INTERNATIONAL SEVEN JOURNAL OF HEALTH RESEARCH
ISSN: 2764-9415

Olfaction unraveled: Anatomy, dysfunctions and implications for health and sensory perception

Olfato desvendado: Anatomia, disfunções e implicações na saúde e percepção sensorial

DOI:10.56238/isevjhv2n2-013
Receiving the originals: 03/04/2023
Acceptance for publication: 24/04/2023

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ABSTRACT
This review addresses the fundamental role of smell in human life, including its function in detecting odors, influencing personal preferences, and social behaviors. The article discusses the anatomy of the olfactory system, covering the structures involved in olfactory detection and processing. The evaluation of olfactory function is explored using different approaches, such as standardized tests, clinical examinations, and imaging techniques, which allow an accurate assessment of olfactory capacity and assist in the diagnosis of olfactory-related disorders. Additionally, conditions such as anosmia and dysosmia are addressed, investigating their causes, impacts, and diagnostic methods. Anosmia may be due to lesions in the olfactory structures or underlying medical conditions, while dysosmias involve qualitative alterations in the perception of smell. The article also discusses the prevalence of olfactory alterations in different contexts, including the COVID-19 pandemic, which has shown association with temporary or persistent loss of smell. Finally, the importance of advancing research in this area for a thorough understanding of the pathophysiology of olfactory alterations is emphasized. This understanding is critical for the development of personalized and effective therapeutic strategies. Collaboration between researchers and healthcare professionals is essential to drive scientific and clinical advances related to this topic. It is hoped that this review will provide a comprehensive overview of olfaction, contributing to a better understanding of olfactory mechanisms and supporting more effective clinical approaches to the diagnosis and treatment of olfactory disorders.

Keywords: Olfactory pathway, Olfaction disorders, Anosmia, Dysosmia, COVID-19.

1 INTRODUCTION

When we breathe, we perceive the smells of life and capture a bit of reality. This chemical perception begins in the nasal cavity and, after following the olfactory pathway and establishing several connections, activates different cortical areas. Thus, smell allows us to sense the aromas of food, flowers, perfumes, and so many other things that surround us. Thus, the olfactory organ and its associated structures are important for perceiving the environment and play a crucial role in survival, health, and well-being.[1,2].

The olfactory nerve, one of the twelve pairs of cranial nerves, plays a fundamental role in the sense of smell. Located in the nasal region, where the odor receptor cells are, it picks up molecules present in the air and transmits nerve impulses to the cerebral cortex through its afferent nerve pathways.

Unfortunately, the olfactory system is susceptible to damage, often as a result of traumatic brain injury.[3]. Such occurrences can result in quantitative or qualitative disturbances of olfaction, with substantial consequences for the safety and quality of life of the individual.[4]These occurrences can result in quantitative or qualitative disturbances of olfaction, with substantial consequences for the safety and quality of life of the individual. In this context, accurate and systematic assessment of olfactory function becomes essential, not only to identify alterations but also to guide appropriate interventions and monitor the progression of the condition over time.

This article aims to elucidate the critical role of the olfactory nerve in chemical perception, exploring its anatomy and the process by which odors are transmitted from the environment to conscious perception in the brain. Through a comprehensive review of the scientific literature, we aim to provide a detailed understanding of the olfactory pathway, its neural connections, and how loss of function, due to damage or disease, can impact an individual's health and well-being. In addition, we will discuss the importance of accurate assessment of the olfactory nerve and present various assessment methodologies, highlighting their relevance in clinical practice.

2 METHOD

In this narrative review, we analyze the anatomy, connections, disorders, and evaluation of the olfactory nerve from an extensive range of scientific literature published in English, Portuguese, and Spanish, without date restriction.

For the scientific literature review, we used the PubMed databases, in addition to Google Scholar and the CAPES Periodicals platform. The keywords used in our search included "olfactory nerve", "olfaction", "olfactory pathway", among other related terms to select the most relevant

INTERNATIONAL SEVEN JOURNAL OF HEALTH RESEARCH
ISSN: 2764-9415

studies. Additionally, we conducted an extensive search in other documents not published in academic journals.

With this approach, we were able to provide a detailed and up-to-date overview of the anatomy of the olfactory nerve, its connections, functions, and clinical evaluation, making this work an informative resource for students and health professionals.

3 RESULTS

After a meticulous appreciation of the scientific literature and gray literature, the findings of this narrative review will be laid out, addressing integral aspects such as the olfactory nerve, olfactory pathways, olfactory disorders, and olfaction assessment. In order to optimize understanding, the data will be systematically structured in distinct sections. This review aims to illuminate the complexity of the human olfactory system, as well as its multifactorial and substantial impact on human existence, from the perception and interpretation of odors to the influence exerted on socialization, individual preferences, and behavior. Thus, this work aims to provide a deeply educational and stimulating examination of this intriguing area, encouraging further reading through the promise of meaningful and comprehensive insights into this remarkable domain.

