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Olfactory implants: international opinion paper on emerging technologies and clinical applications

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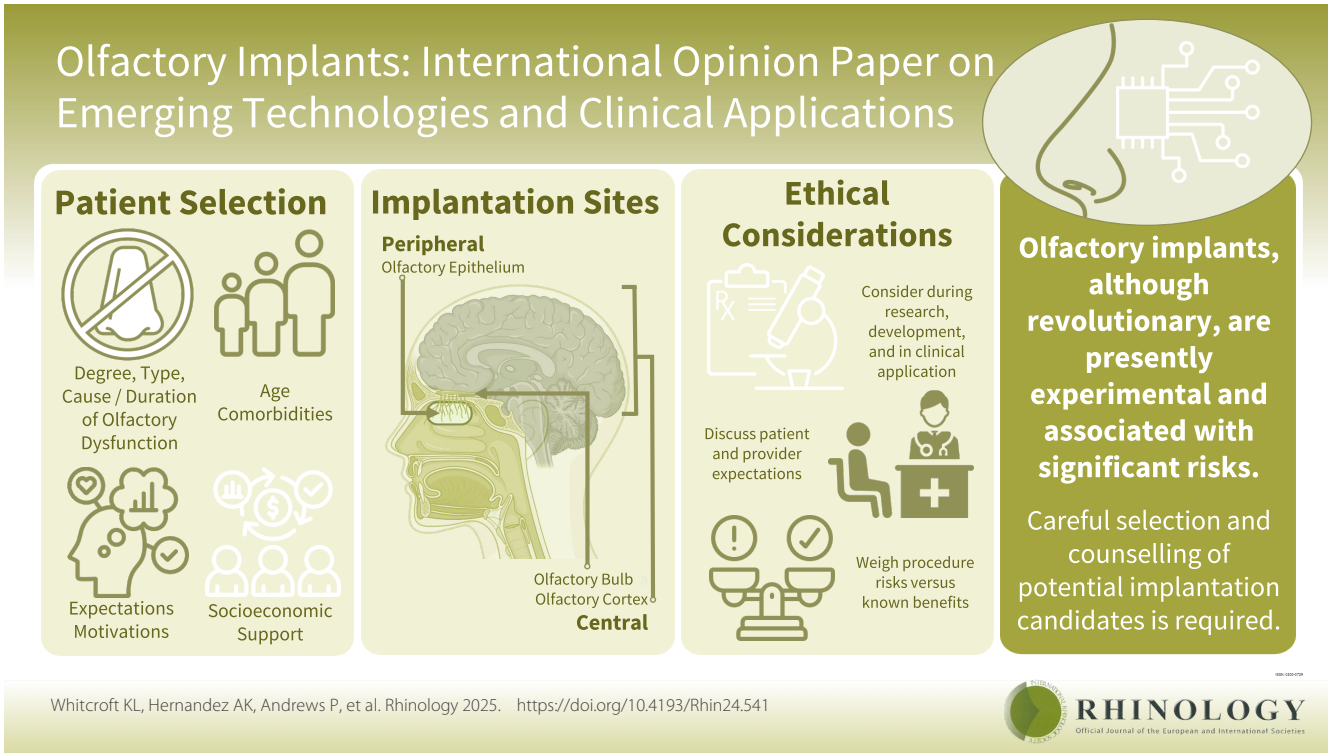
Abstracts

Abstract

Olfactory dysfunction affects a large proportion of the general population and causes significant personal and societal burden. At present, there are limited treatment options available. Though as yet experimental and untested in people, olfactory implants are a novel form of neuroprosthesis, modelled on existing implants for other sensory deficits such as hearing loss. Advances in this field have been rapid, yet there have been no unified efforts to collate current knowledge or guide such advances towards maximum patient benefit. In this Opinion Paper, leaders in the field have come together to provide an overview of current and emerging knowledge and technology relating to olfactory implants. In an effort to guide innovation towards maximum patient benefit, we also provide expert agreed statements on theoretical clinical aspects of olfactory implantation, including patient selection, implantation sites and potential complications, as well as post-implantation support requirements. Technical aspects will be discussed, with a clinical, device orientated focus. Finally, the ethics of olfactory implantation will be considered. We hope this document will serve as a useful roadmap to guide future clinical and basic research in the field.

Key words: Olfaction, anosmia, hyposmia, olfactory implant, neuroproesthesis



Contents

Abbreviations

AP	Action potential
CRS	Chronic Rhinosinusitis
CSF	Cerebrospinal Fluid
DBS	Deep Brain Stimulation
ECoG	Electrocorticography
ENT	Ear Nose Throat (Otolaryngology)
OB	Olfactory Bulb
OD	Olfactory Dysfunction
OE	Olfactory epithelium
OFC	Orbitofrontal Cortex
OI	Olfactory Implant
OSN	Olfactory Sensory Neuron
OT	Olfactory training
PC	Piriform Cortex
PIOD	Post-infectious Olfactory Dysfunction
PTOD	Post-traumatic Olfactory Dysfunction
sEEG	Stereo-electro-encephalography
SND	Sinonasal Disease

Summary of statements

Below is a summary of the statements contained within this document, and their associated Delphi outcome.

Statement 1:

1. Factors to consider regarding eligibility for olfactory implant (OI), include:

1.1. The degree of olfactory loss

- Delphi result: Agreed (score 7-9 = 100%, mean score 8.8)

1.2. Cause of olfactory loss

- Delphi result: Agreed (score 7-9 = 89.5%, mean score 8.2)

1.3. Duration of olfactory loss

- Delphi result: Agreed (score 7-9 = 87%, mean score 7.9)

1.4. Patients' age / cognitive function

- Delphi result: Agreed (score 7-9 = 73.7%, mean score 7.6)

1.5. Volume of the olfactory bulb (OB) (particularly where the OB is stimulation target)

- Delphi result: No consensus (score 7-9 = 68.4%, 1-3 = 13.2%, mean score 7.03)

1.6. Expectations and motivation of patient

- Delphi result: Agreed (score 7-9 = 97.4%, mean score 8.5)

1.7. Socioeconomic support system to allow for post-operative olfactory rehabilitation

- Delphi result: Agreed (score 7-9 = 92.1%, mean score 7.8)

Statement 2:

2. Patients being considered for OIs should undergo full clinical and psychophysical assessment in line with current guidelines. In brief, this should include:

2.1. Standard, detailed clinical history – with particular focus on establishing underlying cause of olfactory dysfunction (OD)

- Delphi result: Agreed (score 7-9 = 100%, mean score 8.9)

2.2. Subjective olfactory assessment, ideally to include a validated questionnaire (e.g., Questionnaire of Olfactory Dysfunction) or other recognised form of subjective assessment (e.g. visual analogue scale [VAS]). Identification of parosmia is important, as this may be associated with higher rates of spontaneous recovery

- Delphi result: Agreed (score 7-9 = 89.5%, mean score 8.4)

2.3. Full ear, nose, and throat (ENT) examination, including nasal endoscopy, with careful inspection of the olfactory cleft as anatomical variations may complicate potential electrode placement

- Delphi result: Agreed (score 7-9 = 97.4%, mean score 8.8)

2.4. Psychophysical assessment using a tool that has been validated for the target population and allows categorisation of severity. Ideally, this should test odour threshold and identification or discrimination.

- Delphi result: Agreed (score 7-9 = 92.1%, mean score 8.6)

2.5. Screening for cognitive impairment and psychiatric conditions. Patients with positive screening tests should undergo further assessment.

- Delphi result: Agreed (score 7-9 = 89.5%, mean score 8.3)

Statement 3:

3. Patients being considered for OIs should undergo

3.1. CT of the nose, paranasal sinuses and anterior cranial fossa to delineate bony anatomy.

- Delphi result: Agreed (score 7-9 = 97.4%, mean score 8.7)

3.2. High resolution magnetic resonance imaging (MRI) to cover the OBs, primary and secondary olfactory networks to delineate normal and abnormal anatomy and suitability for implantation.

- Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.7)

3.3. Angiography to delineate associated vascular structures at risk of injury during implantation.

- Delphi result: No consensus (score 7-9 = 55.3%, 1-3 = 13.2%, mean score 6.6)

Statement 4:

4. All patients should have tried and failed existing treatments in line with current guidelines.

4.1. In all patients except those with sinonasal disease (SND), this should include an extended period of olfactory training (≥3 months).

- Delphi result: Agreed (score 7-9 = 92.1%, mean score 8.4)

4.2. In suspected SND/idiopathic OD, a trial of systemic/intranasal corticoste roids (with appropriate choice of intranasal delivery system) ± nasal surgery should be considered.

- Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.1)

Statement 5:

5. All patients being considered for OI candidacy should undergo a period of multidisciplinary pre-implantation counselling.

- Delphi result: Agreed (score 7-9 = 92.1%, mean score 8.2)

Statement 6:

6. Thorough pre-operative assessment should be undertaken in all patients in whom OI candidacy is considered.

6.1. Absolute and relative contraindications can only be fully defined once device specifics are known, but are likely to include significant co-morbidity, blood dyscrasias and unfavourable anatomy. More generally, individual patient factors should be considered when weighing potential benefits

versus risks of implantation.

• Delphi result: Agreed (score 7-9 = 92.1%, mean score 8.3)

6.2. To mitigate the risk of complications patients should undergo thorough pre-operative assessment/investigation, and surgery should be undertaken by experienced surgeons.

• Delphi result: Agreed (score 7-9 = 100%, mean score 8.8)

6.3. Future studies, prototypes, or simulations should inform future surgical planning to minimise risk of complications and optimise outcomes.

• Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.5)

Statement 7:

7. Patients should undergo a structured programme of olfactory rehabilitation post implantation

7.1. This should include device programming with initial 'safety' odours, followed by commonly encountered odours.

• Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.2)

7.2. Patients should receive multi-disciplinary support during this time.

• Delphi result: Agreed (score 7-9 = 97%, mean score 8.6)

7.3. Standardised outcome measure should be collected at regular post-implantation intervals, including psychophysical tests, patient-reported outcome measures, and tests for cognition/depression.

• Delphi result: Agreed (score 7-9 = 97%, mean score 8.8)

7.4. Complications monitoring including, where indicated, CT scans should be undertaken at regular post-implantation intervals where indicated.

• Delphi result: Agreed (score 7-9 = 81.6%, mean score 7.9)

7.5. Standardised database reporting should be undertaken for safety, and ideally outcomes assessment including a position map of odours for possible optimization of electrode position.

• Delphi result: Agreed (score 7-9 = 97%, mean score 8.5)

Statement 8:

8. Efficacy of stimulated olfactory perception and impact of OD pathophysiology should be taken into account when considering potential stimulation sites:

8.1. Olfactory epithelium: only limited work has shown successful olfactory perception following electrical stimulation. Inter-individual variation in distribution, and potential histological damage associated with OD, complicates stimulation at this site.

• Delphi result: Agreed (score 7-9 = 84.2%, mean score 7.7)

8.2. OB: work in animals and humans has demonstrated activation of the olfactory system following electrical stimulation. Glomerular 'mapping' in humans, and its degree of stereotypy, is at present unknown. Variations in size and shape associated with OD should be kept in mind when considering stimulation in this site.

• Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.3)

8.3. Central olfactory networks: some work has demonstrated olfactory perception following stimulation of upstream structures, though with low response rates. Central stimulation may be favourable in patients with significant damage to the OB. The multi-modal nature of central structures should be kept in mind when considering the efficacy of stimulated olfactory perception and potential side-effects.

• Delphi result: Agreed (score 7-9 = 97%, mean score 8.3)

Statement 9:

9. Regarding OI electrodes and stimulation paradigm:

9.1. Where the OB is target, ideally, the device should be able to connect a high-density microelectrode array of electrodes to address single glomeruli, should be flexible and small, for transcranial or transcribriform approaches, and is easily deployed and secured around the OB.

• Delphi result: Agreed (score 7-9 = 89.5%, mean score 8.1)

9.2. Where higher order olfactory structures are the target, currently available stimulation systems include depth electrodes (deep brain stimulation [DBS]), microelectrodes, and electrocorticography (ECoG) devices, which require different surgical approaches.

• Delphi result: Agreed (score 7-9 = 92.1%, mean score 8.3)

9.3. Ongoing research should address: the prolongation of microelectrode lifespan (through the lowering of electrode impedance and the use of novel material for electrodes and encapsulation); the reduction of foreign body reaction (matching the mechanical stiffness of conformal implants to the surrounding tissues and minimizing the electrode footprint); determining best method of implantation (single glomeruli, whole OB surface).

• Delphi result: Agreed (score 7-9 = 100%, mean score 8.6)

9.3.1. Active surveillance for complications secondary to persistent neurochemical, histological, and behavioural modifications resulting from electrode implantation should be undertaken.

• Delphi result: Agreed (score 7-9 = 100%, mean score 8.7)

9.4. Stimulation timing, sequence of oscillations and potential multiplicity of target site require further study, e.g., respiration-triggered sequences of oscillations aligned with specific time-locked electrical stimulation may best evoke reproducible olfactory precepts.

• Delphi result: Agreed (score 7-9 = 84.2%, mean score 8.0)

Statement 10:

10. The ethical implications of OI should be considered during research and development stages, as well as at the point of clinical application.

10.1. Patients should be consulted during the research/development phase to help inform device priorities.

• Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.6)

10.2. Standardized database reporting of surgical and device/treatment related complications should be undertaken.

• Delphi result: Agreed (score 7-9 = 100%, mean score 8.8)

10.3. Possibility of planned explantation of the device should be considered.

• Delphi result: Agreed (score 7-9 = 100%, mean score 8.7)

Introduction

The human sense of smell is important. Intact olfaction is required to guide nutrition, environmental hazard avoidance and social communication [1]. Accordingly, its dysfunction is linked with decreased quality of life, causing clinical depression in up to one third of patients [2]. Moreover, olfactory dysfunction (OD) is linked with important healthcare outcomes, including neurodegeneration and death [3]. The personal impact of OD is therefore significant.

Prior to the global COVID-19 pandemic, the estimated population prevalence of OD was 22% [2–5], of whom approximately 5% experience complete or near complete loss (anosmia). Different strains of SARS-CoV-2 have caused variable degrees of associated intercurrent acute and post-infectious dysfunction, meaning the true population prevalence of OD is dynamically evolving, and likely higher than these pre-pandemic figures. Nevertheless, using pre-pandemic estimates as a minimum, the societal burden of OD is significant – with anosmia being more common than profound deafness or blindness [5].

