doi:10.1006/exnr.1999.7228.
133. Huisman E, Uylings HBM, Hoogland P V. A 100% increase of dopaminergic cells in the olfactory bulb may explain hyposmia in parkinson's disease. *Mov Disord*. 2004;19(6):687-692. doi:10.1002/mds.10713.
134. Huisman E, Uylings HBM, Hoogland P V. Gender-related changes in increase of dopaminergic neurons in the olfactory bulb of Parkinson's disease patients. *Mov Disord*. 2008;23(10):1407-1413. doi:10.1002/mds.22009.
135. Doty RL, Stern MB, Pfeiffer C, Gollomp SM, Hurtig HI. Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1992;55(2):138-142. doi:10.1136/jnnp.55.2.138.
136. Lötsch J, Daiker H, Hähner A, Ultsch A, Hummel T. Drug-target based cross-sectional analysis of olfactory drug effects. *Eur J Clin Pharmacol*. 2015;71(4):461-471. doi:10.1007/s00228-015-1814-2.
137. Lim JH, Davis GE, Wang Z, et al. Zicam-induced damage to mouse and human nasal tissue. *PLoS One*. 2009;4(10):1-10. doi:10.1371/journal.pone.0007647.
138. Nakamura H, Nonomura N, Fujiwara M, Nakano Y. Olfactory disturbances caused by the anti-cancer drug tegafur. *Eur Arch Otorhinolaryngol*. 1995;252:48-52.
139. Upadhyay U, Holbrook E. Olfactory loss as a result of toxic exposure. *Otolaryngol Clin North Am*. 2004;37(6):1185-1207.
140. Ackerman BH, Kasbekar N. Disturbances of taste and smell induced by drugs. *Pharmacotherapy*. 1996;17(3):482-496. doi:10.1002/j.1875-9114.1997.tb03058.x.
141. Henkin RI. Drug effects on smell and taste. In: Pradhan S, Maickel R, eds. *Pharmacology in Medicine: Principles and Practice*. Bethesda: SP Press Int; 1986:748-753.
142. Doty RL, Bromley SM. Effects of drugs on olfaction and taste. *Otolaryngol Clin North Am*. 2004;37(6 SPEC.ISS.):1229-1254. doi:10.1016/j.otc.2004.05.002.
143. Hastings L, Miller M. Olfactory loss to toxic exposure. In: Seiden A, ed. *Taste and Smell Disorders*. New York: Thieme Medical Publishers; 1997:88-106.
144. Boehm U, Bouloux P-M, Dattani MT, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol*. 2015;11(9):547-564. doi:10.1038/nrendo.2015.112.
145. Yousem DM, Geckle RJ, Bilker WB, McKeown DA, Doty RL. MR evaluation of patients with congenital hyposmia or anosmia. *AJR Am J Roentgenol*.

1996;166(2):439-443. doi:10.2214/ajr.166.2.8553963.

146. Ottaviano G, Cantone E, D'Errico A, et al. Sniffin' Sticks and olfactory system imaging in patients with Kallmann syndrome. *Int Forum Allergy Rhinol*. 2015;5(9):855-861. doi:10.1002/alr.21550.

147. Ros C, Alobid I, Centellas S, Balasch J, Mullol J, Castelo-Branco C. Loss of smell but not taste in adult women with Turner's syndrome and other congenital hypogonadisms. *Maturitas*. 2012;73(3):244-250. doi:10.1016/j.maturitas.2012.07.012.

148. Iannaccone A, Mykytyn K, Persico AM, et al. Clinical evidence of decreased olfaction in Bardet-Biedl syndrome caused by a deletion in the BBS4 gene. *Am J Med Genet*. 2005;132 A(4):343-346. doi:10.1002/ajmg.a.30512.

149. Abolmaali ND, Hietschold V, Vogl TJ, Huttenbrink K-B, Hummel T. MR Evaluation in Patients with Isolated Anosmia Since Birth or Early Childhood. *Am J Neuroradiol*. 2002;23:157-164. http://www.ajnr.org/content/23/1/157.full.

150. Huart C, Meusel T, Gerber J, Duprez T, Rombaux P, Hummel T. The depth of the olfactory sulcus is an indicator of congenital anosmia. *Am J Neuroradiol*. 2011;32(10):1911-1914. doi:10.3174/ajnr.A2632.

151. Karstensen HG, Mang Y, Fark T, Hummel T, Tommerup N. The first mutation in CNGA2 in two brothers with anosmia. *Clin Genet*. 2014;2(607123):293-296. doi:10.1111/cge.12491.

152. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. *PLoS One*. 2014;9(10):1-9. doi:10.1371/journal.pone.0107541.

153. Gopinath B, Sue CM, Kifley A, Mitchell P. The association between olfactory impairment and total mortality in older adults. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2012;67 A(2):204-209. doi:10.1093/gerona/glr165.

154. Konstantinidis I, Hummel T, Larsson M. Identification of unpleasant odors is independent of age. *Arch Clin Neuropsychol*. 2006;21(7):615-621. doi:10.1016/j.acn.2006.05.006.

155. Attems J, Walker L, Jellinger KA. Olfaction and Aging: A Mini-Review. *Gerontology*. 2015;61(6):485-490. doi:10.1159/000381619.

156. Korol DL, Brunjes PC. Unilateral naris closure and vascular development in the rat olfactory bulb. *Neuroscience*. 1992;46(3):631-641. doi:10.1016/0306-4522(92)90150-Z.

157. von Gudden B. Experimentaluntersuchungen ueber das periphere und zentrale Nervensystem. *Arch f Psychiatr u Nervenkrankheiten*. 1870:693-723.

158. Pfaar O, Hüttenbrink KB, Hummel T. Assessment of olfactory function after septoplasty: A longitudinal study. *Rhinology*. 2004;42(4):195-199.

159. Gouveri E, Katotomichelakis M, Gouveris H, Danielides V, Maltezos E, Papanas N. Olfactory dysfunction in type 2 diabetes mellitus: an additional manifestation of microvascular disease? *Angiology*. 2014;65(10):869-876. doi:10.1177/0003319714520956.

160. Alobid I, Enseñat J, Mariño-Sánchez F, et al. Impairment of Olfaction and Mucociliary Clearance After Expanded Endonasal Approach Using Vascularised Septal Flap Reconstruction for Skull Base Tumors. *Neurosurgery*. 2012;72(4):540-546. doi:10.1227/NEU.0b013e318282a535.

161. Risberg-Berlin B, Moller RY, Finizia C. Effectiveness of olfactory rehabilitation with the nasal airflow-inducing maneuver after total laryngectomy: one-year follow-up study. *Arch Otolaryngol Head Neck Surg*. 2007;133(7):650-654. doi:10.1001/archotol.133.7.650.

162. Atanasova B, Graux J, El Hage W, Hommet C, Camus V, Belzung C. Olfaction: A potential cognitive marker of psychiatric disorders. *Neurosci Biobehav Rev*. 2008;32(7):1315-1325. doi:10.1016/j.neubiorev.2008.05.003.

163. Kayser J, Tenke CE, Kroppmann CJ, et al. Olfaction in the psychosis prodrome: Electrophysiological and behavioral measures of odor detection. *Int J Psychophysiol*. 2013;90(2):190-206. doi:10.1016/j.ijpsycho.2013.07.003.

164. Snyder RD, Drummond PD. Olfaction in migraine. *Cephalalgia*. 1997;17(7):729-732. doi:10.1046/j.1468-2982.1997.1707729.x.

165. Holscher T, Seibt A, Appold S, et al. Effects of radiotherapy on olfactory function. *Radiother Oncol*. 2005;77(2):157-163. doi:10.1016/j.radonc.2005.09.015.

166. Rupp CI, Kurz M, Kemmler G, et al. Reduced olfactory sensitivity, discrimination, and identification in patients with alcohol dependence. *Alcohol Clin Exp Res*. 2003;27(3):432-439. doi:10.1097/01.ALC.0000057945.57330.2C.