3.1 THE MULTIDIMENSIONAL IMPACT OF SMELL ON HUMAN LIFE: FROM PERSONAL PREFERENCES TO SOCIAL BEHAVIOR

The human olfactory capacity impressively holds the potential to differentiate a vast spectrum of odorous stimuli. The inherent competence in our olfactory system allows for the discrimination of at least a trillion different odors, which underlines the extraordinary aptitude of this sense compared to others[5].

Throughout the human evolutionary process, the sense of smell has proven crucial, exerting a determining influence on the detection, selection, and preparation of foods, as well as the identification of medicinal, aesthetic, and household products. Odors play a primary role in reconciling nutritional, toxic and sensory/hedonic properties during the preparation and preservation of foods and beverages such as coffee and wine[2,6].

In the complexity of interpersonal communication, the function of smell is multifaceted. In addition to the perception of body odors and fragrances, it plays a crucial role in the detection of pheromones, which are chemical compounds produced by animals with the ability to alter the behavior and physiology of other individuals of the same species. This competence is fundamental for intra- and interspecific communication.[7].

The olfactory ability of human beings is not restricted only to the detection of natural smells. In many cultures, it is common to use scents to mask odors, induce positive emotions, and enhance interpersonal communication. This specialized manipulation of olfactory stimuli can provide insights into anatomical differences in the olfactory system between different species.

Smell goes beyond its role in identifying objects and people, because it also exerts influence on social, emotional, and behavioral aspects. It plays a role in modulating interpersonal relationships and our integration into social groups. In addition, smells influence our individual preferences and personality, and even have economic implications.

For example, by means of smells, we are able to develop affection or aversion to foods or objects. This phenomenon has a significant economic impact, since olfactory preferences can affect purchasing decisions[6].

In short, the most striking influence of smell in our species lies in the modulation of behavior and interpersonal relationships, influencing our integration into social groups or classes, as well as our preferences and personality[6].

3.2 SMELL: THE COMPLEX JOURNEY OF THE CHEMOSENSORY SYSTEM AND ITS IMPACT ON EVERYDAY LIFE

The olfactory system is a complex and refined network responsible for detecting, identifying, and interpreting different odors. The perception of smell results from the interaction between the chemical stimulus, **odor molecules in the air,** and the neuronal receptors located in the nasal cavity. This signal is converted into an action potential and then transmitted along the olfactory pathway to the cortical areas of the brain.

The importance of this chemosensory function is revealed in food, survival, perfumery, marketing, emotions and various therapies[8-11]. In the marketing field, for example, olfaction is strategically used to create sensory experiences that influence consumer behavior. In aromatherapy, essential oils with therapeutic properties are used to promote physical and emotional well-being[12].

The ability to distinguish and react to different odors is evident in the way our system reacts to odors associated with feces, vomit, and decomposition, eliciting a repulsion reaction. Similarly, the perception of body odors can be significantly influenced by the context in which they are perceived. This suggests that exposure to repulsive stimuli can prepare our system to respond to potential microbial threats, illustrating the complex relationship between repulsion, olfaction and health[13].

3.3 ANATOMY OF OLFACTION

The olfactory system, an intricate network of structures from the sensory cells in the nasal mucosa to the brain's interpretation of odors, forms the basis for understanding olfactory disorders. In the following sections, we will take a closer look at this fascinating olfactory anatomy.

3.3.1 The olfactory organ

The **olfactory organ** consisting of part of the nasal mucosa and olfactory glands is the sense organ that specializes in the function of smell. For the odor to reach the cerebral cortex and become conscious, other anatomical structures and many connections are required. The odor conduction pathway begins in the olfactory region of the nasal cavity and continues to the cerebral cortex. In this afferent pathway we find: olfactory receptors and olfactory nerve, olfactory bulb, olfactory tract and olfactory striations.[14].

The human sense of smell distinguishes thousands of volatile compounds due to chemoreceptors in the olfactory region of the nasal cavity, occupying an area of 2.0 to 2.5 cm². With about 50 million receptor cells, each with 8 to 20 cilia and immersed in a 60 µm mucous layer, these neurons interact only with volatile substances that are soluble in mucus. Renewing every 40-60 days, the axon branches reach the olfactory bulb, form glomeruli, and connect to the mitral cells, increasing the sensitivity of the olfactory signal sent to the brain .[21,6]

3.3.2 Olfactory Nerve [I]: Structure and Function.

The olfactory nerve is one of the twelve pairs of cranial nerves and represents the first of them (1st cranial pair). It is a **special afferent nerve** that is responsible for conducting sensory information related to olfaction. It has a complex structure, being composed of multiple nerve filaments that cross the **lamina cribriformis of** the ethmoid bone, located on the roof of the nasal cavity[15,16].

The olfactory **n. is** an **atypical nerve**, considered to be a projection of the CNS or a **nerve tract exteriorized** from the hindbrain. In addition, the olfactory "nerve" does not have a standard organization, i.e. a nerve trunk in the form of a cord or ribbon. It is actually made up of several small nerve fibers that bundle together to cross the **lamina cribriformis of the ethmoid bone**, conducting olfactory information to the **olfactory bulb**[15,17-20] inside the cranial box (Figures 1 and 2).