Despite this, prior to the pandemic, clinical and research interest in OD lagged behind other sensory impairments; total publications are fewer in olfaction compared with other senses (PubMed listings as of October 16, 2024: Vision – 267,787; Hearing – 173,941; Olfaction – 35,567) and the first Nobel Prize in this field was awarded to Linda Buck and Richard Axel in 2004 [6].

Accordingly, intervention options for olfactory impairment are limited, particularly when compared to sensory impairments such as vision or hearing. In the latter, amplification technologies are commonplace: approximately 2 million people in the UK use hearing aids [6], and those with more significant or complex hearing loss may have access to implanted prostheses, including bone anchored hearing aids, middle ear implants, cochlear implants and auditory brainstem implants. Almost three quarters of the UK adult population wear corrective lenses for refractive visual impairment. Approximately 10 million cataract operations are performed globally each year [7,8]. Visual prostheses are also an area of active research – with various ongoing projects targeting different sites along the visual pathway (from retina to visual cortex) [9]. Though much less common than cochlear implants, several retinal implants have received regulatory approval for use in patients.

Whilst the technology for detection of environmental odours exists, as does that required for electrical stimulation along the olfactory pathway – a unified olfactory implant (OI) is a relatively novel idea, with the first patent in this field being awarded to Costanzo and Coelho in 2016 (Figure 1) [7]. With the recent SARS-CoV2 pandemic-driven interest in OD, subsequent progress has, however, been rapid, with different international projects bringing experts in the field together.

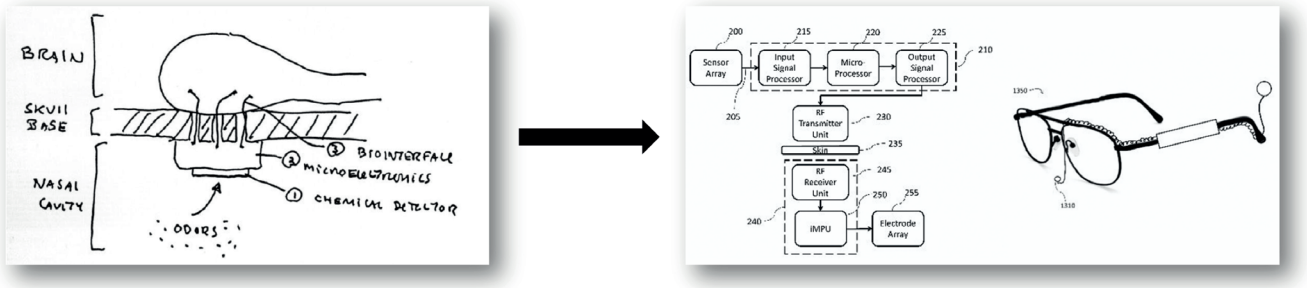
What: a brief introduction to olfactory implants

Putative OIs are currently modelled on neuroprostheses in other sensory modalities. In hearing, vision or the vestibular sense, such devices are structured around two components: first, sensors that can detect environmental stimuli (sounds, visual images, movements; odorant molecules for olfaction); second, processors and stimulators that translate this information into electrical impulses, which can be interpreted by the brain. In olfaction, the historical development of these two basic components, or modules, took place independently, in fields of research that rarely or never intersected.

The sensor module was first conceptualised by Persaud and Dodd in 1982 [8], who demonstrated that a network of electronic chemosensory sensors can be used to discriminate between simple and complex odours. These initial efforts sparked a series of projects, ultimately leading to the development of several types of artificial noses for applications in environmental monitoring, healthcare diagnostics, food quality control and safety. Typically, these sensors consist of a set of units that interact with volatile molecules carried by an air source [9,10]. Depending on the system, these sensors have traditionally comprised materials such as metal/oxide semiconductors, catalytic gases, solid electrolyte gases, polymers, or optical devices. Whilst such sensors vary in form and dimension depending on the technology used, sizes small enough to be contained within 'wearable' devices have already been achieved [11]. With advancing technology, more ecological 'bioelectric noses' have been developed, whereby the sensor contains specific olfactory receptors. Reaction of odorants with these receptor(s) results in signal generation, which is then transduced and processed for pattern recognition, which allows visualization of results based on a given classification system – whose accuracy and reliability depend on the quality and comprehensiveness of the data used to train the device [12]. In 2006, olfactory cell-based biosensors were developed, incorporating a system of microelectrodes to measure extracellular membrane potential changes generated by the interaction of olfactory receptors with odorants [13]. More recently, nanovesicles, created from cells or proteins related to signal transmission, have been used to replicate receptor-mediated signal transmission as observed in the human olfactory system [14]. For a more comprehensive overview of the history and development of bioelectronic noses, please refer to recent articles [12,15].

Regarding the neural stimulation module, knowledge in this field is limited, and has been generated largely by the neuroscientific community. In 1954, Penfield and Jasper demonstrated olfactory perception following electrical stimulation of the olfactory bulbs (OBs) of patients with epilepsy [16]. Following on from this, olfactory perception has also been demonstrated through electrical stimulation of other sites, including the olfactory epithelium, and upstream structures of the central olfactory networks. Each of the approaches described have their own associated advantages and disadvantages, and the success of their resultant olfactory perception appears dependent not just on stimulation target, but also on other aspects of the stimulation paradigm used.

Clinically useful OIs must combine cutting edge technology in both sensor and stimulation modules (Figure 2), in a way that



Hand-drawn sketch of putative olfactory implant

Invention Notebook 1D, p87 (14 Dec 1998)

Costanzo, Virginia Commonwealth University

Images from resultant US patent for 'Olfactory Implant System'

United States Patent 9,517,342 B2 (issued 13 Dec 2016)

Costanzo and Coelho, Virginia Commonwealth University

Figure 1. Historical overview of the development of the first patent for an 'olfactory implant system', issued to Costanzo and Coelho, Virginia Commonwealth University, 2016.

is safe and useful to patients. Precise stimulation target and surgical approaches to implantation – such as transcribriform or transcranial approaches, will be discussed in the following sections.

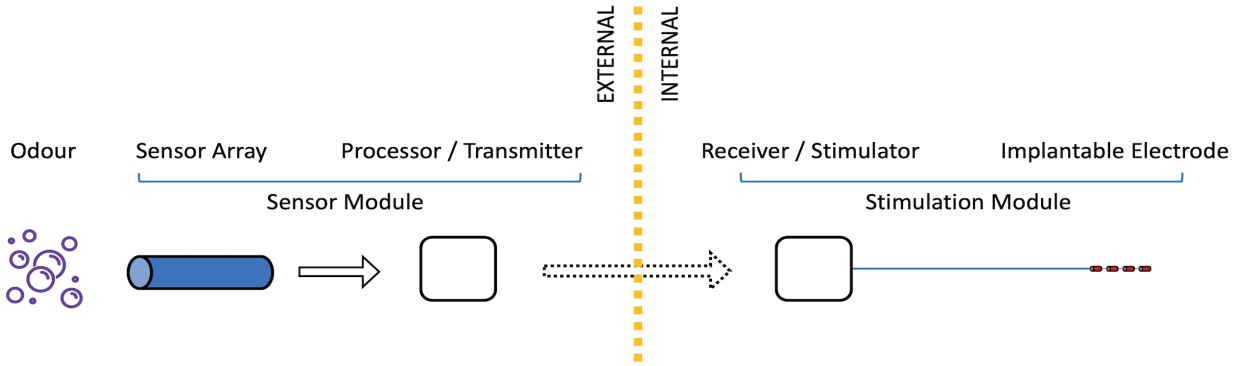


Figure 2. Schematic drawing of the principles of an OI system. Possible targets include the olfactory epithelium, olfactory bulb, piriform cortex, orbitofrontal cortex, amygdala, hippocampus, insula, and nucleus accumbens.

Why: broad aims of olfactory implantation

The needs of patients with OD range from comparatively simple, to highly complex. Identification of odours such as smoke, natural gas or its additives (e.g. mercaptan) or by-products of spoiled foods could help to prevent household accidents and illness, particularly in people with anosmia or more severe hyposmia [17]. More complex olfactory perception – such as is required for food enjoyment or social communication may be more difficult to replicate initially, in part due to the highly personal nature of such perception - which heavily relies on autobiographical/episodic memory and consequently 'higher processing'. However, replication of these more complex functions separates OI from existing 'bioelectronic noses', or devices that can detect environmental odours and alert patients with OD to their presence [12]. Whilst these devices may be helpful in environmental navigation and hazard avoidance, their use is limited to this. Through replication of the personal sensory experience of smell, olfactory implantation could impact on nutrition, mood and ultimately quality of life [1]. Furthermore, given the known link between OD and various medical conditions, such as neurodegeneration [18] and frailty [19], augmentation of the olfactory system through implantation could theoretically affect outcomes in these patients.

Accordingly, an early aim of the prototype olfactory implant is to provide levels of olfactory perception as would be required for environmental hazard avoidance. This is in line with recent survey results showing that patients prioritize regaining perception needed for environmental hazard avoidance, including the ability to detect spoiled foods [20,21]. However, with personalised device programming and advancing technology the ultimate aim of olfactory implantation is to produce levels of sensory function that allow meaningful appreciation of the recipient's olfactory environment. Later aims of OI may include characterisation of the downstream effects of olfactory system stimulation, for example on nutrition, mood, frailty and neurodegeneration.

Overview of document

The following document provides an overview of current and emerging knowledge and technology relating to OIs. In an effort to guide innovation towards maximum patient benefit, we provide expert agreed statements on theoretical clinical aspects of olfactory implantation, including patient selection, implantation sites and potential complications, as well as post-implantation support requirements. Technical aspects will be discussed, with a clinical, device orientated focus. Finally, the ethics of olfactory implantation will be considered.

Methodology

The current literature was systematically reviewed for relevant topics until July 2024. Databases included Medline (PubMed inception – current), Google Scholar (limited to first 1000 results), Embase (Jan 1958 – current), as well as the preprint servers MedRxiv and BioRxiv. Search terms were constructed using truncation, Boolean operators and MeSH mapping, as appropriate. Reference lists and citing literature were hand-searched. Finally, steering group discussions were undertaken at the meetings in Dubai in January 2023 and a specific Meeting on Olfactory Implants, Geneva, Switzerland in December 2023.

All included statements underwent a process of agreement using a modified Delphi process (RAND/UCLA methodology). Statements were initially drafted by the steering group and distributed to all co-authors for review. Authors were asked to score their agreement with the statements based on a category scale (1 – lowest level of agreement – to 9 – highest level of agreement). Results were classified as follows:
Agreed: ≥70% score 7-9, ≤15% score 1-3
Disagreed: ≥70% score 1-3, ≤15% score 7-9
No consensus: results falling between agreed and disagreed

Olfactory implantation: clinical considerations and patient candidacy

Background: what is olfaction and olfactory dysfunction

Under normal physiological circumstances, the human sense of smell requires intact peripheral and central olfactory networks. Following diffusion into the olfactory mucus layer within the nose, odorants activate olfactory receptors – G protein coupled receptors found on the dendritic cilia of olfactory sensory neurons (OSNs) [22]. This interaction is thought to be affected by components within the mucus itself, including odorant binding proteins, and a variety of other solutes that may aid in odorant metabolism [23,24]. The OSN are located within the olfactory epithelium of the olfactory cleft, and their axons (which collectively form Cranial Nerve 1) extend through the foramina of the cribriform plate to the OB, where they synapse with second order neurons (mitral and tufted cells) within specialised cellular regions called glomeruli. Mitral and tufted cell axons then extend to regions of the primary olfactory network, which in turn connects with the secondary olfactory network [25] (Figure 3).

During normal homeostatic conditions, and in response to injury (important given their exposed position), OSN are capable of regeneration from a population of stem cells found within the OE. Such neurogenesis continues into adulthood [26] and mirrors, at least in non-human mammals, neurogenesis within the subventricular zone and the OB [27]. Impairments in this regenerative potential by certain pathological conditions, can also lead to OD and, in addition, underlie spontaneous recovery in some conditions, such as post-infectious OD [25].

The mechanisms by which odour quality is encoded have not yet been fully delineated. Whilst the human olfactory receptor (OR) gene family comprises approximately 400 active genes,

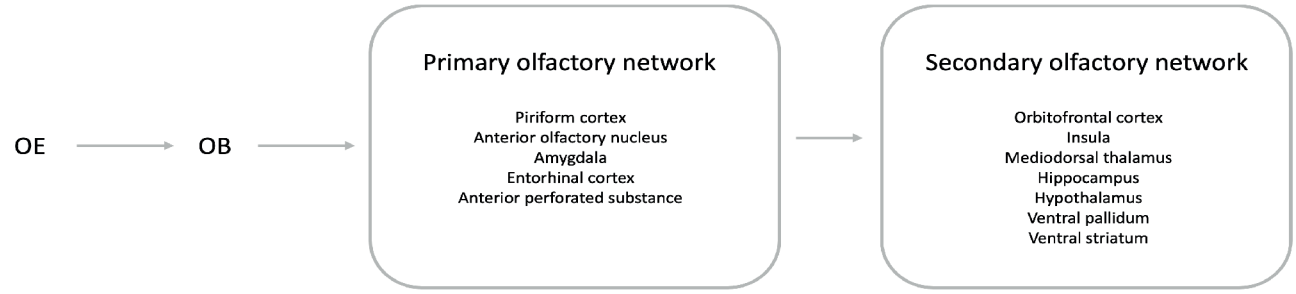


Figure 3. Overview of peripheral and central olfactory networks (modified from ref 18). OE = olfactory epithelium, OB = olfactory bulb.

people can potentially detect millions of distinct odorants [28–30]. This is in part facilitated by complex combinatorial encoding – wherein odour ligands are recognised by a unique combination of OR, and at which they may function as agonists, partial agonists or antagonists. Consequent 'neural fingerprints' are likely further augmented by the unique spatiotemporal characteristics of odour binding, which are determined by an odour's physiochemical properties and those of the nose, nasal mucus layer and OR. Based on rodent models, each glomerulus receives axons from OSNs expressing the same OR type [31,32] – in this way, the pattern and timing of glomerular activation may reflect odour quality, though it is unclear whether this is stereotyped between people. Further tuning of the neural signal may involve top-down input and other excitatory or inhibitory modulation at the level of the primary or secondary olfactory networks. In short, the precise pattern of neural activation and subsequent perceptual quality associated with a particular odour is difficult to predict. Therefore, a patient with an OI is likely to undergo trial and error sessions for implant programming or 'calibration'.