167. Maurage P, Callot C, Chang B, Philippot P, Rombaux P, de Timary P. Olfactory impairment is correlated with confabulation in alcoholism: Towards a multimodal testing of orbitofrontal cortex. *PLoS One*. 2011;6(8):2-8. doi:10.1371/journal.pone.0023190.

168. Maurage P, Callot C, Philippot P, Rombaux P, de Timary P. Chemosensory event-related potentials in alcoholism: A specific impairment for olfactory function. *Biol Psychol*. 2011;88(1):28-36. doi:10.1016/j.biopsycho.2011.06.004.

169. Frye RE, Schwartz BS, Doty RL. Dose-related effects of cigarette smoking on olfactory function. *JAMA*. 1990;263(9):1233-1236. http://www.ncbi.nlm.nih.gov/pubmed/2304239.

170. Katotomichelakis M, Balatsouras D, Tripsianis G, et al. The effect of smoking on the olfactory function. *Rhinology*. 2007;45(4):273-280.

http://www.ncbi.nlm.nih.gov/pubmed/18085020.

171. Vent J, Robinson AM, Gentry-Nielsen MJ, et al. Pathology of the olfactory epithelium: smoking and ethanol exposure. *Laryngoscope*. 2004;114(8):1383-1388. doi:10.1097/00005537-200408000-00012.
172. Yee KK, Pribitkin E a, Cowart BJ, et al. Smoking-associated squamous metaplasia in olfactory mucosa of patients with chronic rhinosinusitis. *Toxicol Pathol*. 2009;37:594-598. doi:10.1177/0192623309338055.
173. Venstrom D, Amoore JE. Olfactory Threshold, in Relation to Age, Sex or Smoking. *J Food Sci*. 1968;33(3):264-265. doi:10.1111/j.1365-2621.1968.tb01364.x.
174. Rushforth SL, Allison C, Wonnacott S, Shoaib M. Subtype-selective nicotinic agonists enhance olfactory working memory in normal rats: A novel use of the odour span task. *Neurosci Lett*. 2010;471(2):114-118. doi:10.1016/j.neulet.2010.01.022.
175. Fonteyn S, Huart C, Deggouj N, Collet S, Eloy P, Rombaux P. Non-sinonasal-related olfactory dysfunction: A cohort of 496 patients. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2014;131(2):87-91. doi:10.1016/j.anorl.2013.03.006.
176. Sendon A. Olfato, psicología y psicoanálisis. In: Soler G, ed. *Olfato Y Gusto. Enfoque Multidisciplinario*. Buenos Aires: Acadia Editorial; 2013:223-230.
177. Pereira LJ, van der Bilt A. The influence of oral processing, food perception and social aspects on food consumption: A review. *J Oral Rehabil*. 2016. doi:10.1111/joor.12395.
178. Ottaviano G, Frasson G, Nardello E, Martini A. Olfaction deterioration in cognitive disorders in the elderly. *Aging Clin Exp Res*. 2016;28(1):37-45. doi:10.1007/s40520-015-0380-x.
179. Hummel T, Rothbauer C, Pauli E, Kobal G. Effects of the nasal decongestant oxymetazoline on human olfactory and intranasal trigeminal function in acute rhinitis. *Eur J Clin Pharmacol*. 1998;54(7):521-528. doi:10.1007/s002280050507.
180. Welge-Lüssen A, Wille C, Renner B, Kobal G. Anesthesia affects olfaction and chemosensory event-related potentials. *Clin Neurophysiol*. 2004;115(6):1384-1391. doi:10.1016/j.clinph.2003.12.028.
181. Soler ZM, Hyer JM, Karnezis TT, Schlosser RJ. The Olfactory Cleft Endoscopy Scale correlates with olfactory metrics in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(3):293-298. doi:10.1002/alr.21655.
182. Lund VJ, Kennedy DW. Quantification for staging sinusitis. The Staging and Therapy Group. *Ann Otol Rhinol Laryngol Suppl*. 1995;167:17-21.
183. Soler ZM, Pallanch JF, Sansoni ER, et al. Volumetric computed tomography analysis of the olfactory cleft in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2015;5(9):846-854. doi:10.1002/alr.21552.

184. Soler G. Evaluación clínica del sentido del olfato: conceptos clínicos básicos y explicación del CCCRC o Test de Connecticut. In: Soler G, ed. *Olfato Y Gusto. Enfoque Multidisciplinario*. Buenos Aires: Acadia Editorial; 2013:65-76.
185. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. 2009;34(5):447-454. doi:10.1111/j.1749-4486.2009.01995.x.
186. Soler ZM, Smith TL, Alt JA, Ramakrishnan VR, Mace JC, Schlosser RJ. Olfactory-specific quality of life outcomes after endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2016;6(4):407-413. doi:10.1002/alr.21679.
187. Philpott CM, Rimal D, Tassone P, Prinsley PR, Premachandra DJ. A study of olfactory testing in patients with rhinological pathology in the ENT clinic. *Rhinology*. 2008;46(1):34-39.
188. Delank KW, Stoll W. Olfactory function after functional endoscopic sinus surgery for chronic sinusitis. *Rhinology*. 1998;36:15-19.
189. Doty RL, McKeown DA, Lee WW, Shaman P. A Study of the Test-retest Reliability of Ten Olfactory Tests. *Chem Senses*. 2005;20(6):645-656. doi:10.1093/chemse/20.6.645.
190. Philpott CM, Wolstenholme CR, Goodenough PC, Clark A, Murty GE. Comparison of subjective perception with objective measurement of olfaction. *Otolaryngol - Head Neck Surg*. 2006;134(3):488-490. doi:10.1016/j.otohns.2005.10.041.
191. Wehling E, Lundervold AJ, Espeset T, Reinvang I, Brämerson A, Nordin S. Even cognitively well-functioning adults are unaware of their olfactory dysfunction: Implications for ENT clinicians and researchers. *Rhinology*. 2015;53(1):89-94. doi:10.4193/Rhino14.081.
192. Cook CE. Clinimetrics Corner: The Minimal Clinically Important Change Score (MCID): A Necessary Pretense. *J Man Manip Ther*. 2008;16(4):E82-E83. doi:10.1179/jmt.2008.16.4.82E.
193. Hedner M, Larsson M, Arnold N, Zucco GM, Hummel T. Cognitive factors in odor detection, odor discrimination, and odor identification tasks. *J Clin Exp Neuropsychol*. 2010;32(10):1062-1067. doi:10.1080/13803391003683070.
194. Cain WS. To know with the nose: keys to odor identification. *Science*. 1979;203(4379):467-470. doi:10.1126/science.760202.
195. Sorokowska a., Albrecht E, Hummel T. Reading first or smelling first? Effects of presentation order on odor identification. *Attention, Perception, Psychophys*. 2014;(April 2016):731-736. doi:10.3758/s13414-014-0811-3.
196. Frank RA, Gesteland RC, Bailie J, et al. Characterization of the Sniff Magnitude Test. *Arch Otolaryngol Neck Surg*. 2006;132(5):532. doi:10.1001/archotol.132.5.532.

197. Gudziol H, Wächter R. Gibt es olfaktorisch evozierte Atemänderungen? *Laryngo-Rhino-Otologie*. 2004;83(6):367-373. doi:10.1055/s-2004-814369.

198. Davidson TM, Murphy C, JB S, et al. Rapid Clinical Evaluation of Anosmia: The Alcohol Sniff Test. *Arch Otolaryngol - Head Neck Surg*. 1997;123(6):591-594. doi:10.1001/archotol.1997.01900060033005.

199. Doty RL, Smith R, McKeown DA, Raj J. Tests of human olfactory function: principal components analysis suggests that most measure a common source of variance. *Percept Psychophys*. 1994;56(6):701-707. doi:10.3758/BF03208363.