Figure 1. Bulb and olfactory tract.

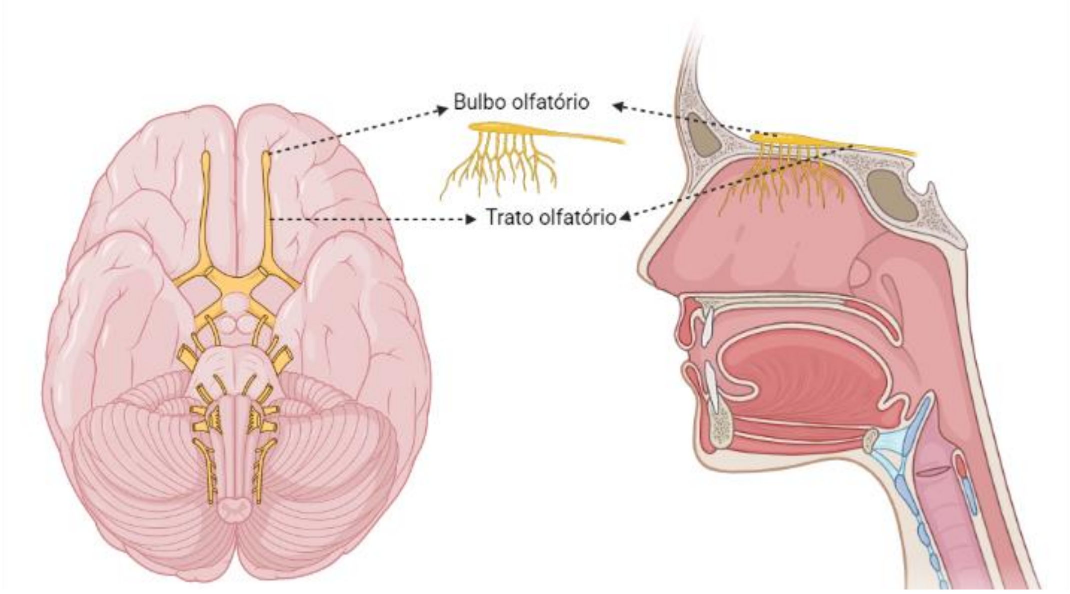

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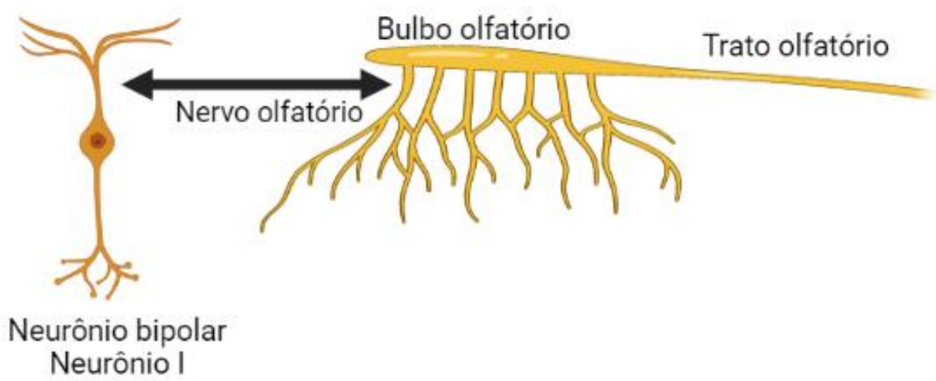
Figure 2: Structures of the olfactory pathway. Bipolar neuron, olfactory nerve, bulb, and olfactory tract.



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3.3.2.1 Origins of the Olfactory Nerve

Cranial nerves are essential structures of the nervous system that connect to the encephalon and transit through the skull. Each cranial nerve has **three distinct origins**: the **real origin**, the **apparent origin in the brain**, and the **apparent origin in the skull**. The real origin corresponds to where the nerve fibers originate, that is, in the pericytes of the neurons. The origin apparent in the skull is the point of entry or exit of the nerve in the skull, through a hole or passage channel.

In turn, the apparent origin in the brain refers to the nerve's connection site with the central nervous system.

It is important to understand the three origins of the cranial nerves to better understand how each nerve acts in our body, and how the diagnosis and treatment in case of injuries or diseases related to these structures should be made. In the case of the olfactory nerve, for example, its origins are:

1. **The actual origin of** the olfactory n. is in the **olfactory region of the** nasal cavity, where the **bipolar neurons** or first order neuron, **Neuron I**, of the olfactory pathway, derived from the CNS, are located. The pericytes of these afferent neurons are distributed in the nasal mucosa of the olfactory region situated in the upper nasal concha, adjacent nasal septum and the roof of the nasal cavity.[21].
2. **The apparent origin in the skull** is in the **lamina cribriformis of the** ethmoid bone, on the roof of the nasal cavity;
3. **The apparent origin in the brain** is in the **olfactory bulb**, an ovoid structure made up of different types of nerve cells. The olfactory receptor neurons in the olfactory bulb are the periglomerular cells, mitral and tufted cells. The mitral and tufted cells are the efferent neurons of the bulb and send their projections to the cerebral cortex.