Regarding airflow, olfaction is possible through two routes: orthonasal olfaction allows detection of environmental odours via antero-posterior airflow (as in breathing/sniffing) and retronasal olfaction allows detection of odours located within the mouth and oropharynx through postero-anterior airflow (facilitated by chewing/swallowing) [25]. Integration of retronasal olfaction with gustatory, chemesthetic and somatosensory sensations forms the basis of the flavour percept. Patients with OD usually experience impairment of both orthonasal and retronasal perception – though in some cases differential levels of impairment may occur. Further, due to its role in the flavour percept, many patients with OD report this as abnormal or impaired 'taste'.

Olfactory dysfunction can be broadly divided into quantitative and qualitative dysfunction. The former describes alteration in the intensity of odours (hyposmia – reduced perception, anosmia – absent perception), whilst the latter describes either altered perception of odour quality (parosmia), or perception of odour in the absence of an odour stimulus (phantosmia) [33]. The alterations of odour quality in qualitative dysfunction are usually described as unpleasant. In most cases, quantitative and qualitative OD co-exist. Parosmia and phantosmia also often occur together, but may also occur independently. See Table 1 for a full set of definitions.

Whilst OD can be attributed to numerous different underlying causes, pre-pandemic work from specialist centres showed that (excluding age-related OD), approximately two-thirds of cases were due to sinonasal, post-infectious or post-traumatic aetiologies. These, and other common causes of OD are listed in Table 2 [34,35]:

Table 1. Definitions, adapted from [1,2].

Orthonasal olfaction	The perception of odorants anteriorly due to airflow from the nostrils to the olfactory clefts, e.g., during sniffing
Retronasal olfaction	The perception of odorants located within the oropharynx, caused by airflow to the olfactory clefts via the nasopharynx during swallowing or nasal exhalation
Normosmia	Normal olfactory function
Hyposmia	Quantitatively reduced olfactory function
Anosmia	Quantitatively reduced olfaction to the extent that the subject has no function that is useful in daily life
Hyperosmia	Quantitatively increased ability to smell odours
Olfactory intolerance	Qualitative olfactory dysfunction where individuals, without odour distortions, complain of a subjectively enhanced sense of smell and are intolerant to everyday odours
Parosmia	Qualitative olfactory dysfunction where individuals, without odour distortions, complain of a subjectively enhanced sense of smell and are intolerant to everyday odours
Phantosmia	Qualitative dysfunction in the presence of an odorant (i.e., distorted perception of an odour stimulus)
Phantosmia	Qualitative dysfunction in the absence of an odorant (i.e., an odorant is perceived without concurrent stimulus, an 'olfactory hallucination')

The ideal patient for OI

The ideal candidate for implantation cannot be fully defined without knowledge of device specifics, such as stimulation target and surgical approach. At this early stage, therefore, candidacy can only be discussed in general terms. With this in mind, the following should be considered.

Table 2. Common causes of OD.

Condition	Examples (where relevant)
Sinonasal disease (SND)	e.g. Chronic rhinosinusitis (± nasal polyposis)
Post-infectious OD	e.g. SARS-CoV-2 and non-SARS-CoV-2 pathogens (PIOD)
Post-traumatic OD	
Aging	
Neurological disease	e.g. Parkinson's and Alzheimer's disease
Congenital OD	
OD associated with drugs/toxins	
Idiopathic OD	
Other	e.g. iatrogenic, tumours, systemic co-morbidities etc.

1) The degree and type of olfactory loss

An important question is whether OI should only be considered for people with complete anosmia or also in people with some remaining olfactory function. The former is most often found in relation to head trauma, or congenital anosmia [36]. In other aetiologies, for example in PIOD – it is unclear how many patients have no residual function, as many report vague olfactory sensations that are difficult to describe, and almost impossible to capture using current olfactory tests [34]. Indeed, the presence or absence of olfactory perception cannot be objectively determined with absolute certainty, even through use of our most advanced available techniques (including functional neuroimaging and olfactory event-related potentials, in which both false positives and false negatives are seen [37]). Therefore, if complete anosmia is a required criterion for OI candidacy (with associated patient motivation being higher in this group [38]) careful assessment is needed, as will be described below.

In early phases of development, achievable olfactory perception and consequent benefit to risk ratio may not be sufficient to justify implantation in patients with milder degrees of impairment. However, as with cochlear implants, advances in technology (i.e., decreasing implantation risks leading to broader indications) may mean such patients will be eligible in the future.

The presence of purely quantitative, qualitative or mixed olfactory impairment should also be considered. In patients with severe quantitative dysfunction, the presence of parosmia indicates residual olfactory function [39], and possibly a better chance of spontaneous recovery than in those with anosmia without parosmia [40–43]. It should be noted, however, that the underlying pathophysiology of parosmia and phantosmia remains unknown. Considering the 'miswiring hypothesis' of parosmia (in which incorrect or incomplete axonal targeting from OSN to OB is thought to occur) – though speculative – the possibility that such patients could have more negative/unpleasant percepts following implantation should be considered [44]. At present, therefore, it is unclear whether patients with purely qualitative dysfunction would benefit from implantation, and further research in this patient group is needed.

2) The cause of olfactory loss

Although more specific considerations require details of the device to be implanted, the cause of OD will affect OI candidacy. Underlying pathophysiology and its associated anatomical ± functional effects on the peripheral/central olfactory system may both affect long term prognosis and suitability for stimulation at different sites. For example, in OD associated with chronic rhinosinusitis (CRS), pathophysiology is thought to be due to initial inflammatory-related dysfunction at the level of the OR, followed by eventual histological remodelling of the olfactory epithelium (OE) ± upstream neuroanatomical changes in regions such as the OB [45–50]. Accordingly, both general and olfactory-specific outcomes are better when treatment is started early, though recovery after long periods of established disease is possible. Stimulation at the OE may not be appropriate or effective in people with marked ongoing inflammation, though bypassing sinonasal disease (for example refractive polyps or scarring due to previous surgery) through stimulation at the OB or further upstream, may potentially be of interest. In PIOD, though pathophysiological mechanisms are still being explored, potentially reversible damage at the level of the OR ± OE likely occurs early in the disease process, which is followed by histological remodelling and potential upstream neuroanatomical changes [51]. Spontaneous recovery occurs relatively frequently in PIOD, likely due to reversible early pathophysiology ± ongoing or renewed neurogenesis. Indeed, it is thought that one third or more of patients experience spontaneous recovery within the first 2-3 years of disease [52,53]. Similar to CRS, stimulation at the OE may not be effective due to underlying disease mechanisms, although this is a theoretical possibility at this time. In conditions in which spontaneous recovery is possible, device adaptations to allow such recovery to occur unincumbered should be considered.

The prognosis in other aetiologies of OD is more guarded. In PTOD, whilst some degree of recovery has been suggested in up to 30% of patients, full recovery is unusual [54–58]. This likely relates to the underlying mechanisms of OD after head injury – which vary from OSN axonal transection to intra-parenchymal haemorrhage, contusion, and gliosis. Whilst ongoing neuro- and axonogenesis may allow reconnection of OSN to the OB, scar tissue at the level of the cribriform plate may impair this process, with central lesions being potentially permanent. However, case reports exist suggesting that delayed recovery is possible in select cases of PTOD [59]. Therefore, in addition to duration of OD, patients with PTOD should undergo sufficient investigation to delineate central lesions and their possible interference with either the implantation device itself, or upstream olfactory processing.

The exact pathophysiology underlying OD due to aging or neurodegeneration are not fully understood. However, it likely involves either widespread progressive changes or primarily central mechanisms. Currently, there is no way to reverse the degeneration that has already occurred. Similar to PTOD, central pathology may prevent appropriate upstream olfactory processing. Implantation for the purposes of olfactory perception in these patients would likely represent a more complex challenge. Similarly, patients with congenital OD, in whom central processing is likely to be divergent from those with normal developmental olfaction, it is unclear whether stimulation at the OE /

OB (in cases of hypoplastic OBs) or even higher order structures would produce olfactory perception comparable to patients with acquired loss.

(3) The duration of olfactory loss

In patients eligible for OI, their impairment should be of sufficient duration that spontaneous recovery, or recovery through treatment, is unlikely. As outlined above, in conditions such as PIOD recovery usually occurs within the first 2-3 years of disease. Indeed in medico-legal investigations, 2 years is commonly cited as the duration beyond which recovery is unlikely [60]. Given the invasive nature of OI, and potential associated risks, a minimum duration of more than 2-3 years from onset of OD would be a prudent duration prior to consideration of OI candidacy except in cases of intentional intraoperative sacrifice of olfactory structures where total bilateral loss is expected. However, the rare possibility of spontaneous recovery after this point should be explained and discussed with all patients being considered for OI. Minimum levels of treatment prior to consideration of OI will be discussed in the section on Treatment of OD Prior to Consideration of OI. With this in mind, it should also be considered that, similar to hearing, a longer period of sensory deprivation could lead to reorganization of central olfactory structures (e.g. lower grey matter), thus reducing performance of OI rehabilitation. Furthermore, the OB over time may become hypoplastic, making implantation very difficult [61,62]. Therefore, very long durations of OD may not be favourable for implantation.

(4) Age and comorbid status

Studies focusing on hearing have demonstrated that the brain retains some neuroplasticity even up to advanced age [63]. Although ageing is associated with worse olfactory function [64], older individuals have been shown to benefit from olfactory training, not only in terms of improvements in olfactory function but also in verbal function and subjective well-being [65]. However, some work has demonstrated no such effect for age in relation to improvements in OB volume after olfactory training [66]. Depending on the actual device installed and the amount of surgery required, patients eligible for OI should be otherwise generally healthy, sufficient at least to undergo the general anaesthetic required during surgical implantation, and to support good cognitive adaptation to their device thereafter. General health and cognition tend to deteriorate with age – and though a maximum age for implantation would be arbitrary – those of more advanced age should be carefully screened and normal scores in standard cognitive tests should be obtained.

(5) The condition of the OB

Where the OB is the stimulation target, its volume and shape should be assessed. It has been shown that OB volume decreases in relation to the degree and the duration of olfactory loss, although this does not necessarily directly correlate with outcomes in OD. Most patients with congenital anosmia have agenesis of the OB [67,68], and in many patients with PTOD, the OBs are not visible in MRI scans [69,70]. However, OB volume has been shown to increase in association with improved olfactory function [71].

As a rule, in candidates being considered for implantation using the OB as target, the OBs should be visible on high resolution MRI.

(6) Patient expectations and motivation

Initial survey work has suggested that approximately one-third of patients with OD would consider OI, even if this involved a neurosurgical approach [38]. With greater knowledge of available devices and implantation technique, and thereby more detailed counselling, this proportion could potentially change.

(7) Social/economic support for ongoing rehabilitation

If the patient qualifies for 1.1 through 1.6, but does not have the appropriate socioeconomic support to enable return for post-operative rehabilitation, they might not be considered a good candidate. For comparison, this is critical in cochlear implant candidacy [72,73].

Statement 1:

1. Factors to consider regarding eligibility for olfactory implant (OI), include:
   - 1.1. The degree of olfactory loss
     - Delphi result: Agreed (score 7-9 = 100%, mean score 8.8)
   - 1.2. Cause of olfactory loss
     - Delphi result: Agreed (score 7-9 = 89.5%, mean score 8.2)
   - 1.3. Duration of olfactory loss
     - Delphi result: Agreed (score 7-9 = 87%, mean score 7.9)
   - 1.4. Patients' age / cognitive function
     - Delphi result: Agreed (score 7-9 = 73.7%, mean score 7.6)
   - 1.5. Volume of the olfactory bulb (OB) (particularly where the OB is stimulation target)
     - Delphi result: No consensus (score 7-9 = 68.4%, 1-3 = 13.2%, mean score 7.03)
   - 1.6. Expectations and motivation of patient
     - Delphi result: Agreed (score 7-9 = 97.4%, mean score 8.5)
   - 1.7. Socioeconomic support system to allow for post-operative olfactory rehabilitation
     - Delphi result: Agreed (score 7-9 = 92.1%, mean score 7.8)

Diagnosis of OD and pre-implantation assessment

Olfactory function can be assessed using different techniques ranging from clinical history to functional imaging and electrophysiology. Importantly, however, the accuracy of olfactory

assessment varies according to the technique employed. In particular, unstructured subjective assessment has been shown to poorly correlate with measured olfactory function. Accordingly, all recent international guidelines recommend against use of isolated clinical history for the assessment of olfaction [43,74]. Rather, subjective assessment should be combined with psychophysical testing, which is considered the clinical and research standard. Unfortunately, a recent survey of international practice in the assessment of olfaction demonstrated that most clinicians do not perform psychophysical testing [75]. This is problematic – inaccurate assessment may lead to incorrect diagnoses, inappropriate treatment planning and meaningless outcomes measurement. When considering invasive treatment strategies such as OIs, it is therefore imperative that potential patients are thoroughly assessed according to current guidelines. Furthermore, assessment of severity of OD is important in order to guide OI candidate selection.

Statement 2:

2. Patients being considered for OIs should undergo full clinical and psychophysical assessment in line with current guidelines. In brief, this should include:

2.1. Standard, detailed clinical history – with particular focus on establishing underlying cause of olfactory dysfunction (OD)

• Delphi result: Agreed (score 7-9 = 100%, mean score 8.9)

2.2. Subjective olfactory assessment, ideally to include a validated questionnaire (e.g., Questionnaire of Olfactory Dysfunction) or other recognised form of subjective assessment (e.g. visual analogue scale [VAS]). Identification of parosmia is important, as this may be associated with higher rates of spontaneous recovery

• Delphi result: Agreed (score 7-9 = 89.5%, mean score 8.4)

2.3. Full ear, nose, and throat (ENT) examination, including nasal endoscopy, with careful inspection of the olfactory cleft as anatomical variations may complicate potential electrode placement

• Delphi result: Agreed (score 7-9 = 97.4%, mean score 8.8)

2.4. Psychophysical assessment using a tool that has been validated for the target population and allows categorisation of severity. Ideally, this should test odour threshold and identification or discrimination.

• Delphi result: Agreed (score 7-9 = 92.1%, mean score 8.6)

2.5. Screening for cognitive impairment and psychiatric conditions. Patients with positive screening tests should undergo further assessment.