200. Jones-Gotman M, Zatorre RJ. Olfactory identification deficits in patients with focal cerebral excision. *Neuropsychologia*. 1988;26(3):387-400. doi:10.1016/0028-3932(88)90093-0.

201. Hornung DE, Kurtz DB, Bradshaw CB, et al. The olfactory loss that accompanies an HIV infection. *Physiol Behav*. 1998;64(4):549-556. doi:10.1016/S0031-9384(98)00112-7.

202. Whitcroft KL, Cuevas M, Haehner A, Hummel T. Patterns of olfactory impairment reflect underlying disease etiology. *Laryngoscope*. 2016;Epub ahead. doi:10.1002/lary.26229.

203. Lötsch J, Reichmann H, Hummel T. Different odor tests contribute differently to the evaluation of olfactory loss. *Chem Senses*. 2008;33(1):17-21. doi:10.1093/chemse/bjm058.

204. Eibenstein A, Fioretti AB, Lena C, Rosati N, Amabile G, Fusetti M. Modern psychophysical tests to assess olfactory function. *Neurol Sci*. 2005;26(3):147-155. doi:10.1007/s10072-005-0452-3.

205. Scadding G, Hellings P, Alobid I, et al. Diagnostic tools in Rhinology EAACI position paper. *Clin Transl Allergy*. 2011;1(1):2. doi:10.1186/2045-7022-1-2.

206. Picillo M, Iavarone A, Pellecchia MT, et al. Validation of an Italian version of the 40-item University of Pennsylvania Smell Identification Test that is physician administered: Our experience on one hundred and thirty-eight healthy subjects. *Clin Otolaryngol*. 2014;39(1):53-57. doi:10.1111/coa.12212.

207. Taherkhani S, Moztarzadeh F, Mehdizadeh Seraj J, et al. Iran Smell Identification Test (Iran-SIT): a Modified Version of the University of Pennsylvania Smell Identification Test (UPSIT) for Iranian Population. *Chemosens Percept*. 2015;8(4):183-191. doi:10.1007/s12078-015-9192-9.

208. Thamboo A, Santos RCD, Naidoo L, Rahmanian R, Chilvers M a., Chadha NK. Use of the SNOT-22 and UPSIT to Appropriately Select Pediatric Patients With Cystic Fibrosis Who Should Be Referred to an Otolaryngologist. *JAMA Otolaryngol Neck Surg*. 2014;140(10):934. doi:10.1001/jamaoto.2014.1650.

209. Doty RL, Shaman P, Dann M. Development of the university of pennsylvania smell identification test: A standardized microencapsulated test of olfactory function. *Physiol Behav*. 1984;32(3):489-502. doi:10.1016/0031-9384(84)90269-5.
210. Saedi B, Sadeghi M, Yazdani N, Afshari A. Effectiveness of FESS in Smell Improvement of Sinusitis Patients. *Indian J Otolaryngol Head Neck Surg*. 2013;65(SUPPL2):283-287. doi:10.1007/s12070-011-0439-8.
211. Shemshadi H, Azimian M, Onsori MA, Azizabadi Farahani M. Olfactory function following open rhinoplasty: A 6-month follow-up study. *BMC Ear Nose Throat Disord*. 2008;8:6. doi:10.1186/1472-6815-8-6.
212. Razmpa E, Saedi B, Safavi A, Mohammadi S. Olfactory function after nasal plastic surgery. *B-ENT*. 2013;9:269-275.
213. Muirhead N, Benjamin E, Saleh H. Is the University of Pennsylvania Smell Identification Test (UPSIT) valid for the UK population? *Otorhinolaryngologist*. 2013;6(2):99-103.
214. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G, Hummel T. "Sniffin" Sticks': Olfactory Performance Assessed by the Combined Testing of Odor Identification, Odor Discrimination and Olfactory Threshold. *Chem Senses*. 1997;22(1):39-52.
215. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: An upgrade based on a group of more than 3,000 subjects. *Eur Arch Oto-Rhino-Laryngology*. 2007;264(3):237-243. doi:10.1007/s00405-006-0173-0.
216. Neumann C, Tsioulos K, Merkonidis C, Salam M, Clark A, Philpott C. Validation study of the "Sniffin' Sticks" olfactory test in a British population: A preliminary communication. *Clin Otolaryngol*. 2012;37(1):23-27. doi:10.1111/j.1749-4486.2012.02431.x.
217. Konstantinidis I, Printza A, Genetzaki S, Mamali K, Kekes G, Constantinidis J. Cultural adaptation of an olfactory identification test: The Greek version of Sniffin' Sticks. *Rhinology*. 2008;46(4):292-296.
218. van Spronsen E, Ebbens F, Fokkens W. Olfactory function in healthy children: normative data for odor identification. *Am J Rhinol Allergy*. 2013;27(3):197-201. doi:nicht verfügbar?
219. Danielides V, Katotomichelakis M, Balatsouras D, et al. Evaluation of prognostic factors for olfaction in nasal polyposis treated by Endoscopic Sinus Surgery. *Rhinology*. 2009;47(2):172-180. http://www.scopus.com/inward/record.url?eid=2-s2.0-68149084758&partnerID=40&md5=7303a5832d93c853cc5ebbc1a8aea3e1.
220. Federspil P, Wilhelm-Schwenk R CJ. Kinetics of olfactory function following endonasal sinus surgery for nasal polyposis. *Rhinology*. 2008;46:184-187.

221. Cain WS, Gent JF, Goodspeed RB, Leonard G. Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. *Laryngoscope*. 1988;98(1):83-88. doi:10.1288/00005537-198801000-00017.

222. Hugh SC, Siu J, Hummel T, et al. Olfactory testing in children using objective tools: comparison of Sniffin' Sticks and University of Pennsylvania Smell Identification Test (UPSIT). *J Otolaryngol Head Neck Surg*. 2015;44(1):10. doi:10.1186/s40463-015-0061-y.

223. Cameron EL, Doty RL. Odor identification testing in children and young adults using the smell wheel. *Int J Pediatr Otorhinolaryngol*. 2013;77(3):346-350. doi:10.1016/j.ijporl.2012.11.022.

224. Schriever VA, Mori E, Petters W, et al. The "Sniffin' Kids" Test - A 14-Item Odor Identification Test for Children. Louis M, ed. *PLoS One*. 2014;9(6):e101086. doi:10.1371/journal.pone.0101086.

225. Kobal G, Klimek L, Wolfensberger M, et al. Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. *Eur Arch Oto-Rhino-Laryngology*. 2000;257(4):205-211. doi:10.1007/s004050050223.

226. Klimek L, Hummel T, Moll B, Kobal G, Mann WJ. Lateralized and bilateral olfactory function in patients with chronic sinusitis compared with healthy control subjects. *Laryngoscope*. 1998;108(1 Pt 1):111-114.

227. Gudziol V, Hummel C, Negoias S, Ishimaru T, Hummel T. Lateralized differences in olfactory function. *Laryngoscope*. 2007;117(5):808-811. doi:10.1097/MLG.0b013e3180330092.

228. Welge-Lüssen A, Gudzio V, Wolfensberger M, Humme T. Olfactory testing in clinical settings - is there additional benefit from unilateral testing? *Rhinology*. 2010;48(2):156-159. doi:10.4193/Rhin09.156.

229. Huart C, Rombaux P, Gérard T, et al. Unirhinal Olfactory Testing for the Diagnostic Workup of Mild Cognitive Impairment. *J Alzheimer's Dis*. 2015;47(1):253-270. doi:10.3233/JAD-141494.

230. Hummel T, Haehner A, Hummel C, Croy I, Iannilli E. Lateralized differences in olfactory bulb volume relate to lateralized differences in olfactory function. *Neuroscience*. 2013;237:51-55. doi:10.1016/j.neuroscience.2013.01.044.