The **bipolar neurons** (Neuron I) send their amyelinic axons (olfactory nerve), which after crossing the **lamina cribriformis of** the ethmoid bone, penetrates the **olfactory bulb,** where it makes the first synapse with the **mitral** and **tufted cells**, called second order neurons or **Neuron II of** the olfactory pathway[15,17-19,21].

3.3.3 Central Pathway: the two neurons of the olfactory pathway

Our sense of smell is a very important and interesting sense. It is responsible for **identifying the odors present in the environment** and in the food we eat. But have you ever stopped to think how the olfactory pathway that allows us to sense these odors works?

The olfactory pathway is direct, that is, it does not synapse in the thalamus like the other afferent pathways[14]. In addition, it has two neurons. The first neuron is called the **I neuron**, which is a **bipolar** receptive neuron found in the olfactory mucosa, and not in a ganglion as occurs in other sensory pathways. This neuron is responsible for receiving the olfactory stimuli and transmitting them to neuron II.

The second neuron, called **neuron II**, is located in the olfactory bulb. It receives the information from neuron I and processes it so that we can perceive the identified odor. It is important to emphasize that this pathway is unique and different from the other sensory pathways because it is not transmitted to the thalamus before reaching the cerebral cortex.

Finally, it is amazing to think about how our olfactory pathway works in such a complex and subtle way at the same time. Even with only two neurons, we are able to identify a wide variety of smells that make our lives more special. Therefore, we should value and take care of our olfactory health so that we can continue to explore this very important sense in our lives.

3.3.3.1 Bulb and Olfactory Tract

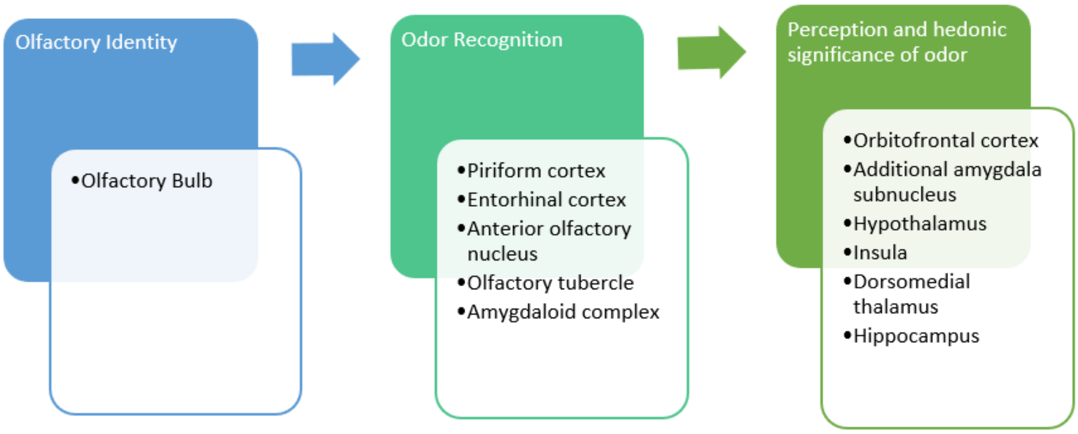
The axons of the cells of the olfactory **bulb** form the **olfactory tract**, which is responsible for conducting the signals to the cerebral cortex - **primary sensory cortex** and **tonsils**, so that we can identify and smell odors. In addition, the **anterior commissure** has fibers that connect the olfactory bulbs to the anterior olfactory nucleus[21,22]. It is thanks to this amazing team of cells and their connections that we are able to appreciate and recognize the different scents that surround us.

The **olfactory tract** is an important structure for our sense of smell. It is located on the underside of the frontal lobe and is about 3 to 3.5 cm long. This tract is composed of axons from the mitral and tufted cells of the olfactory bulb[20,21,23]which form the olfactory **trigone**, i.e. the expanding area of the olfactory tract that divides into olfactory striations.

According to studies, our brain has three types of **olfactory striations**: medial, lateral and intermediate[24]. The **lateral olfactory striatum** is the most developed of all of them and contains most of the fibers that carry olfactory information to different regions of the brain, such as the parahippocampal gyrus, the uncus, preamygdaloid and pre-piriform areas[3,20,23,25]. The **medial olfactory stria, on the other hand,** is thinner and shorter and has fibers that cross the anterior commissure to the olfactory bulb on the opposite side.[23]. This olfactory information is transmitted to different areas of the brain, such as the limbic **system, the hypothalamus** and the **thalamus.**[26]which is fundamental to human behavior and emotions.[27].