• Delphi result: Agreed (score 7-9 = 89.5%, mean score 8.3)

Imaging

With regards to imaging – significant heterogeneity in clinical practice exists. In attempt to address this heterogeneity, recent guidelines provided recommendations for diagnostic imaging. However, in patients being considered for OI, structural assessment of the peripheral and central olfactory pathways should be undertaken, to include the nose, sinuses, OB, as well as the primary and secondary olfactory networks. Any abnormalities in these structures should be fully characterised, in order to determine such abnormalities' impact on potential electrode placement and/or implant function.

Imaging should also be performed at the time of surgery (ideally intraoperatively ± immediately postoperatively), in order to provide detailed information about precise electrode contacts and thereby stimulation targets. Perioperative and postoperative CT, as well as preoperative high-resolution MRI could be used for this purpose, as well as to enable image-guided navigation system use. Pre-operative angiography may also be considered, to delineate the course of vessels at potential risk during implantation. Given the associated invasive nature and potential risks of angiography, CT angiography (CTA) may be preferable in this context.

Statement 3:

3. Patients being considered for OIs should undergo

3.1. CT of the nose, paranasal sinuses and anterior cranial fossa to delineate bony anatomy.

• Delphi result: Agreed (score 7-9 = 97.4%, mean score 8.7)

3.2. High resolution magnetic resonance imaging (MRI) to cover the OBs, primary and secondary olfactory networks to delineate normal and abnormal anatomy and suitability for implantation.

• Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.7)

3.3. Angiography to delineate associated vascular structures at risk of injury during implantation.

• Delphi result: No consensus (score 7-9 = 55.3%, 1-3 = 13.2%, mean score 6.6)

Treatment of OD prior to consideration of OI

Prior to consideration of OI, potential candidates should undergo appropriate treatment according to current guidelines. At present, for all underlying causes of OD, with the exception of SND (for which separate, extensive treatment guidelines exist [76,77]), the strongest level of evidence exists for olfactory training [43,74]. Accordingly, patients should have undergone a minimum period of documented olfactory training of at least 3 months [78]. Given the invasive nature of OI, a longer duration of olfactory training might be preferable. Furthermore, where there is a possibility of an undiagnosed inflammatory condition, a trial of systemic and/or intranasal corticosteroids should be considered, again in line with current guidelines. For patients without signs of sinonasal inflammation, a trial of intranasal corticosteroids using high volume saline douches, drops with appropriate coun-

selling regarding access to the olfactory cleft, or other novel application devices should be considered, as application using standard intranasal sprays are not effective in this group [79,80].

Whilst other therapies such as intranasal calcium buffers, intranasal vitamin A, intranasal injection of platelet-rich plasma or omega-3 supplementation may be of benefit, at present there is insufficient evidence to support their required use prior to consideration for OI. In patients with anatomical abnormalities, e.g. following nasal trauma, surgical techniques such as septorhinoplasty to restore nasal airflow to the olfactory cleft should be considered.

Statement 4:

4. All patients should have tried and failed existing treatments in line with current guidelines.

4.1. In all patients except those with sinonasal disease (SND), this should include an extended period of olfactory training (≥3 months).

- Delphi result: Agreed (score 7-9 = 92.1%, mean score 8.4)

4.2. In suspected SND/idiopathic OD, a trial of systemic/intranasal corticoste roids (with appropriate choice of intranasal delivery system) ± nasal surgery should be considered.

- Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.1)

Pre-implantation counselling

Given the invasive and novel nature of OI, it is important that patients undergo a period of pre-implantation counselling, in which the surgical and research team discuss potential risks, possible financial burden and anticipated perceptual outcomes. It is important that patient and provider expectations should align at this point. A point of contact (e.g., clinical or research nurse) should be available pre- and post-operatively. Consent for research involvement and sharing of data in an accessible patient registry should be sought at this point.

Statement 5:

5. All patients being considered for OI candidacy should undergo a period of multidisciplinary pre-implantation counselling.

- Delphi result: Agreed (score 7-9 = 92.1%, mean score 8.2)

Pre-operative assessment and possible contraindications

All patients should undergo thorough pre-operative assessment, during which potential surgical and anaesthetic risk factors should be identified. Though detailed discussion of contraindications requires knowledge of stimulation site and associated surgical approach, general, relative contraindications are discussed below.

Age

Older individuals are more likely to have chronic systemic or neurological diseases that may impact on the safety of surgery and subsequent recovery. Further, cognition decreases with age, potentially complicating the ability to adapt post-implantation. However, performing the procedure in young individuals may also be challenging, especially as the bony and cartilaginous framework of the nose progressively matures until approximately 16 years of age [81]. Therefore, minimally invasive approaches may be preferable in younger age groups. Furthermore, counselling and issues surrounding consent complicate – though do not preclude – implantation in children.

Sinonasal disease

It is unknown whether/how chronic sinonasal inflammation could affect short and long-term outcomes in olfactory implantation – similar to the situation with chronic otitis media and cochlear implants. In addition to the underlying inflammatory processes in CRS, bacterial biofilms have been documented in these patients [82], which may (especially those with a history of previous nasal surgery) also harbour a unique mix of bacteria [83], resulting in persistent or more severe infection. Post-operative infection could cause complications such as delayed wound healing, dehiscence, and extrusion, if an intranasal route of implantation were used.

Nasal disorders

Recurrent bacterial infections and unusual pathogens should prompt an investigation for possible immunodeficiency (84). Furthermore, granulomatous diseases, such as sarcoidosis, eosinophilic granulomatosis with polyangiitis, and granulomatosis with polyangiitis, are associated with purulent infections, diseased mucosa, septal destruction, and scarring [84], which may compromise sinonasal implant fixation and lead to increased risk of infection. Similarly, patients with cystic fibrosis or primary ciliary dyskinesia may have impaired mucociliary clearance [84], which may also impact postoperative healing. Benign and malignant sinonasal tumours should be evaluated on a case-by-case basis.

Smoking

Smoking has been associated with poor olfactory function [85]. Tobacco smoke causes impairment of mucociliary clearance and suppression of sinonasal innate immunity, both of which may have adverse effects on wound healing [84]. Smoking cessation has been associated with improved mucus properties [86], and fewer histological abnormalities in nasal mucosa [87]. Hence, smoking should be considered a contraindication to OI, particularly where the OE is the intended stimulation target. In patients where the OB or higher order structures are the intended simulation target, failure to quit smoking could also be considered a

relative contraindication, in a way analogous to refusing recommended treatments that could improve their olfactory health.

Operative risks

As for contraindications, detailed discussion of potential complications is dependent on both the device used and the specific surgical procedure. However, thorough pre-operative assessment of the patient's history (including comorbidities), physical exam findings, and diagnostics (including imaging) should be undertaken as part of a general approach to reduce risk. Furthermore, OI surgery should be performed by experienced surgeons (rhinologist/anterior skull base surgeons and/or neurosurgeons) who have been appropriately trained using cadaveric dissection or other simulation methods. Registration of complications in centralized safety databases should be encouraged, to allow for collective learning amongst the OI community. Future studies, prototypes, or simulations should provide new information related to patient safety and necessary precautions to reduce risks.

A brief list of some potential complications that may be incurred can be found in Table 3.

Statement 6:

6. Thorough pre-operative assessment should be undertaken in all patients in whom OI candidacy is considered.

6.1. Absolute and relative contraindications can only be fully defined once device specifics are known, but are likely to include significant co-morbidity, blood dyscrasias and unfavourable anatomy. More generally, individual patient factors should be considered when weighing potential benefits versus risks of implantation.

• Delphi result: Agreed (score 7-9 = 92.1%, mean score 8.3)

6.2. To mitigate the risk of complications patients should undergo thorough pre-operative assessment/investigation, and surgery should be undertaken by experienced surgeons.

• Delphi result: Agreed (score 7-9 = 100%, mean score 8.8)

6.3. Future studies, prototypes, or simulations should inform future surgical planning to minimise risk of complications and optimise outcomes.

• Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.5)

Post-implantation

After cochlear implantation, patients undergo a program of auditory rehabilitation. Accordingly, patients are supported during their period of adaptation to their new sensory input. A similar period of structured rehabilitation should be provided to patients who have undergone olfactory implantation. This should consist of device programming as well as possible olfactory training (OT) (ideally with supporting multi-modal sensory input, e.g. visual ± auditory cues in addition to odours). Targeted exposure to key 'safety' odours (e.g., smoke) could be prioritized first, after which an increasingly diverse repertoire could be introduced, focusing initially on common or particularly 'strong' odorants (Figure 4).

Patients should receive multidisciplinary support post OI where needed, to include specialist research nurses and extended members such as nutritionists or psychologists where required. Regular reviews from the implanting surgical team should be undertaken, and psychophysical smell testing performed periodically, to assess progress and possible background spontaneous recovery.

Statement 7:

7. Patients should undergo a structured programme of olfactory rehabilitation post implantation

7.1. This should include device programming with initial

Table 3. Potential major and minor complications.

Minor	Major
Bleeding Localized nasal infection Headache / pain Frontal sinus stenosis Nasal airway obstruction (e.g., scarring, synechiae)	Seizures Bleeding (subarachnoid, intracranial haemorrhage, periorbital ecchymosis, retrobulbar hematoma) Cerebrospinal fluid leak Intracranial infections (e.g. abscess [subdural empyema, cerebral abscess] or inflammation [Encephalitis, Meningitis]) Pneumocephalus Cerebrovascular disease Brain tissue direct trauma (e.g. sequelae of frontal lobe parenchymal damage) Electrode migration / extrusion / damage Periorbital cellulitis Subperiosteal abscess of the frontal bone (Pott puffy tumour) Vision Impairment/Loss Nasal septal necrosis Qualitative olfactory dysfunction (Phantosmia / Parosmia)

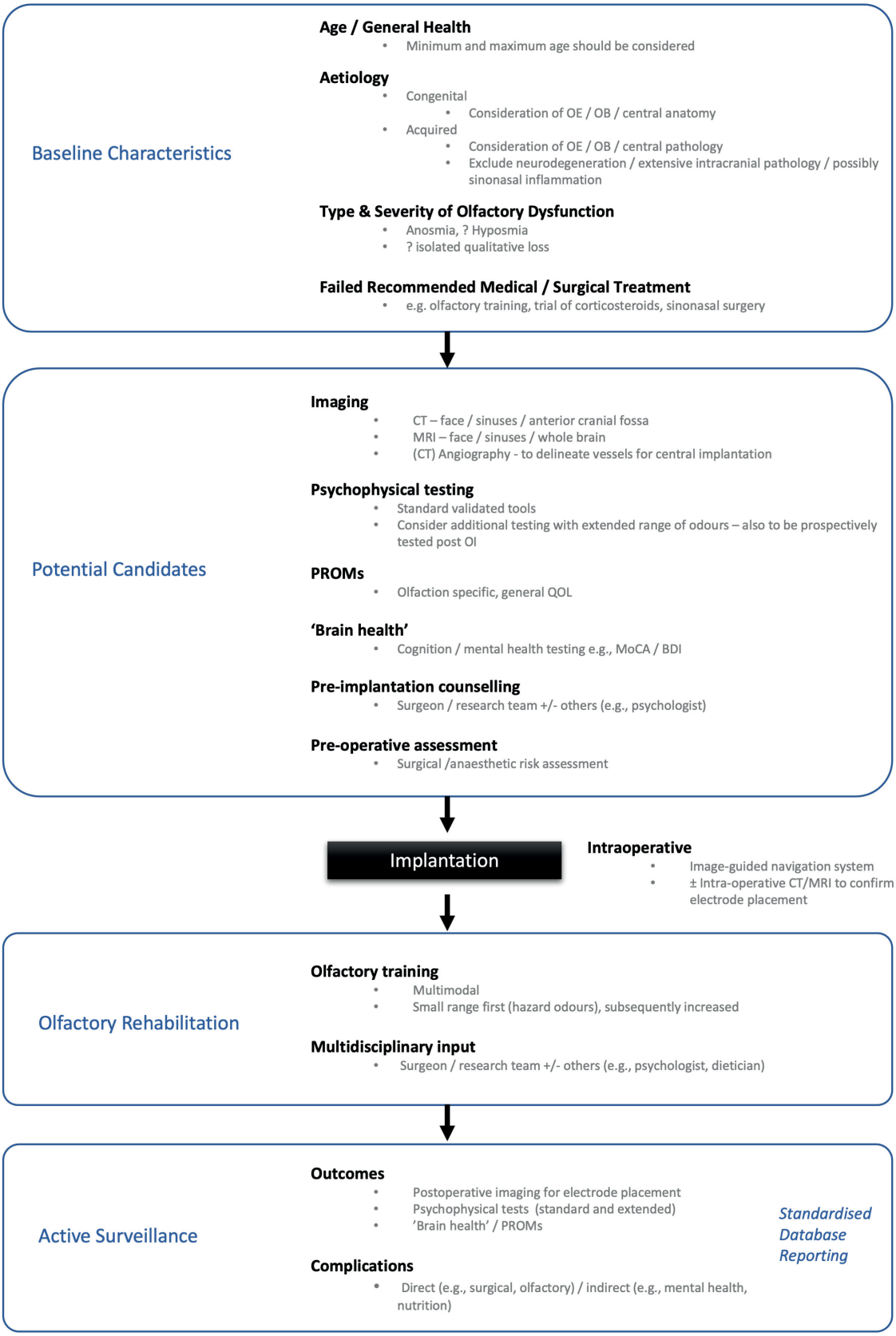


Figure 4. Overview of patient selection process and post implantation care. '?' denotes patient groups in whom there is unclear utility of implantation at present.

'safety' odours, followed by commonly encountered odours.

• Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.2)

7.2. Patients should receive multi-disciplinary support during this time.

• Delphi result: Agreed (score 7-9 = 97%, mean score 8.6)

7.3. Standardised outcome measure should be collected at regular post-implantation intervals, including psychophysical tests, patient-reported outcome measures, and tests for cognition/depression.

• Delphi result: Agreed (score 7-9 = 97%, mean score 8.8)

7.4. Complications monitoring including, where indicated, CT scans should be undertaken at regular post-implantation intervals where indicated.

• Delphi result: Agreed (score 7-9 = 81.6%, mean score 7.9)

7.5. Standardised database reporting should be undertaken for safety, and ideally outcomes assessment including a position map of odours for possible optimization of electrode position.