231. Gudziol V, Paech I, Hummel T. Unilateral reduced sense of smell is an early indicator for global olfactory loss. *J Neurol*. 2010;257(6):959-963. doi:10.1007/s00415-009-5445-3.

232. Gudziol V, Lötsch J, Hähner A, Zahnert T, Hummel T. Clinical significance of results

from olfactory testing. *Laryngoscope*. 2006;116(10):1858-1863. doi:10.1097/01.mlg.0000234915.51189.cb.

233. Doty RL, Marcus A, William Lee W. Development of the 12-Item Cross-Cultural Smell Identification Test(CC-SIT). *Laryngoscope*. 1996;106(3):353-356. doi:10.1097/00005537-199603000-00021.
234. Hummel T, Konnerth CG, Rosenheim K, Kobal G. Screening of olfactory function with a four-minute odor identification test: Reliability, normative data, and investigations in patients with olfactory loss. *Ann Otol Rhinol Laryngol*. 2001;110(10):976-981. doi:10.1177/000348940111001015.
235. Rawal S, Hoffman HJ, Chapo AK, Duffy VB. Sensitivity and Specificity of Self-Reported Olfactory Function in a Home-Based Study of Independent-Living, Healthy Older Women. *Chemosens Percept*. 2014;7(3-4):108-116. doi:10.1007/s12078-014-9170-7.
236. Ni R, Michalski MH, Brown E, et al. Optimal directional volatile transport in retronasal olfaction. *Proc Natl Acad Sci*. 2015;112(47):14700-14704. doi:10.1073/pnas.1511495112.
237. Heilmann S, Strehle G, Rosenheim K, Damm M, Hummel T. Clinical assessment of retronasal olfactory function. *Arch Otolaryngol Head Neck Surg*. 2002;128(4):414-418. doi:ooa10079 [pii].
238. Renner B, Mueller CA, Dreier J, Faulhaber S, Rascher W, Kobal G. The Candy smell test: A new test for retronasal olfactory performance. *Laryngoscope*. 2009;119(3):487-495. doi:10.1002/lary.20123.
239. Hummel T, Landis B, Huttenbrink K-B. Smell and Taste Disorders. *Curr Top Otorhinolaryngol Head Neck Surg*. 2011;10:1-15. doi:10.1016/j.fsc.2011.10.011.
240. Wolf A, Illini O, Uy D, Renner B, Mueller CA. A new extension to the Taste Strips test. *Rhinology*. 2016;54(1):45-50. doi:10.4193/Rhin14.266.
241. Landis BN, Welge-Luessen A, Bramerson A, et al. "taste Strips" - A rapid, lateralized, gustatory bedside identification test based on impregnated filter papers. *J Neurol*. 2009;256(2):242-248. doi:10.1007/s00415-009-0088-y.
242. Mueller C, Kallert S, Renner B, et al. Quantitative assessment of gustatory function in a clinical context using impregnated "taste strips." *Rhinology*. 2003;41(1):2-6.
243. Walliczek U, Negoias S, Hähner A, Hummel T. Assessment of chemosensory function using "Sniffin' Sticks", taste strips, taste sprays, and retronasal olfactory tests. *Curr Pharm Des*. 2016:1-8.
244. Pavlidis P, Gouveris H, Gorgulla H, Hast H-J, Maurer J. Electrogustometry and Contact Endoscopy Findings in Patients With Head and Neck Malignancies Treated With Chemotherapy, Radiotherapy, or Radiochemotherapy. *Chem Senses*.

2015;40(3):165-171. doi:10.1093/chemse/bju060.

245. Moura RGF, Cunha DA, Caldas ASC, da Silva HJ. Quantitative evaluation of taste in childhood populations: a systematic review. *Braz J Otorhinolaryngol*. 2015;81(1):97-106. doi:10.1016/j.bjorl.2014.04.002.
246. Sipiora M., Murtaugh M., Gregoire M., Duffy V. Bitter taste perception and severe vomiting in pregnancy. *Physiol Behav*. 2000;69(3):259-267. doi:10.1016/S0031-9384(00)00223-7.
247. Rombaux P, Huart C, Mouraux A. Assessment of chemosensory function using electroencephalographic techniques. *Rhinology*. 2012;50(1):13-21. doi:10.4193/Rhino11.126.
248. Kobal G, Hummel C. Cerebral chemosensory evoked potentials elicited by chemical stimulation of the human olfactory and respiratory nasal mucosa. *Electroencephalogr Clin Neurophysiol Potentials Sect*. 1988;71(4):241-250. doi:10.1016/0168-5597(88)90023-8.
249. Hummel T, Knecht M, Kobal G. Peripherally obtained electrophysiological responses to olfactory stimulation in man: Electro-olfactograms exhibit a smaller degree of desensitization compared with subjective intensity estimates. *Brain Res*. 1996;717(1-2):160-164. doi:10.1016/0006-8993(96)00094-7.
250. Knecht M, Hummel T. Recording of the human electro-olfactogram. *Physiol Behav*. 2004;83(1 SPEC. ISS.):13-19. doi:10.1016/j.physbeh.2004.07.024.
251. Gottschlich M, Hummel T. Effects of handedness on olfactory event-related potentials in a simple olfactory task. *Rhinology*. 2015;53:149-153. doi:10.4193/Rhino14.204.
252. Lundström JN, Gordon AR, Alden EC, Boesveldt S, Albrecht J. Methods for building an inexpensive computer-controlled olfactometer for temporally-precise experiments. *Int J Psychophysiol*. 2010;78(2):179-189. doi:10.1016/j.ijpsycho.2010.07.007.
253. Savic I. Imaging of brain activation by odorants in humans. *Curr Opin Neurobiol*. 2002;12(4):455-461. doi:10.1016/S0959-4388(02)00346-X.
254. Lundstrom JN, Boesveldt S, Albrecht J. Central processing of the chemical senses: An overview. *ACS Chem Neurosci*. 2011;2(1):5-16. doi:10.1021/cn1000843.
255. Decker JR, Meen EK, Kern RC, Chandra RK. Cost effectiveness of magnetic resonance imaging in the workup of the dysosmia patient. *Int Forum Allergy Rhinol*. 2013;3(1):56-61. doi:10.1002/alr.21066.
256. Higgins TS, Lane AP. What is the best imaging modality to investigate olfactory dysfunction in the setting of normal endoscopy? *Laryngoscope*. 2014;124(1):4-5. doi:10.1002/lary.23892.
257. Huart C, Rombaux P, Hummel T. Plasticity of the Human Olfactory System: The Olfactory Bulb. *Molecules*. 2013;18(9):11586-11600.

doi:10.3390/molecules180911586.