INTERNATIONAL SEVEN JOURNAL OF HEALTH RESEARCH
ISSN: 2764-9415

Figure 3. Schematic to illustrate the olfactory pathway and its connections, highlighting the importance of this system in the identification, recognition, and perception of odors.



The **olfactory bulb** is recognized as the encoding center for olfactory identity. From it, olfactory information is directed to the primary olfactory cortex via the olfactory tract. The primary olfactory **cortex** encompasses large areas of the ventral **temporal lobe**, with the **piriform cortex** being its main component. In addition, olfactory information is distributed extensively throughout the brain. In this context, the **orbitofrontal cortex** stands out as the secondary olfactory cortex. Recent research indicates the involvement of the **thalamus in olfactory** identification, hedonic processing, olfactory control and attention[28,29].

3.4 OLFACTORY NERVE EVALUATION APPROACH

When assessing olfactory dysfunction, it is essential to take a systematic approach, including a detailed olfactory history, examinations, and investigation of associated symptoms. Understanding the quality, laterality, and the patient's perception of the loss assists in identifying the cause, taking into account factors such as nasosinusal symptoms, viral infections, head trauma, and occupational exposures[4].

To evaluate the integrity of the olfactory pathway, it is necessary to determine whether the odor is real or perceived, whether the alteration occurs on one or both sides, and to collect the patient's history. During the history taking, it is essential to investigate the patient's personal and family disease history, as well as when the symptoms appeared, their intensity, and related signs or symptoms. It is also necessary to analyze whether the onset was acute or gradual[4].

It is important to consider a history of head trauma or viral infections, which often cause sudden loss of smell. This condition is different from allergic rhinitis, nasal polyps, or tumors, which usually have a slower evolution of symptoms[30]. In addition, it is crucial to ask about possible occupational exposures to toxic substances, as well as smoking, medication, or illicit drug use (Chart 1).

Table 1. Substances toxic to the nasal mucosa, olfactory region, that can alter the sense of smell.

Substance	Reference
Amebicides and anthelmintics: Metronidazole, nizidazole	31
Local anesthetics: Cocaine, Procaine, Tetracaine	30
Antidepressants: amitiptriline	31
Intravenous antibiotics: Aminoglycosides (gentamicin)	31
Antimicrobials: Quinolones, Macrolides, Griseofulvin, Neomycin, Tetracyclines	30
Antirheumatics: mercury salts, D-penicillamine, gold, colchicine, allopurinol	30,31
Antithyroid drugs: Propylthiouracil, Thiouracil	30
Cardiovascular: ACE inhibitors, Nifedipine, Amlodipine	30,32
Volatile organic compounds: Formaldehyde	31
Inhalation drugs: cocaine and crack	31
Gastric: Cimetidine	30
Immunosuppressants: Metrotrexate, azathioprine	31
Heavy metals: mercury, and lead hair dyes	31
Opioids	30
Sympathomimetics	30
Intranasal saline solutions: Acetylcholine, Menthol, Zinc sulfate	30,32
Betablockers, calcium channel blockers	32

3.4.1 Olfactory Tests and Clinical Approaches

After completing the initial anamnesis, it is time to perform the olfactory test. A number of evaluation methods are employed in these tests or olfactory examinations, such as the electro-olfactogram, olfatometer test, olfactory threshold test or minimal perceptible odor, olfactory-pupillary reflex, olfactory-respiratory reflex, and olfactory nerve evoked potentials[33].

Nasal examination is essential to investigate olfactory disorders. Anterior rhinoscopy identifies deformities that cause conductive loss of smell, while endoscopy evaluates the nasal cavity and nasal pharyngeal part for signs of inflammation or other abnormalities. Additional examinations should be guided by the history or findings of the nasal examination, including neurological or head and neck examinations as necessary[4].

Suspicion of olfactory nerve damage should be considered when symptoms such as periorbital ecchymosis, nasal liquoric fistula, epistaxis, nasal fracture, and proptosis are present[3].

3.4.1.1 Standardized Approaches

Standardized tests are fundamental in quantifying and monitoring people with olfactory alterations, allowing differentiation between anosmia, severe hyposmia, and other dysosmias. One example is the *University of Pennsylvania Smell Identification Test (*UPSIT), which includes 40 different odors[32].

Instrumental assessments face challenges in clinical practice, while subjective assessments, although faster, are less reliable. Quantitative methods, such as UPSIT, have a partially objective character and require the cooperation of the individual[34].

The following are examples of tests mentioned in the literature, along with a link to more information:

1. University of Pennsylvania Smell Identification Test - UPSIT was developed by Richard L. Doty and collaborators at the *Monell Chemical Senses Center* and the *University of Pennsylvania School of Medicine* https://sensonics.com/product-category/smell-products/
2. The *Barcelona Olfactory Test* (BAST-24) is a sensory test that evaluates the olfactory and gustatory capacity in adults. This kit (figure 4) is used both in research and for diagnostic purposes in hospitals, doctors' offices, and research centers. The odors are packaged on a solid base in airtight, numbered boxes. The test includes 20 odors to evaluate the olfactory nerve, four for the trigeminal nerve, five gustatory and one neutral[35]. The essences used are standardized and suitable for cosmetic and/or pharmaceutical use. The vehicle for these essences is harmless, allowing the application of the test for about 2 years.[36]. https://www.olfabast.com/producto/test-diagnostico-sensorial-bast-24/

Figure 4. BAST-24 sensory test that allows determination of olfactory and gustatory ability in adults.