• Delphi result: Agreed (score 7-9 = 97%, mean score 8.5)

Implants and stimulation: technology, techniques and potential pitfalls

In the following sections, the technological aspects of olfactory implantation and associated specific surgical considerations will be discussed, with a particular focus on stimulation target and technique. For detailed discussion of the 'sensor module' – we would refer readers to the available literature on artificial and bioelectronic noses [9,12,15].

Stimulation targets

Based on our knowledge of olfactory physiology, electrical stimulation can be targeted at various sites within the olfactory system, including the periphery - the olfactory epithelium - or central structures - including the OB and upstream regions such as the piriform cortex (PC). In the following section, stimulation will be discussed at these different levels (see also Table 4).

The olfactory epithelium

Stimulation at the level of the OE aims to replicate initial stimulus conduction, thereby activating all physiological upstream structures. In theory this could produce 'ecological' perception. At birth, the OE is located as a continuous sheet within the olfactory cleft – an anatomical region bounded by the cribriform plate superiorly, the superior septum medially, and the middle and superior turbinates laterally [111]. Whilst some degree of spatial organisation or 'rhinotopy' has been shown in animals [112,113], its extent is not completely clear in humans. With advancing age and cumulative pathological insults, the overall extent of the OE decreases, and it may develop a patchy distribution due to interspersion of metaplastic respiratory or squamous epithelium [51,114] – though OE has been shown to be consistently present immediately below the cribriform plate, even at advanced age [115]. In a recent cadaveric study of OE histology (mean age at death 74.1years), whilst there was inter-individual variation, Fitzek and colleagues demonstrated that the OE extended on average '*1.0 cm below the cribriform plate, 0.7 cm posterior to the anterior attachment of the middle turbinate, 1.7 cm above the inferior edge of the middle turbinate, and 0.4 cm anterior to the sphenoid face*' [116]. Together, interindividual variation in distribution of OE, lack of clear rhinotopy and respiratory/squamous metaplasia complicate stimulation at this site.

Perhaps in line with this, studies investigating olfactory perception following stimulation of the OE have demonstrated varying results. Early work from Uziel and colleagues demonstrated specific or 'formed' olfactory percepts such as 'almond' (n=5), 'burnt' (n=3), or 'vanilla' following electrical stimulation of the OE [92]. In contrast, another early study failed to demonstrate olfactory perception following electrical stimulation, though when such stimulation followed odour exposure it reproduced the prior percept [93]. In more recent work, generalised olfactory perception (e.g. 'sweet, chemical, and fragrant') was evoked through electrical stimulation at the middle turbinate in 8 out of 31 participants [98]. Aoyama and colleagues recently demonstrated irritating intranasal chemosensation using non-invasive electrical stimulation at the nasal bridge and the dorsal surface of the neck – postulated to cause activation of the olfactory nerve. However, underlying mechanisms for these perceptions have yet to be fully elucidated, with either activation of the olfactory and trigeminal nerve or of the trigeminal nerve alone being possible [97]. In several other studies, no olfactory perception could be elicited following stimulation of the OE [94,96]. Instead, sensations like 'tingling' or 'flashes of light' have been described, depending partly on the applied voltage – with subliminal stimulation leading to more unpleasant perceptions.

Table 4. Overview of electrical stimulation on the olfactory system (Modified from Gunder et al. [3])

Source (year)	Study population	Target stimulation area	Methods (Type of Stimulation)	Type of stimulation device	Results
Electrical stimulation of the olfactory epithelium					
Althaus (1881) [4]	1 patient with trigeminal dysfunction	Nasal cavity mucous membrane	eStim with a current of "thirty-five pairs of plates"	unspecified	Perception of phosphorous smell
Aronsohn (1884, 1886) [5,6]	6 subjects	Nasal cavity (unspecified)	eStim at 2.5 mA mentioned (but unclear if same for all participants), nasal cavity filled with 0.73% Na Cl solution at 38 °C for stimulation	Platinum wire surrounded by rubber tube	Odour perception like the smell that arises "when one very slowly and carefully lights a Swedish match", current of 0.1 to 0.2 mA are sufficient to stimulate an olfactory sensation
Uziel (1973) [7]	21 healthy subjects and 6 OD patients	Olfactory epithelium	eStim using various electrodes (Ag, Ag-AgCl, NaCl) either cathodic or anodic, stimulus duration 5s (rectangular current), can deliver a pulse with intensity varying from 0 to 500 µA	Focal electrodes: Pure silver wire surrounded with polyvinyl sheath, Fine polyvinyl catheter containing a silver rod coated with silver chloride in contact with a silver chloride solution	For anodal stimulation odour perception "almond" (n=5), "burnt" (n=3), vanilla (n=1) and "purulent" (n=1).
Straschill et al. (1983) [8]	10 healthy subjects, 5 epilepsy patients	Olfactory epithelium	eStim (60 Hz, duration 15 s, same current was used which elicited taste sensations when applied to the tongue) and presentation of olfactory stimuli	Silver ball electrode	No olfactory sensation followed eStim. Phosphenes were observed at higher stimulus intensities. Suppression of olfactory sensation when odorants were presented during stimulation. Olfactory perception was suppressed when odorants were presented concurrently with stimulation. In some cases, re-experiencing of odours occurred when eStim was applied shortly after odorant presentation. Unpleasant olfactory sensation followed eStim (n=3, with a history of temporal lobe epilepsy)
Ishimaru et al. (1997) [9]	5 healthy subjects	Olfactory epithelium	eStim via Ag electrode, electrical current of 2 mA for 0.5 ms, stimulation rate 2 Hz	Bipolar silver sphere electrode	No generation of olfactory sensations but tactile sensations were noted. Pain sensations were observed when stimulating electrode was outside of the olfactory cleft and touching the respiratory mucosa.
Ishimaru et al. (2002) [10]	14 subjects (including 12 patients with OD)	Olfactory epithelium	Prior to testing, 0.1% epinephrine was applied to olfactory cleft, eStim 2 mA, 0.5 ms duration	Bipolar electrode	No olfactory sensation
Weiss et al. (2016) [11]	50 subjects (Experiment 1); 16 subjects (Experiment 2)	Olfactory epithelium, superior and middle turbinates	eStim using a battery-powered electronic stimulator: [Experiment 1: lasting for 0.5, 1, 2, and 3 s, with ISI of 30-50 s, starting at 50mV and incrementally increasing until sensation of any kind (currents ranging from 50-800 µA, Experiment 2: average current 200 µA, with odours of "rose", "chocolate", and "manure"]	Pure-silver stimulating macro-electrode	Minimal modulation of presented olfactory stimuli. No generation of olfactory sensations by eStim, sensations described as electrical current, pinpricks, or cooling inside the nostril.

Table 4 *continued*. Overview of electrical stimulation on the olfactory system (Modified from Gunder et al. [3])

Source (year)	Study population	Target stimulation area	Methods (Type of Stimulation)	Type of stimulation device	Results
Karunanayaka et al. (2023) [13]	31 healthy subjects	Olfactory epithelium (middle turbinate)	eStim (rectangular-shaped weak electrical pulses in different frequencies [0–30 kHz], and currents [1–5 mA]), stimulus duration 10s, inter-stimulus interval 60 s	Arduino microcontroller, two silver electrodes	For different stimulation parameters 22 olfactory sensations: chemical and fragrant smell sensations in 8 participants (1 mA, 70 Hz), sweet smell sensation in 8 participants and chemical smell sensations in 6 participants (1 mA, 10 Hz)
Electrical stimulation of the OB and other brain areas in humans					
Penfield, Jasper (1954) [14]	1 subject	OB	eStim parameters unspecified	Unspecified	Unpleasant odour sensation (seemed like "manure")
Holbrook et al. (2019) [15]	5 CRS patients	OB (intended site of stimulation, but actual placement over olfactory mucosa, along the lateral lamella of the cribriform plate at the anterior, middle, and posterior ethmoid)	Trans-ethmoidal eStim of the OB. Square wave current of repetitive pulses at 1 to 3.17 Hz frequency, intensity from 1 to 20 mA, duration from 0.2 to 0.3 ms, intensity increased by steps of 1 mA until smell perception or discomfort	Monopolar or bipolar electrodes	Odour perceptions (n=3): onion-like, antiseptic, sour, fruity, bad. Only tactile perceptions for the rest
Andy (1967) [16]	1 epilepsy patient	Amygdala and hippocampus (right-sided)	eStim parameters unspecified but stimulation of the amygdala: after-discharge lasted 21 s and spread to the adjoining hippocampus; hippocampus: discharge lasted 16 s with minimal spread to the amygdala.	Intracranial bipolar electrodes	eStim of amygdala elicited olfactory sensation (foul), but eStim of hippocampus did not result in olfactory sensation.
Nashold and Wilson (1970) [22]	5 with neurological disease (parkinsonian tremor n=3, chorea n=1, intractable cranial pain n=1)	Thalamus (ventral lateral [for tremor and chorea], dorsolateral mesencephalon at the level of the colliculus [for pain])	eStim via depth electrodes on the awake patients	Fine depth electrodes	Electrostimulation of the thalamus: various olfactory impressions (rubber, smoky/burnt, chloroform, clove) in 3 patients.
Hummel et al. (2005) [25]	11 PD patients	Sub-thalamic nucleus	Bilateral DBS with an impulse width of 60 µs, a stimulation frequency of 130Hz, and an amplitude of 2.8–3.4V.	DBS electrodes	Odour discrimination improved while DBS
Okun et al. (2007) [23]	5 patients with chronic and severe treatment- refractory OCD	NAc, anterior limb of the internal capsule	Patients received either actual testing or sham testing. 0 to 8 V, pulse width of 210 or 90 or 450 µs, frequency 135 Hz.	Monopolar DBS electrodes	Smells were associated with stimulation in the most ventral lead positions in the NAc, described as metallic (n=6), odd (n=10), sweet (n=4), strange (n=4), roses/oil/almonds (n=13).
Fonoff et al. (2010) [26]	1 advanced PD patient	Sub-thalamic nucleus	Chronic monopolar stimulation, 1.7 V right and 2 V left, pulse width 210 µs, frequency 130 Hz.	DBS electrodes	Improvement of odour identification (Brief Smell Identification Test Score: 8, normal) after 5 months.
Kumar et al (2012) [17]	16 children with focal epilepsy	Subdural space in the areas of the gyrus rectus, medial orbitofrontal gyrus	Biphasic pulses, frequency 50Hz, pulse duration 300 µs, train duration ranged up to 5 s, Current intensity from 3 to 9 mA.	A pair of subdural electrodes	Stimulation near OB or olfactory tract: olfactory sensations (n=11). Among these, 9 reported unpleasant smells (bitterness, smoke, garbage) and 2 reported pleasant smells (strawberry, good food). These sensations were elicited after stimulation near the OB, the olfactory tract.

Table 4 *continued*. Overview of electrical stimulation on the olfactory system (Modified from Gunder et al. [3])

Source (year)	Study population	Target stimulation area	Methods (Type of Stimulation)	Type of stimulation device	Results
Mazzola et al. (2017) [18]	221 drug-refractory epilepsy patients	Insula	Bipolar square pulses of current, frequency 50 Hz, pulse duration 0.5 ms, train duration of 5 s, intensity between 0.2 and 3.5 mA.	Stereotactic depth electrodes (only contacts in the grey matter)	Olfactory sensations from stimuli at mediodorsal insula in 15 out of 550 stimulations, especially in the mid-dorsal part of the insula (posterior short gyrus).
Fox et al. (2018) [19]	22 intractable focal epilepsy patients	OFC	Bipolar eStim, alternative wave square current with 50 Hz, 2-8 mA and pulse width of 200-300 ms. Sham stimulation included for some patients. Open-ended questions with follow-up questions.	Subdural grid / strip electrode arrays (n=9), depth electrodes (n=12), or a mix of both (n=1)	Olfactory (n=13), gustatory (n=3), somatosensory (n=8) and affective (n=2) changes occurred. Olfactory phenomena were largely neutral or unpleasant. Left lateralization of stimulations elicited more negative events while right sided stimulation elicited more neutral effects. Most of the effects after stimulation around the transverse orbital sulcus, none in the anterior part of the OFC.
Bérard et al. (2021) [20]	8 temporal lobe epilepsy patients	OFC, anterior hippocampus	Biphasic pulses, frequency 50 Hz, 0.2 ms duration, monopolar, maximal stimulation 4mA.	Stereotactic depth electrodes (stimulation only on the most distal contact)	Stimulation at medial OFC: pleasant olfactory perception (n=5), such as coffee or lemon. Specific locations: olfactory sulcus, medial orbital sulcus, or medial orbitofrontal gyrus. Increasing stimulation amplitude changed the percept identification in 3 of the 5 patients.
Li et al. (2023) [21]	302 medically refractory epilepsy patients	Insula, amygdala, OFC, middle/superior temporal cortex, pars orbitalis/superior frontal cortex, postcentral gyrus, rostral ACC	Biphasic eStim with pulse width of 0.3 ms and 5 s duration, frequency 50 Hz. Intensity ranged from 0.1 to 6 mA.	SEEG bipolar electrode	Chemosensory perception (olfaction, gustation and chemesthesis) elicited in 21 patients. Highest response rate (1.8%) in the insula, especially along the central sulcus axis. Mostly unpleasant sensations and predominantly olfactory percepts.
Zhang et al. (2023) [24]	48 drug resistant epilepsy patients	Amygdala	eStim using high-frequency stimulation (50Hz, pulse duration 300 µs, train duration of 5 s), bipolar mode of stimulation to adjacent contacts. Stimulus intensities ranged from 0.5 to 8mA	Multi-lead SEEG electrodes	250 responses evoked, 12 olfactory responses in 4 patients, including peculiar/obnoxious odours, sour smells, and smells associated with visual hallucinations

µs microseconds, ACC anterior cingulate cortex, Ag silver, Ag-AgCl-NaCl silver-silver-chloride-sodium-chloride, CI cochlear implant, NaCl sodium chloride ,CRS chronic rhinosinusitis, EEG electroencephalography, ENT ear nose throat, eStim electrical stimulation, fMRI functional magnetic resonance imaging, Hz hertz, kHz kilohertz, mA milliampere, n number, NAc nucleus accumbens, OB olfactory bulb, OCD obsessive-compulsive disorder, OFC orbitofrontal cortex, PD Parkison's disease, s seconds, SEEG stereoelectroencephalography, STN subthalamic nucleus, DBS deep brain stimulation, V volts.

