Position paper on olfactory dysfunction*

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Abstract

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 for smell loss 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 the full set of recommendations are outlined in the main document, points include the following:

- Patients with suspected olfactory loss should undergo a full examination of the head and neck, including rigid nasal endoscopy with small diameter endoscopes.
- 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.

Statement: All authors agree on the sections entitled "recommendations".

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. Definitions of terminology used in olfactory research/practice.

Term	Olfactory function and dysfunction
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 odour (i.e. distorted perception of an odour stimulus).
Phantosmia	Qualitative dysfunction in the absence of an odour (i.e. an odour is perceived without concurrent stimulus, an 'olfactory hallucination').
Orthonasal olfaction	The perception of odour anteriorly due to airflow from the nostrils to the olfactory clefts, e.g. during sniffing.
Retronasal olfaction	The perception of odour 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.

*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 (GA2LEN) 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 Odour 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 [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.

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.

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

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.

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. 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 com-

mon 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 immunohisto-chemical 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.

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

Table 3. Abbreviated list of agents and medications that have been reported to affect olfaction. Adapted from ref: [16,136–143].

Agents	Medications
Acids	Anaesthetics (local)
Benzene	• Cocaine hydrochloride
Cadmium	• Procaine hydrochloride
Chlorine	• Tetracaine hydrochloride
Ethyl acetate	
Formaldehyde	Antimicrobials
Hydrazine	• Aminoglycosides
Hydrogen sulphide	• Macrolides
Lead	• Penicillins
Mercury	• Tetracyclines
Nitrous gases	• Terbinafine
Paint solvents	
Silicon dioxide	Antithyroid medications
Trichloroethylene	• Propylthiouracil
Zinc gluconate	• Thiouracil
	Chemotherapy
	Alpha-Receptor Antagonists

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 B12 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 post-traumatic 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 hard-wood 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 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 a form of threshold 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 odour 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 odour 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].
c
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. 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.

Table 4. Different psychophysical tests.

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

Olfactory testing in children

Measuring olfactory ability in children can be challenging since attention span can be limited and, for example, pairing of odour names with smells may be age and location dependent [122]. 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 odours 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) [117,232].

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 medicolegal 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 opaci-

fication 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.

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

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

Author	Year	Study Type	Treatment Method Medication	Study Population; N	Results
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 sino-nasal disease, but also in other aetiologies

Author	Year	Study Type	Treatment Method	Study Population; N	Results
			Medication		
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	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 monthsv
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

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].

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).

Surgery

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

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

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; n=97	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

generally improves following functional endoscopic sinus surgery [73,188,210,219,220,258,260,315–327]. 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. A recent study examining olfactory outcomes after surgery for CRS utilised the QOD-NS questionnaire and 40-item SIT, and demonstrated greatest improvement 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.

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.

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.

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

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
Altun 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; n=42	Improvement in olfaction with successful closure of 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	Nasal surgery	Patients undergoing nasal surgery (differing aetiologies); n=80	Most marked improvement in septoplasty group
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

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