Source: https://www.olfabast.com/producto/test-diagnostico-sensorial-bast-24/

3. *Sniffin Sticks* (Burghardt®, Wedel, Germany), developed by Hummel in 1997 and validated in several European countries, is a psychophysical test that allows the evaluation of the patient's sense of smell. It consists of three tests: olfactory threshold, identification, and discrimination. Although its complete and systematic application is challenging in routine clinical practice, it is a fundamental tool for assessing and monitoring olfactory performance as a function of physiological events, such as aging, or pathological events.[34]. Some examples are the n-Butanol Threshold Test (Figure 5) and the 2-Phenyl Ethanol Threshold Test, which determine the olfactory threshold. There is also the Discrimination Test, which evaluates the ability to distinguish odors, and the *Kids Ident Test*, aimed at children between 6 and 17 years old. https://www.burghart-mt.de/en/online-shop/standard_tests/

Figure 5. Extended n-Butanol test for detailed olfaction analysis, consisting of three assessments: threshold, identification and discrimination ((Burghardt® , Wedel, Germany).

Source: https://www.burghart-mt.de/en/online-shop/standard_tests/

4. *Connecticut Chemosensory Clinical Research Center* (CCCRC)[37]Founded in 1983, the CCCRC is a research institution devoted to chemosensory disorders, based at the University of Connecticut School of Medicine. In the area of olfactory assessment, the CCCRC has developed several diagnostic instruments, including the Connecticut Olfactory Test (COT) and the University of Pennsylvania Odor Identification Test (UPSIT). In addition, the CCCRC focuses on investigating correlations between olfactory dysfunction and various medical conditions, such as Alzheimer's disease.

Within the range of evaluative tools, two specific tests stand out: the olfactory threshold test and the identification test.

In the olfactory threshold test, the participant is asked to identify the most diluted concentration of N-butanol[38,39] in a dilution series, choosing between the options "odor" or "odorless". This procedure must be performed correctly four times to ensure the accuracy of the result.

On the other hand, the identification test presents a series of 10 different odors stored in vials, the goal of which is to challenge the participant to select the correct description from a set of 20 proposed options. The individual's ability to correctly identify these odors provides a valuable indication of his or her olfactory functioning.

In clinical practice, olfaction can be assessed with subjective tools such as visual scales, smell tests, and questionnaires. Psychophysical olfactory tests encompass odor detection, memory, identification, and discrimination, and are culturally limited due to regional dependence.[40].

The traditional clinical evaluation of olfactory function employs a variety of aromatic substances with distinct and recognizable odors, including coffee powder, garlic, mint, cinnamon, clove, camphor, and lemon extract. To ensure the accuracy of the evaluation, the investigation is conducted in one nostril at a time, starting with the side that is allegedly altered. In this process, the non-examined nostril is occluded to avoid interference.[3,19,21,22,41].

The evaluation protocol consists of four main steps. Initially, the patient is asked to **inhale** the odor with his eyes closed, to avoid any visual clues that might influence his perception. Next, they are asked to indicate whether or not they are able to **detect the odor** presented. The third step involves **rating** the odor as pleasant or unpleasant, providing a hedonic evaluation of the stimulus. Finally, the patient is challenged to **identify** the odor presented.

Despite the usefulness of this traditional approach, it is important to highlight its limitations. A primary disadvantage is the inherent subjectivity of the assessment, which can be influenced by individual factors, including patient age. Therefore, it is essential to consider these variables when interpreting the results.

3.4.2 Imaging in the Evaluation of Olfactory Dysfunction

Several imaging techniques, such as magnetic resonance imaging (MRI), computed tomography (CT), single photon emission computed tomography (SET), and positron emission tomography (PET), assist in the investigation of olfactory pathways and the diagnosis of olfactory loss. The technique chosen depends on the context of symptoms and patient history[32].

Computed tomography (CT) of the paranasal sinuses is a useful imaging exam for detecting nasosinusal inflammatory diseases, nasal cavity tumors, and cranioencephalic traumas, allowing the identification of possible fractures that compromise olfactory function. This test contributes to a more precise diagnosis of the causes of olfactory dysfunctions and to directing the appropriate treatment.[31].

Magnetic resonance imaging (MRI) of the skull and paranasal sinuses is indicated in idiopathic cases of persistent olfactory dysfunction for more than three months, as well as for investigation of tumors, arteriovenous malformations, post-trauma intracranial hemorrhages, ischemia, and aplasia of the olfactory bulb. The evaluation of the dimensions of the olfactory bulb, although it does not have robust levels of evidence, may provide prognostic information, since reduced sizes or the absence of the olfactory bulb indicate a lower prospect of therapeutic success[31].