Interestingly, activation of the central olfactory system following stimulation of OE has also been observed. Using fMRI, Weiss and colleagues demonstrated alteration in activity of deep brain structures (e.g., the PC), after sub-threshold intranasal electrical stimulation immediately prior to the scanning session. The authors concluded that electrical stimulation of the OE caused altered central olfactory processing without olfactory perception [96]. Another study using EEG revealed evoked potentials from the ipsilateral frontal region following OE stimulation [94].

Since almost all fragrances simulate both the olfactory and trigeminal systems [117], trigeminal stimulation may potentially augment olfactory sensation. Badran et al., demonstrated increased sensitivity to guaiacol following trigeminal nerve stimulation or transcranial direct current stimulation [118]. Further, trigeminal stimulation may aid in the recipient patient's ability to locate the

source of an odour [119].

Surgical approach to placement

Placement of electrodes for stimulation of the OE should theoretically be possible using an endoscopic endonasal approach, potentially under either general or local anaesthesia. Therefore, of the different target stimulation sites, the OE is the simplest, and likely safest. Long-term complications from intranasal electrodes, however, should be considered. The nose and the sinuses are not sterile, and infection and crusting around the implanted electrode (similar to an intranasal foreign body) is possible. Submucosal placement of electrodes could mitigate some of these issues, and deserve further research. Whilst healthy nasal mucosa is an effective barrier that limits inflammation, this is not the case in patients with chronic rhinosinusitis (CRS) – in whom barrier dysfunction leads to chronic inflammation, histological remodelling and clinical symptoms [76]. Such patients are therefore at increased risk of complications and intranasal implantation may therefore be inappropriate in this group.

The use of externally placed (transcutaneous) electrodes may allow non-invasive simulation of the OE ± OB [97,120]. However, more work is needed to demonstrate the utility of this approach in vivo.

The olfactory bulb

The olfactory bulbs are paired neuronal structures found immediately ventral to the frontal lobes, and dorsal to the cribriform plate. They are cortical-like with a lamellar architecture, containing various cell types, including mitral and tufted cells (second order neurons), interneurons and glia. OSN axons synapse within the OB within specific structures called glomeruli. Each glomerulus receives axons from OSN with the same OR type (i.e. monoallelic), resulting in some degree of spatial organization [111,121]. Furthermore, previous work has demonstrated significant variation in glomerular size, shape and location within the human OB [122]. This 'spatial fingerprint' is additionally augmented by the effects of differential odorant absorption characteristics, their potential subsequent interactions with the nasal mucus and nasal aerodynamics, together creating a complex spatiotemporal neural fingerprint [25]. Despite this, in theory, selective stimulation of the OB could mimic different odour activation patterns. Finally, when considering stimulation at this site, it is important to note that the shape and size of the OB is relatively plastic, reflecting olfactory function (with a range of volumes in one study from 37-98mm^3 and 41-97mm^3 for left and right sides respectively) [123,124]. For example, the OB atrophies with age [116], and has been shown to increase in volume with improved olfaction following treatment [71]. This highlights the potential interindividual differences that may affect stimulation of the OB, as well as the importance of thorough pre-operative imaging for any potential OI recipients.

Due to the invasive nature of direct OB stimulation, the majority of studies to date have been performed in animals [125–128]. In one such study, using a CI electrode, a localized field potential response was generated by direct stimulation of different areas of the rodent OB [125]. In humans, an early study from Penfield and Jasper described unpleasant olfactory sensations (e.g.: burning rubber, stench or manure) following invasive intraoperative electrical stimulation of the OB in patients with epilepsy [16]. In a later human study, using a transcribriform stimulation approach in patients who had undergone previous ethmoidectomy, Holbrook and colleagues demonstrated olfactory sensations in 3 of their 5 subjects [99]. The elicited olfactory perception was reproducible after applying lidocaine intranasally to induce a temporary anosmia. The authors therefore concluded that the perception demonstrated was due to stimulation of the OB, rather than the OE.

Surgical approach to placement

Stimulation of the OB could be achieved through external, intranasal or intracranial stimulation [129,130]. Although further investigation is likely to yield a greater variety of approaches and options, optimal intranasal and intracranial implantation positions, and their associated surgical approaches were investigated by Menzel and colleagues in a recent cadaveric study [129]. For the intranasal approach a U-shaped mucosal flap was elevated from the axilla of the middle turbinate, and an electrode was placed immediately ventral to the cribriform plate, following which the mucosal flap was repositioned. Advantages of this approach include ease of surgical placement, and relative safety regarding CSF leakage or ascending infections. However, the distance of the intranasal electrode to the OB is relatively large due to intervening skull base, which could result in reduced spatial specificity due to higher required stimulation. Regarding intracranial placement, the following approaches were investigated: through a widened ostium of fila olfactoria (endoscopic), after performing a Draf IIb procedure (endoscopic), through a wider transcribriform approach (endoscopic) and a combined approach with an endoscopic and frontal osteoplastic flap. The first of these approaches seemed particularly promising – allowing close positioning of the electrode to the OB and an acceptable level of surgical invasiveness. The Draf IIb procedure provided a good overview of the surgical area, however, may result in frontal sinus ostium obstruction after placement of the implant. In another study, Benkhatar and colleagues suggested a midline OI with stimulating electrodes placed either extracranially, immediately ventral to the cribriform plate, or extradurally, medially between the two OB – facilitated by transseptal transcribriform removal of the posterior two-thirds of the crista galli [130]. The 'receiver-stimulator' was placed behind

the hairline, with connection between the two facilitated by nasal bone minitrephination. Compared to the intracranial approaches described by Menzel and colleagues, the extradural approach of Benkhatar et al., may be more invasive, however there is no quantitative comparison at present. Both transcranial and transcribriform approaches are theoretically associated with complications, including but not limited to: cerebrospinal fluid leak, local or ascending infections (e.g., meningitis, subdural empyema, cerebral abscess, cavernous or superior sagittal sinus thrombosis, (haemorrhage and direct brain tissue injury). These risks tend to increase with the complexity of surgery and are contingent upon both the invasiveness of the procedure and individual anatomical considerations. Furthermore, Benkhatar and colleagues demonstrated high rates of simulated CSF leak associated with transcribriform techniques [130]. Inadvertent skull base injury requires primary closure using appropriate reconstructive techniques. Potential risks should be mitigated by thorough analysis of preoperative imaging [129], and use of intraoperative image-guided navigation systems where available. Together, the placement of an intracranial intradural stimulating device on the OB may appear technically easier (larger working space and room for anchoring) and safer (notably regarding CSF leak and infection) through a transcranial route than through an endonasal one. Preliminary work by Coelho et al., suggests a supraorbital keyhole craniotomy, performed through a cosmetically appealing brow incision, is feasible in as much as 95% of potential candidates. This approach, familiar to neurosurgeons, can afford direct line-of-sight to the OB without violation of the sinus mucosa or orbit. While such an approach may serve to mitigate the risks of CSF and meningitis compared with a trans-nasal approach, it may involve some additional degree of risk from frontal lobe retraction and vascular injury, even with angled endoscopic instrumentation [131]. In general, approaches which preserve the peripheral olfactory anatomy should also be given special consideration, in order to allow underlying spontaneous recovery, and to facilitate return to baseline where potential explant was considered.

Central olfactory networks

Structures of the central olfactory networks can be divided into primary (those that receive direct neuronal input from the OB) and secondary (those that do not receive direct input). The primary network includes the PC, anterior olfactory nucleus, amygdala, entorhinal cortex and anterior perforated substance. The secondary network includes the orbitofrontal cortex (OFC), insula, hippocampus, and thalamus as well as other structures. Anatomically, these regions range in size and relative accessibility – with the OFC being comparatively large and easily accessible and the PC comprising a thin volume of cortex connecting the frontal and temporal lobes. Furthermore, these structures are multimodal and therefore do not uniquely subserve olfaction. This must be kept in mind when considering non-olfactory side effects from their stimulation.

With regards to the central olfactory networks, the majority of the existing literature has been produced during epilepsy research. Mazzola and colleagues performed stimulation of the insula using stereotactically placed depth electrodes in patients undergoing presurgical evaluation for medically refractive epilepsy (stereo-EEG): 221 patients underwent a total of 651 stimulations, of which only 6 elicited an olfactory percept [106]. Also in patients undergoing stereo-EEG, Li and colleagues demonstrated chemosensory (olfactory, gustatory or chemesthetic) responses in 21 of 301 patients, and 53 of 21,661 stimulation sites, with the highest response rate being found in the insula [109]. In the OFC, Bérard et al., and Fox et al., demonstrated olfactory perception using stereo-EEG (SEEG) and electrocorticography (ECoG), respectively [107,108]. Kumar and colleagues also reported olfactory sensations in 11 out of 16 children with focal epilepsy using electrocorticography (ECoG) at the ventral frontal lobe. The elicited percepts were mostly unpleasant (9 out of 11 patients), and were most successful when located proximal to the OB or tract (irrespective of hemisphere side) [105]. With regards to other regions, deep brain stimulation (DBS) in the ventral part of the nucleus accumbens (NAc) has been shown to elicit some chemosensory percepts [103] (for details of DBS see Appendix 1). Finally, Zhang and colleagues demonstrated olfactory sensations in 4 out of 48 patients who underwent electrical stimulation of the amygdala [110]. In summary, it appears that stimulation across different central sites could potentially produce olfactory percepts, although to different degrees and with varying reliability [132].

Surgical approach to implantation

To stimulate intracranial structures, the following can be considered: non-invasive procedures such as magnetic or direct current fields [133,134], minimally invasive procedures targeting cranial nerves as an entry into the brain [135] or invasive procedures with an transcranial approach through craniotomy and stereotactic electrode placement within the region of interest.

Long-term electrode implantation for the purposes of monitoring or stimulating neuronal activity, is relatively well-established in therapeutic contexts (e.g., DBS and brain-computer interfaces, auditory brainstem implants). Nevertheless, electrical implantation of the central olfactory networks, upstream of the OBs, is accompanied by multiple challenges, both generic and specific.

Generic challenges include direct/indirect brain injury, CSF leak, local and intracranial infections [136–138]. Specific challenges in central olfactory implantation include the size, shape and

location of olfactory eloquent structures. For example, whilst the PC – being the first recipient of input from the OB – would offer a theoretically attractive target, it is comparatively small, has a curved shape, and has both frontal and temporal divisions, making it challenging to achieve precise implantation [139–142]. Because of its curved shape, its thickness is reduced to only 1–2 mm [141]. Inadvertent propagation of applied electrical current beyond the target structure could occur, with unwanted side effects of non-target stimulation. This poses a theoretical issue for any small target structure. Also, the proximity of arteries in these regions poses a risk of haemorrhage during implantation, and the angle of implantation therefore has to be chosen carefully [143].

Despite these issues, implantation could be considered for the OFC, insula, PC, amygdala, nucleus accumbens and medial temporal lobe. For more specific information, see Appendix 1.

Statement 8:

8. Efficacy of stimulated olfactory perception and impact of OD pathophysiology should be taken into account when considering potential stimulation sites:

8.1. Olfactory epithelium: only limited work has shown successful olfactory perception following electrical stimulation. Inter-individual variation in distribution, and potential histological damage associated with OD, complicates stimulation at this site.

• Delphi result: Agreed (score 7-9 = 84.2%, mean score 7.7)

8.2. OB: work in animals and humans has demonstrated activation of the olfactory system following electrical stimulation. Glomerular 'mapping' in humans, and its degree of stereotypy, is at present unknown. Variations in size and shape associated with OD should be kept in mind when considering stimulation in this site.

• Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.3)

8.3. Central olfactory networks: some work has demonstrated olfactory perception following stimulation of upstream structures, though with low response rates. Central stimulation may be favourable in patients with significant damage to the OB. The multi-modal nature of central structures should be kept in mind when considering the efficacy of stimulated olfactory perception and potential side-effects.

• Delphi result: Agreed (score 7-9 = 97%, mean score 8.3)

Which electrodes?

Generic considerations about chronic implants

A. Stimulation vs recording for chronic use

A chronic implant is an implantable hardware allowing to 'write in' (stimulation) or 'read out' (recording) electrophysiological information directly from the brain. Long term implantation requires the electrodes to survive for an extended period of time in a harsh environment where the technology must be resilient to delamination, swelling, corrosion, dissolution, fouling, etc. [144]. Corrosion may be prevented by modern approaches [145]. It is noteworthy that novel encapsulation materials and technologies are being developed to ensure long-term in-vivo performance [146].

B. Inflammation

Tissues react to the presence of a foreign body with an inflammatory response, also called foreign body reaction, resulting in the formation of encapsulating tissue (comprised of a dense layer of glial cells of up to several hundred µm thick). This layer electrically insulates electrodes from the target neurons [147]. Lessons may potentially be learnt from peripheral nerve stimulation (e.g. hypoglossal nerve stimulation), in which close circumferential contact between stimulating electrodes and nerves and dynamic activation pattern, mitigate the effects of formation of encapsulating tissue and electrode corrosion, respectively.

C. Materials

All materials must be suitable for chronic implantation [146, 148-152]. It has been shown that an implant's stiffness impacts on the inflammatory response, i.e., materials that are significantly stiffer than the brain tissue will create a larger inflammatory response. It is believed that the mechanical mismatch induces micro-movement of the implant with respect to the brain which maintains the inflammatory state long-term [152–154]. Minimizing the final implant footprint and especially its cross-section is crucial to decrease the foreign body reaction [155,156]. Altogether, soft [154] and flexible [157] designs/constructs are highly desirable when fabricating microelectrode arrays. These materials not only reduce the inflammatory response, but also conform better to the tissue topography. This close contact creates a highly efficient interface, enabling both high-fidelity recording with improved signal-to-noise ratio and enhanced stimulation for a given potential when stimulating.

D. Resolution

Small electrodes are desirable when small volumes of tissue are targeted for stimulation. Asplund and co-workers estimated that 1 mm^3 of cortex houses a staggering 50,000 neurons [156]. This density far outstrips the capabilities of current technology, as evidenced by commercially available probes that offer only 16 electrode sites in a similar area. A multitude of small electrodes are achievable with microfabrication technologies; however, the limited electrode surface area available to interact with the biological environment induces a large electrochemical impedance. Large impedances not only limit the transduction of voltage to current when stimulating but also lowers the recording quality [158]. Finally, a high resolution is achieved fabricating an array of

microelectrodes, yet incorporating a multitude of microelectrodes onto a small implant presents a wiring challenge. While multiplexing [159] and multi-layered fabrication techniques [156] offer potential solutions, these methods increase both the cost and complexity of the fabrication process.