258. Ehnhage A, Olsson P, Kolbeck KG, et al. Functional endoscopic sinus surgery improved asthma symptoms as well as PEFR and olfaction in patients with nasal polyposis. *Allergy Eur J Allergy Clin Immunol*. 2009;64(5):762-769. doi:10.1111/j.1398-9995.2008.01870.x.
259. Golding-Wood DG, Holmstrom M, Darby Y, Scadding GK, Lund VJ. The treatment of hyposmia with intranasal steroids. *J Laryngol Otol* . 1996;110(February):132-135.
260. Jankowski R, Bodino C. Olfaction in patients with nasal polyposis: Effects of systemic steroids and radical ethmoidectomy with middle turbinate resection (nasalisation). *Rhinology*. 2003;41(4):220-230.
261. Alobid I, Benitez P, Cardelus S, et al. Oral plus nasal corticosteroids improve smell, nasal congestion, and inflammation in sino-nasal polyposis. *Laryngoscope*. 2014;124(1):50-56. doi:10.1002/lary.24330.
262. Banglawala SM, Oyer SL, Lohia S, Psaltis AJ, Soler ZM, Schlosser RJ. Olfactory outcomes in chronic rhinosinusitis with nasal polyposis after medical treatments: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2014;4(12):986-994. doi:10.1002/alr.21373.
263. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6 Suppl 1:S22-209. doi:10.1002/alr.21695.
264. Hopkins C, Philpott C, Crowe S, et al. Identifying the most important outcomes for systematic reviews of interventions for rhinosinusitis in adults: Working with Patients, Public and Practitioners. *Rhinology*. 2016;54(1):20-26. doi:10.4193/Rhino15.199.
265. Chong LY, Head K, Hopkins C, Philpott C, Schilder AGM, Burton MJ. Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2016;2016(4). doi:10.1002/14651858.CD011996.pub2.
266. Chong LY, Head K, Hopkins C, Philpott C, Burton MJ, Schilder AGM. Different types of intranasal steroids for chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2016;2016(4). doi:10.1002/14651858.CD011993.pub2.
267. Head K, Chong LY, Hopkins C, Philpott C, Schilder AGM, Burton MJ. Short-course oral steroids as an adjunct therapy for chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2016;2016(4). doi:10.1002/14651858.CD011992.pub2.
268. Head K, Chong LY, Hopkins C, Philpott C, Burton MJ, Schilder AGM. Short-course oral steroids alone for chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2016;2016(4). doi:10.1002/14651858.CD011991.pub2.
269. Joanne R, Wytske F, Yee CL, Claire H. Surgical versus medical interventions for chronic rhinosinusitis with nasal polyps. *Cochrane Database Syst Rev*. 2014;(12).

doi:10.1002/14651858.CD006991.pub2.

270. Schriever VA, Merkonidis C, Gupta N, Hummel C, Hummel T. Treatment of smell loss with systemic methylprednisolone. *Rhinology*. 2012;50(3):284-289. doi:10.4193/Rhino.11.207.
271. Jiang R-S, Wu S-H, Liang K-L, Shiao J-Y, Hsin C-H, Su M-C. Steroid treatment of posttraumatic anosmia. *Eur Arch Otorhinolaryngol*. 2010;267(10):1563-1567. doi:10.1007/s00405-010-1240-0.
272. Jiang RS, Twu CW, Liang KL. Medical treatment of traumatic anosmia. *Otolaryngol Head Neck Surg*. 2015;152(5):954-958. doi:10.1177/0194599815571272.
273. Seo BS, Lee HJ, Mo J-H, Lee CH, Rhee C-S, Kim J-W. Treatment of Postviral Olfactory Loss With Glucocorticoids,. *Arch Otolaryngol Head Neck Surg*. 2009;135(10):1000-1004.
274. Heilmann S, Just T, Göktas O, Hauswald B, Hüttenbrink K-B, Hummel T. Effects of systemic or topical administration of corticosteroids and vitamin B in patients with olfactory loss. *Laryngorhinootologie*. 2004;83(11):729-734. doi:10.1055/s-2004-825676.
275. Tian J, Pinto JM, Xin Y, et al. Dexamethasone affects mouse olfactory mucosa gene expression and attenuates genes related to neurite outgrowth. *Int Forum Allergy Rhinol*. 2015;5(10):907-918. doi:10.1002/alr.21586.
276. Guo KJ, Zhao FC, Guo Y, Li FL, Zhu L, Zheng W. The influence of age, gender and treatment with steroids on the incidence of osteonecrosis of the femoral head during the management of severe acute respiratory syndrome: a retrospective study. *Bone Joint J*. 2014;96-B(2):259-262. doi:10.1302/0301-620X.96B2.31935.
277. Gong LL, Fang LH, Wang HY, et al. Genetic risk factors for glucocorticoid-induced osteonecrosis: A meta-analysis. *Steroids*. 2013;78(4):401-408. doi:10.1016/j.steroids.2013.01.004.
278. Dilisio MF. Osteonecrosis Following Short-term, Low-dose Oral Corticosteroids: A Population-based Study of 24 Million Patients. *Orthopedics*. 2014;37(7):e631-6. doi:10.3928/01477447-20140626-54.
279. Gudziol V, Hummel T. Effects of Pentoxifylline on Olfactory Sensitivity. *Arch Otolaryngol Head Neck Surg*. 2009;135(3):291-295. doi:10.1097/00006534-198006000-00008.
280. Henkin RI, Velicu I, Schmidt L. An open-label controlled trial of theophylline for treatment of patients with hyposmia. *Am J Med Sci*. 2009;337(6):396-406. doi:10.1097/MAJ.0b013e3181914a97.
281. Sorokowska A, Drechsler E, Karwowski M, Hummel T (2016) Effects of olfactory training: a meta-analysis. Rhinology (in press)

282. Meusel T, Albinus J, Welge-Luessen A, Hähner A, Hummel T. Short-term effect of caffeine on olfactory function in hyposmic patients. *Eur Arch Oto-Rhino-Laryngology*. 2016. doi:10.1007/s00405-015-3879-z.

283. Gudziol V, Muck-Weymann M, Seizinger O, Rauh R, Siffert W, Hummel T. Sildenafil Affects Olfactory Function. *J Urol*. 2007;177(1):258-261. doi:10.1016/j.juro.2006.08.060.

284. Gudziol V, Pietsch J, Witt M, Hummel T. Theophylline induces changes in the electro-olfactogram of the mouse. *Eur Arch Oto-Rhino-Laryngology*. 2010;267(2):239-243. doi:10.1007/s00405-009-1076-7.

285. Kurahashi T, Shibuya T. Ca2+-dependent adaptive properties in the solitary olfactory receptor cell of the newt. *Brain Res*. 1990;515(1-2):261-268. doi:10.1016/0006-8993(90)90605-B.

286. Zufall F, Shepherd GM, Firestein S. Inhibition of the Olfactory Cyclic-Nucleotide Gated Ion Channel by Intracellular Calcium. *Proc R Soc L B Biol Sci*. 1991;246(1317):225-230. isi:A1991GX98500005.

287. Panagiotopoulos G, Naxakis S, Papavasiliou A, Filipakis K, Papatheodorou G, Goumas P. Decreasing nasal mucus Ca++ improves hyposmia. *Rhinology*. 2005;43(2):130-134.

288. Whitcroft KL, Merkonidis C, Cuevas M, Haehner A, Philpott CM, Hummel T. Intranasal sodium citrate improves olfaction in post-viral hyposmia. *Rhinology*. 2016;54:1-6. doi:10.4193/Rhino16.054.

289. Whitcroft KL, Ezzat M, Cuevas M, Andrews P, Hummel T. The effect of intranasal sodium citrate on olfaction in post-infectious loss: results from a prospective, placebo-controlled trial in 49 patients. *Clin Otolaryngol*. 2016:1-7. doi:10.1111/COA.12789.

290. Drews T, Hummel T. Treatment Strategies for Smell Loss. *Curr Otorhinolaryngol Rep*. 2016;4(2):122-129. doi:10.1007/s40136-016-0115-3.

291. Haehner A, Habersack A, Wienecke M, Storch A, Reichmann H, Hummel T. Early Parkinson's disease patients on rasagiline present with better odor discrimination. *J Neural Transm*. 2015;122(11):1541-1546. doi:10.1007/s00702-015-1433-1.

292. Schopf V, Kollndorfer K, Pollak M, Mueller CA, Freiherr J. Intranasal insulin influences the olfactory performance of patients with smell loss, dependent on the body mass index: A pilot study. *Rhinology*. 2015;53(4):371-378. doi:10.4193/Rhino15.065.

293. Haehner A, Hummel T, Wolz M, et al. Effects of rasagiline on olfactory function in patients with Parkinson's disease. *Mov Disord*. 2013;28(14):2023-2027. doi:10.1002/mds.25661.

294. Lyckholm L, Heddinger S, Parker G, et al. A Randomized, Placebo Controlled Trial of Oral Zinc for Chemotherapy-Related Taste and Smell Disorders. *J Pain Palliat Care Pharmacother*. 2012;26(2):111-114. http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=2011600753&site=ehost-live.