Imaging is indicated when intracranial or nasosinusal neoplasms, neurological, central, congenital causes, and traumatic brain injury are suspected. CT is the preferred modality for evaluating nasosinusal disorders, while MRI is more appropriate for neurological conditions or traumatic brain injuries. The other modalities are not recommended for routine diagnostic investigation of anosmia. However, they can provide valuable information in the context of research or in the presence of suspected functional impairment of the olfactory system and associated neurological pathways[32].

3.5 SMELL AND ITS DISORDERS S

Olfaction disorders can be quantitative (anosmia, hyposmia, hyperosmia) or qualitative[4]. The olfactory pattern that is considered normal is called **normosmia**[32]. Chart 2 shows the terms used to describe olfactory functions and dysfunctions, along with their corresponding definitions.

Table 2. Definitions of disorders and other aspects related to olfaction.

TERMS	TYPE[31]	DEFINITION[42]
Anosmia	Quantitative	Total loss of smell or "smell loss".
Hyposmia or microsmia	Quantitative	Partial loss of sense of smell, i.e. reduced ability to perceive odors.
Hyperosmia	Quantitative Qualitative	Exaggerated sense of smell, increased perception of odors
Dysosmia	Qualitative	Distorted sense of smell, altered odor perception and includes the perception of odors without a stimulus present (phantosmia) and altered perception of an odor after stimulus (parosmia and troposmia).
Parosmia	Qualitative	Perversion of smell.

Cacosmia	Qualitative	Unpleasant perception of a certain odor, with or without the chemical stimulus.
Olfactory agnosia	Qualitative	Inability to identify or classify an odorant.
Presbiosmia	Quantitative	Age-related hyposmia.
Osmophobia	Qualitative	Intolerance or aversion to specific odors.
Euosmia	Qualitative	Sensation of pleasant odor[31].
Olfactory aphasia		Loss of odor denomination
Retronasal sense of smell	Quantitative Qualitative	Odor detection from the oral cavity during swallowing of food[31,43].
Orthonasal sense of smell	Quantitative Qualitative	Perception of nasal odors during inspiration[31,43].

Table 2 presents an overview of olfaction disorders, providing definitions and characteristics of each. In addition, it includes aspects related to olfaction, such as retronasal olfaction and orthonasal olfaction. This information is relevant for understanding the diversity of problems that can affect the sense of smell, and assists in the diagnosis and treatment of these conditions.

The analysis of the duality between the proposed olfaction types, orthonasal (nose-smelling) and retronasal (mouth-smelling), is extremely relevant for a detailed understanding of olfactory perception. This approach allows us to investigate how these different mechanisms of odor detection and processing influence our sensory experience, and provides important insights for areas such as neurobiology and sensory therapies.[43].

With the aging process, there are changes in the olfactory threshold and a prevalence of specific age-related olfactory disorders called presbymbiosmia. This condition is related to the loss of olfactory receptors and a significant decrease in olfaction starting at age 65, which is accompanied by a decline in olfactory function, affecting the olfactory epithelium and bulb, resulting in a reduction in glomeruli and mitral cells, with individuals over 90 years of age presenting less than 30% of these structures; in addition, more than half of people between 65 and 80 years of age have olfactory impairment, increasing to more than three-fourths after 80 years of age.[44-46].

3.5.1 Anosmia: impacts and challenges on the perception of smell and taste

Anosmia, an olfactory disorder characterized by general or specific loss of[47] of smell, is classified into conductive and sensorineural. Conductive anosmia is caused by nasosinusal conditions, such as rhinitis, rhinosinusitis, polyps, and tumors[32]. On the other hand, sensorineural anosmia involves congenital, toxic, and neurological causes. A study of subjects with non-conductive olfactory dysfunction showed that anosmia was more common in congenital and post-traumatic cases .[32].

In a 2004 study of the population of Skövde, Sweden, the overall prevalence of olfactory dysfunction in adults was 19.1%, including cases of hyposmia and anosmia. More specifically, the prevalence of anosmia reached 5.8%, highlighting the significant presence of this disorder in the population. It was also confirmed that the prevalence of anosmia shows an increasing trend with advancing age. Moreover, individuals with nasal polyps and diabetes mellitus showed a statistically significant association with an increased risk of anosmia.[48].

The diagnosis of anosmia initially involves taking the patient's history and performing a physical examination in order to identify the cause of the loss or alteration of smell. Often, patients report changes in taste perceptions. A detailed medical history helps to determine the onset of the disorder and possible associated factors such as virus-related olfactory loss, often associated with cold or flu symptoms[32].

After the anamnesis, the physical examination is focused on the head and neck area, nasal cavities, sinuses, cranial nerves, and mental status. If neurological disease or related symptoms are suspected, additional neurological examinations may be necessary. Nasal endoscopy is used to examine the olfactory fissures for lesions, masses, or nasosinusal disease and has proven to be more effective for diagnostic purposes than anterior rhinoscopy[32].