The ideal device to stimulate the OB

Taking the OB as hypothetical stimulation target, and considering the points discussed above, the ideal device would feature a dense array of electrodes capable of addressing single glomeruli, whose diameters range from 30 to 200 µm in mammals [160]. For minimum invasiveness, an OI device would be flexible and wrap partly around the OB to address its external surface, similar to cuff electrodes. It would be inserted (either via a transcribriform approach or craniotomy), deployed and self-positioned around the OB once inserted. Arrays of electrodes with diameters and inter-electrode distance down to 5 µm diameter are easily achievable with standard microfabrication tools, but the challenges reside in other points. First, although it may be of little practical concern, electrodes may corrode and dissolve when used for electrical stimulation: these electrodes would, thus, need to be thick enough to survive chronic stimulation. Second, a strategy that could be used to increase their lifetime is to reduce microelectrode impedance, for instance, increasing their effective surface area by roughening the material used. Third, addressing single glomeruli over the whole surface of the OB would result in a large number of electrodes. The routing and wiring would thus represent a technical challenge, adding to the data collection and processing power necessary to treat a large number of signals.

Brain stimulation devices

Devices for brain stimulation are widely available on the market, though at different stages of regulatory approval. The main types used today include intracortical microelectrodes, and depth electrodes [152]. Intracortical microelectrodes are small shafts that are implanted in the cortex and target shallow layers of cells. Depth electrodes are placed along the length of centimetre-long shafts that reach deeper structures of the brain [161]. EcOG – though used primarily for recording rather than stimulation (which at present can only be used for short term purposes, for example during exploratory epilepsy surgery), uses electrodes placed on a flat substrate between the dura mater or between the dura mater and the brain – and may have greater application in the future.

A more detailed discussion on brain stimulation devices, including: intracortical microelectrodes, depth electrodes, and EcOG may be found under Appendix 2.

Stimulation type – neural oscillations

Brain activity manifests electrical oscillations, which are repetitive rhythms of neuronal firing. In humans, neuronal activations are usually recorded as Local Field Potentials (LFP) [162,163]. The timing and sequence of oscillations found in the different structures of the olfactory system seem to play an important role for olfactory sensations. There is a synchronization of breathing rhythms between the PC, the amygdala and the hippocampus especially during the inspiration phase [164-166] - three structures known to be responsive to odorous stimulation. Thus the connectivity between structures of the primary olfactory cortex aligns with the breathing frequency, and probably as a consequence, this modifies the primary olfactory cortex's ability to sample odours. In addition, theta, beta and gamma oscillations are found in the primary olfactory cortex during olfactory processing in a specific sequence [165].

Altogether, the results of these studies suggest that the PC, the amygdala, or the hippocampus could be interesting targets for electrical stimulation with an OI. Other regions, including the OFC, insula and the NAc may also be of interest. However, as described above, the various studies show inconsistencies in perceptual outcome, with a low response rate. This may be due to technical challenges such as the area covered by the stimulation itself. But it may also come from the fact that the stimulations described are not delivered as a form of embedded frequencies.

Further research is required to determine whether one stimulation site is sufficient. Although it has been shown that there is a specific chain of events [167], from the PC to the OFC, passing through the limbic system among others, olfactory processing is in fact organized in different networks (sensory, memory, and cognitive) [168,169]. To increase this complexity, some feedback information follows a top-down pathway, for example from the amygdala to the PC or the OB to the OE [170]. These issues require attention when planning successful electrical stimulation and choosing suitable stimulating sites, and it might be that two or more brain structures require simultaneous stimulation, or with a slight delay, for successful and/or efficient olfactory perception.

In summary, electrical stimulation may be most successful when pulses are applied with a specific onset (aligned with inhalation), precise timing (to be studied) and with a specific sequence of events (theta followed by beta and gamma).

Statement 9:

9. Regarding OI electrodes and stimulation paradigm:
   9.1. Where the OB is target, ideally, the device should be able to connect a high-density microelectrode array of electrodes

Table 5. Comparison of stimulation devices in the head and neck.

	CI	Hypoglossal neurostimulation	OI
Indication	Severe to profound hearing loss	Obstructive sleep apnoea	Olfactory impairment
Patient contraindication	Auditory neuropathy, intracranial lesions, cognitive impairment, certain middle and inner ear disease	Central apnoea	See discussion in text
Nerve	Auditory nerve (CN VIII, sensory)	Hypoglossal nerve (CN XII, motor)	Olfactory nerve (CN I, sensory) and/or trigeminal nerve (CN V, sensory)
Sensor	Microphone – speech processor - transmitter	Detection of apnoeic episodes from a sensor located on the chest wall	Chemical sensor intra- (?) extra- (?) nasal
Energy	External part of the device	Implantable pulse generator	Intra- (?) extra- (?) nasal/cranial device
Stimulation	Continuous	Continuous or non-continuous	Continuous
Electrodes	Multi-contact Semi-rigid	Multi-contact Semi-rigid	Multi-contact Semi-rigid
Location of the electrodes	Cochlea	Wrapped around the hypoglossal nerve	Probably intracranial, extradural, close to the OB (?) Intranasal (?)
Efficiency	High due to tonotopy in the cochlea and the auditory cortex	Controlled by selective stimulation between fibres innervating different muscles (opening or closure the upper airway)	Unknown but probably activating OB OFC Transformation of olfactory signal to trigeminal perception
Selection of the patients	Multidisciplinary Audiological testing MRI	Multidisciplinary Sleep lab	Multidisciplinary Olfactory ± trigeminal tests MRI

CI cochlear implant, CN cranial nerve, MRI magnetic resonance imaging, OB olfactory bulb, OFC orbitofrontal cortex, OI olfactory implant

to address single glomeruli, should be flexible and small, for transcranial or transcribriform approaches, and is easily deployed and secured around the OB.

• Delphi result: Agreed (score 7-9 = 89.5%, mean score 8.1)

9.2. Where higher order olfactory structures are the target, currently available stimulation systems include depth electrodes (deep brain stimulation [DBS]), microelectrodes, and electrocorticography (ECoG) devices, which require different surgical approaches.

• Delphi result: Agreed (score 7-9 = 92.1%, mean score 8.3)

9.3. Ongoing research should address: the prolongation of microelectrode lifespan (through the lowering of electrode impedance and the use of novel material for electrodes and encapsulation); the reduction of foreign body reaction (matching the mechanical stiffness of conformal implants to the surrounding tissues and minimizing the electrode footprint); determining best method of implantation (single glomeruli, whole OB surface).

• Delphi result: Agreed (score 7-9 = 100%, mean score 8.6)

9.3.1. Active surveillance for complications secondary to persistent neurochemical, histological, and behavioural modifications resulting from electrode implantation should be undertaken.

• Delphi result: Agreed (score 7-9 = 100%, mean score 8.7)

9.4. Stimulation timing, sequence of oscillations and potential multiplicity of target site require further study, e.g., respiration-triggered sequences of oscillations aligned with specific time-locked electrical stimulation may best evoke reproducible olfactory precepts.

• Delphi result: Agreed (score 7-9 = 84.2%, mean score 8.0)

Where to place an energy source

Regarding the energy source, different implants located in the ENT area share common features (Table 5). A wired/wireless connection between the energy source and the stimulating electrode must exist. For the CI, for example, the energy source is the external part of the device and is located behind the auricle. For hypoglossal neurostimulation, the energy source is inside a pulse generator located in the anterior chest wall.

The question of location remains open: whether the energy source must be internal (e.g. in the olfactory cleft) or external (e.g. in the temporal area). If the energy source is internally located, it must be biocompatible. If the energy source is externally

located, the cable connected to the stimulating electrode needs to be placed under the skin, which is a challenge in the area of the face around the nose. In the transseptal transcribriform approach recently described by Benkhatar and colleagues, the receiver was placed under the scalp, behind the hairline (see section on Surgical approaches for implantation for more details). If possible for the energy source, this could provide a cosmetically acceptable solution for many patients [130]. As long as the array lead wire is thin enough it can be tunnelled (i.e. in the subperiosteal plane) to anywhere more posteriorly in the hair-bearing scalp where the receiver/stimulator would lie. The dimensions of the energy source are also of primary importance because, if internally placed, it must fit the olfactory cleft or a volume created by surgery e.g. in the maxillary sinus. There is always a trade-off between volume reduction and energy capacity. Due to recent advances, one can consider that in rechargeable devices, the volume of the battery is less than 2 cm^3 per stimulating electrodes [171].

Another problem to be considered for internally located power sources is how the battery is replaced after several years. This should be done, ideally, under local anaesthesia without removing the implanted device. In battery-powered devices, energy consumption is essential as it impacts the time between recharge and device longevity.

Another option for the energy source is to use a battery where the energy is transmitted by radiofrequency. Such devices exist for the hypoglossal neurostimulation where a flat battery is placed subdermally in the submandibular area near the hypoglossal nerve endings. One can hypothesize that such devices could be efficient for the electrode near the olfactory epithelium or near the OB if embedded under the skin of the forehead. Wireless charging battery systems also exist and could be used while the user is asleep.

Ethics of olfactory implantation

The hypothetical OI, though a much-anticipated step in the therapeutic field, carries with it several ethical issues.

There are four pillars of medical ethics: beneficence, non-maleficence, autonomy, and justice. It is generally accepted that any medical intervention must respect these 4 pillars [172]. The most obvious question for the OI concerns the principles of beneficence and non-maleficence. Indeed, although the idea of developing an implant to improve or restore olfactory function is laudable, there are many uncertainties concerning its efficacy and its tolerability. In other words, can we guarantee that such an implant will benefit the patient without harming him or her?

A probable target for implantation is the OB. This requires intracranial access and is therefore relatively invasive. Moreover, as mentioned above, after the perioperative period, various adverse effects or complications may arise. Such an implant can therefore only be considered as ethically acceptable if the benefits outweigh the risks.

There is no doubt that restoring normal or subnormal olfactory function would justify the risks involved. But what if the implant could only detect a few smells? If only a few scents could be detected, those that would be preferred would certainly be those to improve hazard detection, and to enhance the pleasures associated with odour detection, particularly for food. Detecting odours associated with various environmental hazards could be considered a survival system. However, there are currently detectors for gas, smoke and spoiled food. Indeed, a wearable, 'sniffing smartwatch' that can detect environmental odours has already been demonstrated [11]. So, the main advantage of taking a surgical risk, in this scenario, would be to provide constant hazard detection.

It is an ethical imperative to fully discuss patient and provider expectations, prior to consideration of candidacy. Allowing patients to experience everyday smells (e.g., food, body odours) could certainly improve their quality of life. However, it is unlikely that the device would, at least initially, represent the multitude of smells that surround us. So, one question that should be discussed is whether patients would consider their quality of life satisfactory if they only smelled a restricted spectrum of odours. Referring to existing sensory implants, it is hoped to develop an OI that performs as well as CI. CI faithfully reproduces hearing and can be considered as a reference in the field of sensory implants. However, other implant types, like retinal implants, have produced much more controversial results. These implants provide low resolution pixelated pictures, which may seem insufficient for a normal-sighted person. However, it has been reported that some blind people considered even rudimentary perception as a significant improvement in their everyday life [173]. This suggests that, depending on context, even a slight restoration of a sense can be perceived as positive by patients. Likewise, the earliest days of cochlear implantation were marked by poor speech understanding that by today's hearing professionals would be considered poor. Nonetheless, deaf patients themselves felt the results to be nothing short of miraculous.

It is also important to consider the possibility that expectations may not be met, or that a complication may arise. Notably, studies on electrical stimulation of olfactory structures have shown that electrical stimulation can induce various types of odours, including parosmias. Given that parosmias are typically perceived as negative and have a strong impact on quality of life, having an implant that induces parosmias could even worsen patients' condition. The possibility that it may not work or that there may be a complication also may necessitate explantation [174]. But in this scenario, if explantation is undertaken, it is uncertain whether the patient will at least return to his or her pre-implant function. Indeed, working on olfactory structures also runs the risk of altering residual olfaction. As such, and as was true with cochlear implantation, initial candidates must be those with complete anosmia with the least to "lose". In addition, depending on the device design, a wirelessly accessible OI may be prone to cybersecurity issues. Wireless access may be important for programming and monitoring that can be done remotely. However, it can also run the risk of the device being disabled or hacked [175], and the risk of serious harm may increase for intracranially implanted devices. These important issues will have to be investigated and openly discussed with patients who are candidates for implantation.

Finally, the financial implications and associated healthcare equity of olfactory implantation must be considered. Whilst OI remain in the experimental stage, funding for such work will be provided by research grants, and access limited to select patients. However, looking forward to the position where OI could be available as a treatment option to the public, the associated costs and equitable access to such treatments must be considered. With this in mind, the healthcare equity of cochlear implants act as a good parallel. Cochlear implantation (CI), continues to face significant global challenges in achieving healthcare equity [176]. Disparities in access, utilization, and outcomes are heavily influenced by the social determinants of health, including socioeconomic status (SES), education, ethnicity, and geographic location. Worldwide, low- and middle-income countries experience significant inequities due to limited CI programs, insufficient public funding, and workforce shortages, leaving many eligible patients without access to this technology. Even in high-income nations, marginalized groups such as ethnic minorities and individuals from lower SES backgrounds often encounter delays in diagnosis and treatment or are unable to afford care. For example, global CI utilization rates remain below 15%, reflecting systemic barriers to access and affordability [176]. Addressing these disparities requires a multifaceted approach that includes expanding CI programs in underserved regions, increasing government subsidies or insurance coverage, and investing in healthcare infrastructure and professional training. These issues should be kept in mind when developing potential olfactory implantation programmes. However, further consideration should be given to the cost to benefit ratio for OI, which may differ from that of CI. One may argue that the putative olfactory implant more heavily subserves quality of life than the cochlear implant. That being said, environmental safety, nutrition and mental health, as well as other unknown long-term effects of olfactory implantation may better justify their cost. Further work in this area is required.

In conclusion, the important ethical challenge for the development of OIs is to identify the potential benefits that patients can expect and to balance them against the potential risks.

Statement 10:

10. The ethical implications of OI should be considered during research and development stages, as well as at the point of clinical application.