295. Reden J, Lill K, Zahnert T, Haehner A, Hummel T. Olfactory function in patients with postinfectious and posttraumatic smell disorders before and after treatment with vitamin A: A double-blind, placebo-controlled, randomized clinical trial. *Laryngoscope*. 2012;122(9):1906-1909. doi:10.1002/lary.23405.

296. Henkin RI, Schultz M, Minnick-Poppe L. Intranasal theophylline treatment of hyposmia and hypogeusia: a pilot study. *Arch Otolaryngol Head Neck Surg*. 2012;138(11):1064-1070. doi:1392510 [pii]\r10.1001/2013.jamaoto.342.

297. Reden J, Herting B, Lill K, Kern R, Hummel T. Treatment of postinfectious olfactory disorders with minocycline: A double-blind, placebo-controlled study. *Laryngoscope*. 2011;121(3):679-682. doi:10.1002/lary.21401.

298. Quint C, Temmel AF, Hummel T, Ehrenberger K. The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study. *Acta Otolaryngol*. 2002;122(8):877-881. doi:10.1080/003655402/000028054.

299. Hummel T, Heilmann S, Hüttenbriuk K-B. Lipoic acid in the treatment of smell dysfunction following viral infection of the upper respiratory tract. *Laryngoscope*. 2002;112(11):2076-2080. doi:10.1097/00005537-200211000-00031.

300. Hummel T, Reden KRJ, Hähner A, Weidenbecher M, Hüttenbrink KB. Effects of olfactory Training in patients with olfactory loss. *Laryngoscope*. 2009;119(3):496-499. doi:10.1002/lary.20101.

301. Haehner A, Tosch C, Wolz M, et al. Olfactory Training in Patients with Parkinson's Disease. *PLoS One*. 2013;8(4):1-7. doi:10.1371/journal.pone.0061680.

302. Geissler K, Reimann H, Gudziol H, Bitter T, Guntinas-Lichius O. Olfactory training for patients with olfactory loss after upper respiratory tract infections. *Eur Arch Oto-Rhino-Laryngology*. 2014;271(6):1557-1562. doi:10.1007/s00405-013-2747-y.

303. Damm M, Pikart LK, Reimann H, et al. Olfactory training is helpful in postinfectious olfactory loss: A randomized, controlled, multicenter study. *Laryngoscope*. 2014;124(4):826-831. doi:10.1002/lary.24340.

304. Altundag A, Cayonu M, Kayabasoglu G, et al. Modified olfactory training in patients with postinfectious olfactory loss. *Laryngoscope*. 2015;125(8):1763-1766. doi:10.1002/lary.25245.

305. Konstantinidis I, Tsakiropoulou E, Bekiaridou P, Kazantzidou C, Constantinidis J. Use of olfactory training in post-traumatic and postinfectious olfactory dysfunction.

Laryngoscope. 2013;123(12):85-90. doi:10.1002/lary.24390.

306. Fleiner F, Lau L, Goktas O. Active olfactory training for the treatment of smell disorders. *Ear Nose Throat J*. 2012;91(5):198-203.
307. Wang L, Chen L, Jacob T. Evidence for peripheral plasticity in human odour response. *J Physiol*. 2004;554(Pt 1):236-244. doi:10.1113/jphysiol.2003.054726.
308. Konstantinidis I, Tsakiropoulou E, Constantinidis J. Long term effects of olfactory training in patients with post-infectious olfactory loss. *Rhinology*. 2016;54(2):170-175. doi:10.4193/Rhino15.264.
309. Negoias S, Pietsch K, Hummel T. Changes in olfactory bulb volume following lateralized olfactory training. *Brain Imaging Behav*. 2016:1-8. doi:10.1007/s11682-016-9567-9.
310. Poletti SC, Michel E, Hummel T. Olfactory Training Using Heavy and Light Weight Molecule Odors. *Perception*. 2016. doi:10.1177/0301006616672881.
311. Kollndorfer K, Fischmeister FPS, Kowalczyk K, et al. Olfactory training induces changes in regional functional connectivity in patients with long-term smell loss. *NeuroImage Clin*. 2015;9:401-410. doi:10.1016/j.nicl.2015.09.004.
312. Mori E, Petters W, Schriever VA, Valder C, Hummel T. Exposure to odours improves olfactory function in healthy children. *Rhinology*. 2015;53(3):221-226. doi:10.4193/Rhin14.192.
313. Sharma R, Lakhani R, Rimmer J, Hopkins C. Surgical interventions for chronic rhinosinusitis with nasal polyps. *Cochrane Database Syst Rev*. 2014;(11):CD006990. doi:10.1002/14651858.CD006991.pub2.
314. Rimmer J, Fokkens W, Chong LY, Hopkins C. Surgical versus medical interventions for chronic rhinosinusitis with nasal polyps . *Cochrane Database Syst Rev* . 2014;12(12):CD006991. doi:10.1002/14651858.CD006991.pub2.www.cochranelibrary.com.
315. Lund VJ, Holmstrom M, Scadding GK. Functional endoscopic sinus surgery in the management of chronic rhinosinusitis. An objective assessment. *J Laryngol Otol*. 1991;105(10):832-835.
316. Lund VJ, MacKay IS. Outcome assessment of endoscopic sinus surgery. *J R Soc Med*. 1994;87(2):70-72. http://www.ncbi.nlm.nih.gov/pubmed/18357704.
317. Blomqvist EH, Lundblad L, Anggård a, Haraldsson PO, Stjärne P. A randomized controlled study evaluating medical treatment versus surgical treatment in addition to medical treatment of nasal polyposis. *J Allergy Clin Immunol*. 2001;107(2):224-228. doi:10.1067/mai.2001.112124.
318. Perry BF, Kountakis SE. Subjective Improvement of Olfactory Function After Endoscopic Sinus Surgery for Chronic Rhinosinusitis. *Am J Otolaryngol*.

2003;24(6):366-369. doi:10.1053/S0196-0709(03)00067-X.

319. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. *Laryngoscope*. 2004;114(5):923-930. doi:10.1097/00005537-200405000-00027.
320. Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. *Rhinology*. 2005;43(1):2-10.
321. Bonfils P. Evaluation of the combined medical and surgical treatment in nasal polyposis. I: functional results. *Acta Otolaryngol*. 2007;127(4):436-446. doi:10.1080/00016480600895078.
322. Minovi A, Hummel T, Ural A, Draf W, Bockmuhl U. Predictors of the outcome of nasal surgery in terms of olfactory function. *Eur Arch Oto-Rhino-Laryngology*. 2008;265(1):57-61. doi:10.1007/s00405-007-0409-7.
323. Litvack JR, Mace J, Smith TL. Does olfactory function improve after endoscopic sinus surgery? *Otolaryngol - Head Neck Surg*. 2009;140(3):312-319. doi:10.1016/j.otohns.2008.12.006.
324. Olsson P, Stjärne P. Endoscopic Sinus Surgery improves olfaction in nasal polyposis, a multi-center study. *Rhinology*. 2010;48(2):150-155. doi:10.4193/Rhin09.097.
325. Ehnhage A, Olsson P, Kolbeck K-G, Skedinger M, Stjarne P. One Year after Endoscopic Sinus Surgery in Polyposis: Asthma, Olfaction, and Quality-of-Life Outcomes. *Otolaryngol -- Head Neck Surg*. 2012;146(5):834-841. doi:10.1177/0194599811435638.
326. Schriever VA, Gupta N, Pade J, Szewczynska M, Hummel T. Olfactory function following nasal surgery: A 1-year follow-up. *Eur Arch Oto-Rhino-Laryngology*. 2013;270(1):107-111. doi:10.1007/s00405-012-1972-0.
327. Baradaranfar MH, Ahmadi ZS, Dadgarnia MH, et al. Comparison of the effect of endoscopic sinus surgery versus medical therapy on olfaction in nasal polyposis. *Eur Arch Oto-Rhino-Laryngology*. 2013;271(2):311-316. doi:10.1007/s00405-013-2553-6.
328. Poirrier AL, Ahluwalia S, Goodson A, Ellis M, Bentley M, Andrews P. Is the Sino-Nasal Outcome Test-22 a suitable evaluation for septorhinoplasty? *Laryngoscope*. 2013;123(1):76-81. doi:10.1002/lary.23615.
329. Randhawa PS, Watson N, Lechner M, Ritchie L, Choudhury N, Andrews PJ. The outcome of septorhinoplasty surgery on olfactory function. *Clin Otolaryngol*. 2016;41(1):15-20. doi:10.1111/coa.12463.
330. Richardson BE, Vanderwoude EA, Sudan R, Leopold DA, Thompson JS. Gastric Bypass Does Not Influence Olfactory Function in Obese Patients. *Obes Surg*.