10.1. Patients should be consulted during the research/development phase to help inform device priorities.

- Delphi result: Agreed (score 7-9 = 94.7%, mean score 8.6)

10.2. Standardized database reporting of surgical and device/treatment related complications should be undertaken.

- Delphi result: Agreed (score 7-9 = 100%, mean score 8.8)

10.3. Possibility of planned explantation of the device should be considered.

- Delphi result: Agreed (score 7-9 = 100%, mean score 8.7)

Conclusions

OI-driven olfactory perception could revolutionize the treatment of patients with permanent and disabling olfactory loss. However, at present olfactory implants remain experimental, with significant potential associated risks, and have not yet been trialled in people. Careful selection and counselling of potential implantation candidates is required, as outlined in the preceding sections. Together, this document aimed to provide an outline of current technology, possible targets, patient selection, limitations, and potential complications of implantation. It is hoped that this will be a useful resource and roadmap for the years to come.

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Authorship contributions

KLW: Conceptual design, writing of manuscript, editing of manuscript, production of figures, integration of co-author comments, participation in Delphi exercise; AKH: Writing of content, editing of manuscript, integration of co-author comments, participation in Delphi exercise; TH: Conceptual design, writing

of content, integration of co-author comments, administrative support, participation in Delphi exercise; MB, CH, CSSL, CM, DP, PR, SW: Writing of content and participation in Delphi exercise; PA, AA, HB, CB, FC, RMC, VD, WE, APF, SG, CAH, EHH, JWH, MK, IK, SPL, BNL, AM, EM, TM, HN, ZMP, CP, WP, RMR, PS, RS: Review of content and participation in Delphi exercise.

Conflicts of interest

No conflicts of interest to declare.

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Appendix

Appendix 1. More information on deep brain stimulation

DBS

The primary objective of DBS surgery is to achieve precise and accurate placement of each electrode at the intended target location. Common indications include Parkinson's Disease, tremors, dystonia, epilepsy, cluster headache, neuropathic pain, and several psychiatric disorders. The optimal placement of the electrode is determined by the patient's clinical result and their ability to tolerate any unintended consequences that may arise from off-target stimulation.

DBS has been used for the treatment of epilepsy using two different methods: open-loop (application of stimulation for specified periods and thereafter discontinuing it) and closed-loop (system stimulates in response to neural activity [e.g., seizure activity] that can be detected by sensors). These methods may involve either low-frequency stimulation (LFS) ranging from 1 to 10 Hz, or high-frequency stimulation (HFS) exceeding 100 Hz. HFS has been used in both open-loop and closed-loop approaches [153,169,170].

LFS elicits a neuromodulatory impact on the tissue [171,172]. Increased pulse widths can induce desynchronization in a larger proportion of the neuronal population. The length of stimulation is also influenced by the style of stimulation. In closed-loop stimulations, the duration is typically brief. On the other hand, open-loop stimulations may have a wide range of durations. Common stimulation parameters for DBS in movement disorders satisfactorily include amplitudes between 2 mA and 4 mA, with a frequency between 90 and 210 Hz and pulse duration of 60-90 microseconds. The stimulation is performed continuously without breaks and is biphasic to prevent tissue damage [137] and typically cathodic, meaning the active contact is programmed negative relative to the stimulator casing [173]. Contacts can be programmed independently or in combination (anodic and cathodic). Adequate amplitude stimulation leads to neuron depolarization, generating an action potential, while subthreshold stimulations can still alter the neurons' own firing rates. The stimulation threshold varies with fibre thickness [174,175]. Cathodic stimulation causes depolarization and is more power-efficient, but anodic stimulation, causing local hyperpolarization, has shown better clinical outcomes at the same amplitude [176]. This effect depends on the electrode orientation relative to the stimulated fibres, likely because anodic stimulation predominantly excites orthogonal nerve fibres, while cathodic stimulation modulates longitudinally running fibres [177].

Although electrode placement is very precise, side effects may arise from the spread of current to neighbouring fibres or nuclei. Directional electrodes have been particularly designed to regulate the intensity of stimulation depending on the spatial position inside the target region using longitudinal and transversal current steering orientations. This feature may help reduce the aforementioned impact on surrounding structures [178].

The DBS electrode consists of a flexible polymer fibre that contains a semi-rigid retractable metallic stylet. The conductor wires are embedded into the fibre wall [179]. Although the distortion of the inserted electrodes is minimal, it can be seen on postoperative imaging. One of the factors contributing to the difference between targeted and real location of the electrode can be due to brain shift [180]. In practice, deep electrodes are not sensitive to brain shift, due to "neighbouring structures". In contrast, cortical electrodes are more prone to error due to brain shifting [181].

Most of the morbidity associated with DBS may be attributed to: 1) problems with the treatment itself, 2) hardware issues, and 3) stimulation complications. Complications associated with hardware include infections and erosion, electrode migration, hardware malfunction/breakdown, and electrical component failure. The prevailing rates of infection in individuals with chronic DBS vary from 5% to 10% [182,183]. The incidence of hardware-related complications per electrode-year were found to be 8.4% 2 decades ago (2002, 2009) [184–187] and are nowadays better, due to technical improvement [185]. Recent research has shown a significant improvement in the precision of DBS electrode placement with the use of image guidance for direct anatomical targeting [188] and the use intraoperative imaging for correct placement confirmation. It is important to acknowledge that the precision of DBS surgery may be influenced by many variables, including the specific stereotactic system used, the proximity of the electrode trajectory to the ventricle, and the existence of intracranial air. The present stereotactic frames, which are surgical instruments used for the insertion of electrodes, together with robotized systems, often exhibit an inherent average geometrical inaccuracy of around 1 mm [189–192].

Specific targets

• Orbitofrontal cortex: SEEG electrodes are suitable for exploration of the OFC. They are equipped with electrode connections capable of spanning from the lateral cortical convexity to the medial cortex. However, it is difficult to achieve precise placement with such electrodes, which may affect subsequent stimulation efficacy/specificity. For chronic stimulation, DBS may be considered.

• Insula: Implantation of an electrode into the insula has been

shown to be a safe procedure. When the hypothesis indicates opercular participation, orthogonal electrodes are implanted. However, oblique electrodes provide a greater sampling rate of the insular region [193].

• Piriform Cortex: The PC is involved in epilepsy, particularly in cases of mesial temporal lobe epilepsy (TLE) where unpleasant olfactory auras can occur [194–196]. It is comparatively small, and its curved shape makes it challenging to achieve precise implantation of an electrode in the central area between the frontal and temporal regions [131–134]. Because of its curved shape, the thickness of the PC is reduced to only 1–2 mm [133]. Additionally, the location of the middle cerebral artery introduces a possible complication of electrode implantation [135].

• Amygdala: The precise magnitude of electrical current propagation originating from the electrodes and its interaction with cerebral architecture remains uncertain, representing a significant constraint on the efficacy or specificity of electrical brain stimulation. To address the possible adverse effects of amygdala stimulation, it is essential for forthcoming research to concentrate on precise electrode placement and stimulation settings that may selectively influence sub-nuclei within the amygdala.

• Nucleus Accumbens: The potential therapeutic use of DBS targeting the NAc is being investigated in the context of refractory psychiatric conditions, including obsessive-compulsive disorder, major depressive disorder, and substance use disorder [197,198]. Davidson et al. placed electrodes in the NAc around 2.5 mm anterior and 4 mm ventral to the anterior boundary of the anterior commissure [199].

• Medial temporal lobe: The medial temporal lobe is a crucial component in the process of recording episodic memories that include many forms of spatial and temporal information and is vulnerable to aging and Alzheimer's disease [200]. The electrodes are typically implanted orthogonally through the middle temporal structures in the medial temporal lobe [201–204].

Appendix 2. Brain stimulation devices

A. Intracortical Microelectrodes

Intracortical microelectrodes are electrodes placed along the shaft of small needles placed in an array configuration that penetrate in the cortex [205]. The needles are typically fabricated out of silicon and the length of the needles is limited to reach shallow layers of neurons in the cortex. This type of electrode can have a large resolution - to the extent of recording single action potentials (AP) of neurons - but its use is limited by the damage done to the tissue due to the number of penetrating needles and their stiffness. Due to their high spatial resolution (up to 0.2 mm) [206], APs are excellent candidates as biomarkers for stimulation devices. Extracellularly recorded typical APs can reach amplitudes up to 500μV [207], with varying frequencies [208]. But there are known firing rate instabilities in intracortical neural interfaces. Unaddressed instabilities can impair performance by introducing biases in decoded movements. Therefore, recalibration processes are necessary to maintain the stability of the feedback signal [209]. Furthermore, neural tissues are highly viscoelastic and soft, contrasting sharply with the traditionally rigid materials used in neural implants. This mismatch can lead to poor integration, inflammation, and ultimately, diminished efficacy of these implants. Therefore, the development of new, softer materials is important, that mimic the mechanical properties of neural tissues to enhance integration and reduce adverse reactions [146]. The type of device used nowadays is usually implanted for less than 30 days but can be used for chronic implantation through Investigational Device Exemptions.

B. Depth electrode

Depth electrodes are centimetre-long arrays with electrodes placed along their length, typically used for sEEG and for DBS. While the first type is used on the short term and is approved for less than 30 days implantations, DBS systems are approved for chronic stimulation. DBS systems comprise a signal generator implanted in the chest or abdomen of the patients and are used, for the treatment of chronic movement disorders like Parkinson's Disease, essential tremor or dystonia, or psychiatric disorders like depression or obsessive-compulsive disorder. The electrodes typically used have between 4 and 8 contacts. They are made of platinum-iridium and are 1.5mm in length, separated by insulating material ranging from 0.5mm to 1.5mm. To create a more complex and directional stimulation field, axially divided contacts have been developed and implemented in clinical practice [210].

C. Electrocorticography

ECoG is performed by placing electrodes on the surface of the cortex and is generally meant for recording brain signals, but it can also be used for temporary stimulation [211]. It requires a surgical procedure for placement and devices available on the market are only approved for short term or intraoperative stimulation. While ECoG's applications are currently limited to the brain's surface, it is of great interest to develop highly flexible and compliant devices providing access to sulci (folds) of the brain [146]. Companies such as Neurosoft Bioelectronics (https://

neurosoft-bio.com/technology), Wise (https://wiseneuro.com/), InBrain Neuroelectronics (https://inbrain-neuroelectronics.com/), Blackrock Neurotech (https://blackrockneurotech.com/), CorTec (https://www.cortec-neuro.com/) and others, are at the forefront of developing these soft and flexible implants for routine clinical use. Traditional ECoG placement requires a craniotomy, a large skull opening matching the size of the array. To limit the surgical invasiveness, research is exploring the minimally invasive deployment/insertion of ECoG arrays through a burr hole (~ 1cm^2) or a slit (length based on the implant's size and ~ 800 µm in width) using fluidic pressure [212] or a stiff guide [213] for deployment and insertion, respectively.

Nerve stimulation devices

Because the OB has the shape of a high aspect ratio cylinder, in this respect it resembles peripheral nerves. Peripheral nerve stimulation and spinal cord stimulation devices benefit from years of development of electrical interfaces for both recording and stimulation [214,215] that could be thought to be adapted to the OB. As for the neural implants, most of these are meant for short-term implantation or for animal research, but some of these devices have made it to the market for chronic implantation, such as for sacral nerve (for bladder and bowel problems), vagal nerve (to treat epilepsy and depression) or hypoglossal nerve (to treat sleep apnoea) stimulation. The least invasive version of nerve electrical interfaces is commonly referred to as cuff electrodes. Cuff electrodes could be of particular interest to stimulate the OB because - as their name indicates - they are capable of wrapping around the target nerve: with electrodes placed on the inside surface of the device ensuring a good contact with the nerve around its whole perimeter. Typical cuff electrodes however only comprise a few contacts, even though MicroProbes (Gaithersburg, MD, USA) for example proposes cuff electrodes for nerve diameters from 5 mm down to 56 µm and with flexibility on cuff length, number of contacts and their arrangement, such as 24 electrical contacts distributed along the perimeter of different rings as illustrated in Figure 5. The electrodes are in hundreds of µm thick for stimulation, illustrating the requirement for thick electrodes when voltages are applied to electrodes in saline environments.

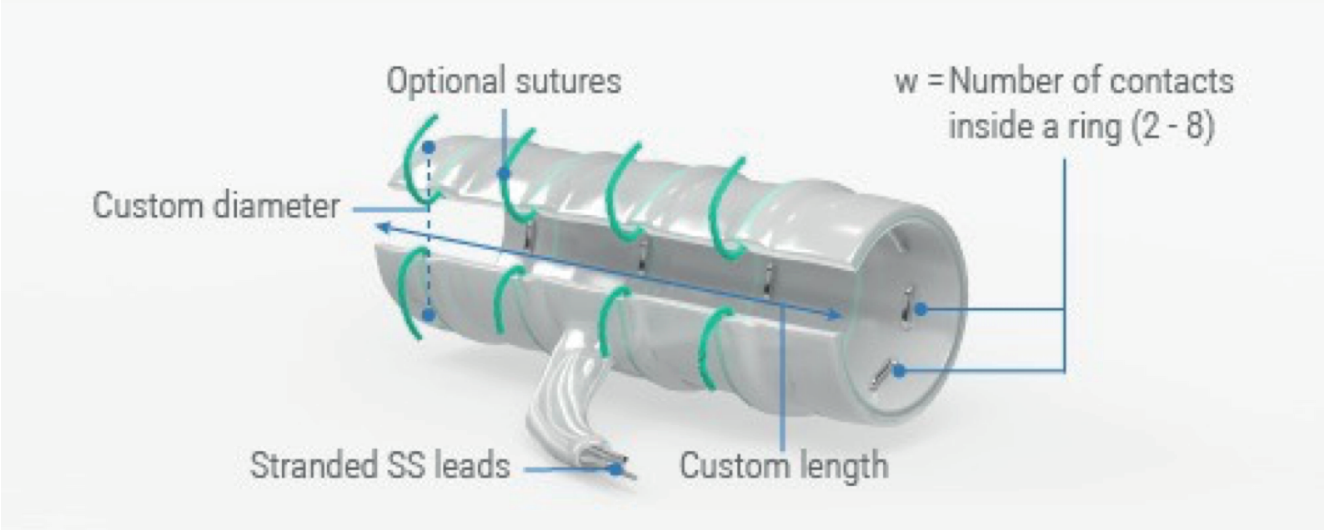

Figure 5. Illustration of a cuff electrode proposed by MicroProbes (permission to publish by MicroProbes, Gaithersburg, MD, USA).

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