2012;22(2):283-286. doi:10.1007/s11695-011-0487-x.

331. Altun H, Hanci D, Altun H, et al. Improved Gustatory Sensitivity in Morbidly Obese Patients After Laparoscopic Sleeve Gastrectomy. *Ann Otol Rhinol Laryngol* . 2016:558-562. doi:10.1177/0003489416629162.
332. Leopold DA, Schwob JE, Youngentob SL, et al. Successful Treatment of Phantosmia With Preservation of Olfaction. *Arch Otolaryngol - Head Neck Surg*. 1991;117(12):1402-1406. doi:10.1001/archotol.1991.01870240094016.
333. Leopold DA, Hornung DE. Olfactory cocainization is not an effective long-term treatment for phantosmia. *Chem Senses*. 2013;38(9):803-806. doi:10.1093/chemse/bjt047.
334. Morrissey DK, Pratap U, Brown C, Wormald P-J. The role of surgery in the management of phantosmia. *Laryngoscope*. 2016;126(3):575-578. doi:10.1002/lary.25647.
335. Altun H, Hanci D. Olfaction improvement after nasal septal perforation repair with the "cross-stealing" technique. *Am J Rhinol Allergy*. 2015;29(5):e142-e145. doi:10.2500/ajra.2015.29.4208.
336. Leopold D. Distortion of Olfactory Perception: Diagnosis and Treatment. *Chem Senses*. 2002;27(7):611-615. doi:10.1093/chemse/27.7.611.
337. Stevens CN, Stevens MH. Quantitative effects of nasal surgery on olfaction. *Am J Otolaryngol*. 1985;6(4):264-267. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=4037228.

CORRESPONDING AUTHOR:

Thomas Hummel, M.D.; Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany; phone +49-351-458-4189; thummel@mail.zih.tu-dresden.de

TABLES:

Table 1:

Normosmia	Normal olfactory function.
Hyposmia *(or 'microsmia')*	Quantitatively reduced olfactory function.
Functional Anosmia	Quantitatively reduced olfaction to the extent that the subject has no function that is useful in daily life.
Anosmia	Absence of all olfactory function.
Specific Anosmia *(or 'partial anosmia')*	Quantitatively reduced ability to smell a specific odour despite preserved ability to smell most other odours. Thought to be a normal physiological trait with little clinical significance [12].
Hyperosmia *(or 'superosmia')*	Quantitatively increased ability to smell odours to abnormal level. This form of olfactory dysfunction is extremely rare, but has been described, for example, in association with migraine [13].
Parosmia *(or 'dysosmia', 'cacosmia', 'euosmia' or 'troposmia')**	Qualitative dysfunction in the presence of an odorant (i.e. distorted perception of an odour stimulus).

Phantosmia	Qualitative dysfunction in the absence of an odourant (i.e. an odourant is perceived without concurrent stimulus, an 'olfactory hallucination').
Orthonasal olfaction	The perception of odourants anteriorly due to airflow from the nostrils to the olfactory clefts, e.g. during sniffing.
Retronasal olfaction	The perception of odourants located within the oropharynx, caused by airflow to the olfactory clefts via the nasopharynx during swallowing or nasal exhalation. Retronasal olfaction forms the basis of flavour perception.

Table 2:

Conductive dysfunction	Resulting from blockage of odourant transmission to the olfactory neuroepithelium.
Sensorineural dysfunction	Resulting from damage/loss of the olfactory neuroepithelium or nerve.
Central dysfunction	Resulting from damage/loss of the olfactory processing pathways of the central nervous system.

Table 3:

Agents	Medications
Acids	Anaesthetics (local)
Benzene	*a.* cocaine hydrochloride
Cadmium	*b.* procaine hydrochloride
Chlorine	*c.* tetracaine hydrochloride
Ethyl acetate	
Formaldehyde	Antimicrobials
Hydrazine	*a.* aminoglycosides
Hydrogen sulphide	*b.* macrolides
Lead	*c.* penicillins
Mercury	*d.* tetracyclines
Nitrous gases	e. terbinafine
Paint solvents	
Silicon dioxide	Antithyroid medications
Trichloroethylene	*a.* propylthiouracil
Zinc gluconate	*b.* thiouracil
	Chemotherapy
	Alpha-Receptor Antagonists

Table 4:

Psychophysical test	Olfactory components assessed
"Sniffin' Sticks" (original version)	Threshold, discrimination, identification
Connecticut Chemosensory Clinical Research Center Test	Threshold, identification
T & T Olfactometer	Threshold, identification
University of Pennsylvania Smell Identification Test	Identification
Smell Diskettes Test	Identification
Cross-Cultural Smell Identification Test	Identification
Pocket Smell Test	Identification
San Diego Odor Identification Test	Identification
Scandinavian Odour Identification Test	Identification
Smell Threshold Test	Threshold
Olfactory Perception Threshold Test	Threshold
Barcelona Smell Test (BAST-24)	Odour detection, identification, memory
Odourized Marker Test	Identification
Snap & Sniff Olfactory Test System	Threshold
Open Essence	Identification

Table 5:

Author	Year	Study Type	Treatment Method	Study Population; N	Results
			Medication		
Whitcroft *et al.* [289]	2016	Prospective, controlled	Intranasal sodium citrate	Patients with post-infectious olfactory loss n=49	Significant improvement in composite threshold and identification scores after treatment compared to placebo
Whitcroft *et al.* [288]	2016	Prospective, controlled	Intranasal sodium citrate	Patients with olfactory loss of mixed cause n=57	Significantly improved identification scores in patients with post-infectious loss compared to placebo
Jiang *et al.* [272]	2015	Prospective, controlled	Zinc and steroid	Traumatic anosmia n=145	Zinc and steroid application showed significant improvement compared to “no treatment”; no difference in effectiveness between zinc and steroid

Tian *et al.* [275]	2015	Experimental	Dexamethasone injection	Laboratory mice	Expression of genes in olfactory mucosa positively affected by glucocorticoids
Haehner *et al.* [291]	2015	Cross-sectional, controlled	Rasagiline therapy	Patients with Parkinson's disease n=224	Rasagiline treated patients presented with significantly better odour discrimination when Parkinson's disease duration was less than 8 years
Schöpf *et al.* [292]	2015	Prospective, controlled	Intranasal insulin	Patients with post-infectious olfactory loss n=10	Immediate (short term) improvement of olfaction in 2 of 10;
Haehner *et al.* [293]	2013	Prospective, controlled	Rasagiline treatment	Patients with Parkinson's disease n=34	No significant improvement; however study end point not yet reached
Schriever *et al.* [270]	2012	Retrospective	Systemic methyl-prednisolone	All aetiologies of patients with smell loss n=425	Best improvement in patients with sinonasal disease, but also in other aetiologies

Lyckholm *et al.* [294]	2012	Prospective, controlled	Oral zinc	Chemotherapy-related smell disorders n=58	No improvement in smell loss
Reden *et al.* [295]	2012	Prospective, controlled	Vitamin A treatment	Patients with post-infectious and posttraumatic smell loss n=52	No significant effect
Henkin *et al.* [296]	2012	Prospective	Topical and systemic administration of theophylline	Patients with viral illness, allergic rhinitis, head trauma, congenital hyposmia, other chronic disease processes n=10	Oral theophylline treatment improved taste and smell acuity in 6/10 after 2-12 months. Intranasal theophylline treatment improved taste and smell acuity in 8/10 after 4 weeks
Reden *et al.* [297]	2011	Prospective, controlled	Minocycline treatment	Patients with post-infectious smell loss	No significant effect

				n=55	
Panagiotopoulos *et al.* [287]	2011	Prospective	Sodium citrate buffer solution to the nasal cleft	Patients with unspecified olfactory loss (5), head trauma (1), nasal surgery (7) and post-infectious (18), n=31	Measured improvement in 97% of patients with one hour; 74% noticed improvement
Jiang *et al.* [271]	2010	Prospective	Oral high-dose steroids	Posttraumatic anosmia n=116	Improvement in some patients; possibly spontaneous recovery
Henkin *et al.* [280]	2009	Prospective	Systemic administration of theophylline in increasing doses over 2-8 months	Patients with smell loss n=312	Subjective smell loss improved in 157 patients (50.3%)
Gudziol & Hummel [279]	2009	Prospective	Pentoxifylline, either i.v. or orally	Patients being treated for otological conditions n=19	Improvement in odour thresholds

Seo *et al.* [273]	2009	Prospective, controlled	Corticosteroids combined with Ginkgo biloba	Patients with post-infectious smell loss n=71	Similar improvement both in treatment with corticosteroids combined with Ginkgo biloba and in treatment only with corticosteroids
Heilmann *et al.* [274]	2004	Prospective	Oral prednisolone; local corticosteroids; systemic Vitamin B	Patients with olfactory dysfunction (differing aetiologies) n=192	Improvement following systemic and local corticosteroids; also improvement with systemic Vitamin B after 6 months
Quint *et al.* [298]	2002	Prospective, controlled	Caroverine application	Non-conductive olfactory disorders n=77	Significant improvement of odour identification
Hummel *et al.* [299]	2002	Prospective	Oral application of alpha-lipoic acid	Olfactory loss following respiratory infections n=23	Significant improvement of olfaction; more pronounced in patients <60 years of age

Table 6:

Author	Year	Study Type	Study Population; N	Results
Olfactory training				
Konstantinidis *et al.* [308]	2016	Prospective, controlled	Post-infectious olfactory loss n=111	Both short (16 weeks) and long term (56 weeks) training produced significantly improved olfactory function compared with control - with long term significantly better than short
Negoias *et al.* [309]	2016	Prospective, controlled	Healthy participants	Unilateral olfactory training produced significant increase in bilateral OB volume
Poletti *et al.* [310]	2016	Prospective	Post-infectious and posttraumatic olfactory loss n=96	Training with light molecular weight molecules produced significantly improved PEA threshold compared to heavy weight

				molecules
Kollndorfer *et al.* [311]	2014	Prospective, controlled	Post-infectious anosmia n=7	Olfactory training induced changes in functional connectivity evidenced with fMRI
Altundag *et al.* [304]	2015	Prospective, controlled	Post-infectious olfactory loss n=85	Longer olfactory training with change of odour was effective for odour discrimination and identification
Mori *et al.* [312]	2015	Prospective, controlled	Healthy children (age 9-15) n=72	Improved threshold and identification in training group compared with non-training
Damm *et al.* [303]	2014	Prospective, controlled	Post-infectious olfactory loss n=144	Olfactory training was significantly more effective with high concentration of odours and dysfunction <12 months
Geißler *et al.* [302]	2014	Prospective	Post-infectious olfactory loss n=39	Longer duration of (≥32 weeks) increased effectiveness of training

Konstantinidis *et al.* [305]	2013	Prospective, controlled	Post-traumatic and post-infectious olfactory loss n=119	Significant improvement in both groups
Haehner *et al.* [301]	2013	Prospective, controlled	Patients with Parkinson's disease n=70	Significant increase in olfactory function
Fleiner *et al.* [306]	2012	Retrospective	Olfactory loss of differing aetiologies n=46	Improvement of olfaction
Hummel *et al.* [300]	2009	Prospective, controlled	Patients with olfactory dysfunction excluding sinonasal disease n=56	Improvement of olfactory sensitivity
Wang *et al.* [307]	2004	Prospective, controlled	Patients anosmic to androstenone n=33	Increased sensitivity following repeated exposure

Table 7:

Author	Year	Study Type	Treatment Method	Study Population; N	Results
			Surgery		
Morrissey *et al.* [334]	2016	Retrospective	Surgical resection of olfactory neuroepithelium	Patients with peripheral phantosmia n=3	Resolution of phantosmia
Hanci *et al.* [331]	2016	Prospective	Laparoscopic Sleeve Gastrectomy	Morbidly obese patients with smell disorder n=54	Improvement of olfaction following surgery
Randhawa *et al.* [329]	2016	Prospective	Functional septorhinoplasty	All patients listed for functional septorhinoplasty n=43	Statistically significant improvement in screening odour identification scores, but no proven clinical benefit
Altun *et al.* [335]	2015	Prospective	Nasal septal perforation repair	Patients with septal perforation and smell disorder	Improvement in olfaction with successful closure of

				n=42	defect; closure success in 92.8%
Razmpa *et al.* [212]	2013	Prospective	Aesthetic septorhinoplasty	Patients with normal olfaction and no nasal functional abnormalities n=102	No significant change in odour identification scores post-operatively
Schriever *et al.* [326]	2013	Prospective	Septoplasty ± reduction of turbinates	All patients listed for nasal septal/turbinate surgery n=44	No significant improvement in olfactory function at 3.5 months
Richardson *et al.* [330]	2012	Prospective	Gastric bypass surgery	Morbidly obese patients n=55	Gastric bypass patients were more likely to have olfactory dysfunction pre-operatively than controls, but function was not affected by surgery

Pade *et al.* [73]	2008	Prospective	Septoplasty ± reduction of turbinates	All patients listed for nasal septal/turbinate surgery n=150	At mean 4 months post op: 13% improved function, 81% stable function, 7% deterioration in function
Philpott *et al.* [187]	2008	Prospective	Nasal surgery	Patients undergoing nasal surgery (differing aetiologies) n=80	Most marked improvement in septoplasty group
Leopold [336]	2002	Review article	Intranasal removal of olfactory epithelium	Patients with phantosmia n=18	Resolution of phantosmia in all but one patient
Leopold *et al.* [332]	1991	Prospective	Intranasal removal of olfactory epithelium	Patient with unilateral phantosmia n=1	Resolution of phantosmia and return of olfactory function
Stevens *et al.* [337]	1985	Prospective	Nasal surgery	Patients undergoing nasal surgery (differing aetiologies) n=100	Similar numbers of improved olfaction and no change in olfaction

LEGENDS FOR TABLES:

Table 1: Definitions of terminology used in olfactory research/practice.

Table 2: Definition of olfactory dysfunction according to anatomical location of lesion.

Table 3: Abbreviated list of agents and medications that affect olfaction (adapted from ref [16,136–143])

Table 4: Different psychophysical tests available.

Table 5: Summary of current clinical and experimental evidence for medication therapy in olfactory dysfunction (adapted from ref [290]).

Table 6: Summary of current evidence for olfactory training (adapted from ref [290]).

Table 7: Summary of current evidence regarding the utility of surgery in olfactory dysfunction (adapted from ref [290]). Evidence regarding surgery for CRS has not been included as this has been extensively described elsewhere (e.g. [86]).