Research by Bitter et al. (2010) using morphometry and MRI revealed marked anatomical changes in specific brain areas of anosmic patients. The most significant changes, notably atrophies, were observed primarily in the medial prefrontal cortex. Furthermore, these changes were found to be pronounced in patients whose disease duration exceeded two years. Atrophy was also present in brain regions related to the sense and memory of smell[49].

Anosmia affects the ability to detect and consume appropriate foods. Studies show that individuals with a loss of sense of smell have difficulty identifying spoiled foods, resulting in the accidental consumption of foods unfit for consumption. In addition, olfaction disorders can cause social, psychological, and nutritional problems. Anosmia can lead to serious consequences, such as gas accidents, eating spoiled food, depression, and eating disorders[13,22,50].

During the pandemic of COVID-19 **sudden anosmia** with uncertain duration and reversibility was observed[51]. This symptom was a warning sign of SARS-Cov-2 infection.[52]. Other studies have highlighted besides **anosmia**, the disorders of **hyposmia**, **parosmia** and **dysgeusia**. In patients followed up in the post-COVID-19 period, parosmia and phanthosmia were observed.[53]. It appears that SARS-Cov-2 can cause lesions in the cells of the olfactory epithelium and neuronal cells .[24]

COVID-19-related anosmia shows a clinical correlation with the expression of angiotensin-converting enzyme receptor 2 (ACE2) in olfactory cells, the etiology of which may be related to the invasion and replication of the SARS-CoV-2 virus in the respiratory epithelium[54,55].

3.5.2 Osmophobia: understanding olfactory sensitivity

Patients with **osmophobia** may experience anxiety, nausea, or discomfort in response to certain smells, such as perfume (lavender, musk, mint/mint, floral) and smoke. The cause of osmophobia has yet to be determined, but it may be related to psycho-emotional or neurological changes. Therefore, this sensitivity to odors is used, for example, in differential diagnosis of headache because of its prevalence in patients with migraine[56,57].

Treatment for osmophobia may include cognitive-behavioral therapy (CBT) and medication to help combat the symptoms according to the patient's medical history.

3.5.3 Qualitative olfactory disturbances: olfactory dysosmias and hallucinations

Dysosmias are qualitative alterations of smell, which include parosmia and phantosmia. Parosmia is characterized by the distorted perception of a specific odor. A classic example is when an individual interprets the smell of coffee as if it were the smell of dirt. Phantomophilia, also known as olfactory hallucination, is the perception of smells in the absence of external odorous stimuli.[58,59].

Associated with both conditions is cacosmia, defined as an unpleasant odor perception, an unpleasant phantosmia. Cacosmia can manifest itself either in the form of parosmia, when associated with an external stimulus, or in the form of phantosmia, when it occurs without a specific odorous stimulus. It is important to note that individuals with olfactory dysfunction may experience these conditions singly or in combination, and that there may be progression between the different types of alterations, such as a transition from anosmia to parosmia[58,59].

Olfactory hallucinations, which include phantosmia, are clinically correlated with olfactory neuropathies and psychiatric disorders. Evidence points to activation of the limbic circuitry and sensory areas of the brain in such conditions. The etiology of these disorders is multifactorial, including genetic factors, traumatic injuries, and metabolic conditions. Treatment is usually symptomatic and directed at the underlying cause.

Qualitative olfactory distortions, such as phantomesia, represent alterations in olfactory perception that may have both peripheral and central causes. These disorders can manifest unilaterally, but in about a quarter of cases, a progression to involve both nostrils is observed. This progression may be due to dysfunctions in the primary olfactory neurons and their support cells in both nostrils, or it may be triggered by a central process activated by one of the nasal cavities[59].

3.6 PREVALENCE AND IMPACT OF OLFACTORY DYSFUNCTION: GLOBAL PERSPECTIVES AND IMPLICATIONS OF THE COVID-19 PANDEMIC

In several studies conducted globally until 2016, the prevalence of olfactory disorders was found to range from 1.4% to 24.5% in the general population[47]. Such studies exposed a scenario of considerable olfactory impairment, with nuances due to different age groups and other particularities of the studies.

As reported in a systematic review and meta-analysis published in 2021, the overall prevalence of olfactory dysfunction in a sample of 175,073 healthy individuals aged 18 to 101 years was estimated at 22.2%. This prevalence was significantly higher when assessed using objective olfactory tests compared to subjective tests and showed higher values in studies using expanded identification tests and in populations with a mean age of more than 55 years. The data suggest that the prevalence of olfactory dysfunction in the general population is intrinsically linked to the test method applied and the age of the population evaluated.[60].

However, the pandemic of COVID-19, which began in late 2019, has affected these statistics substantially. Smell disturbance is one of the most recurrent symptoms of the disease, which has likely raised the prevalence around the world. Therefore, it is reasonable to assume that the current data, especially post-pandemic, shows an increase in the prevalence of these disorders, highlighting the need for continued research and public health actions focused on this issue.

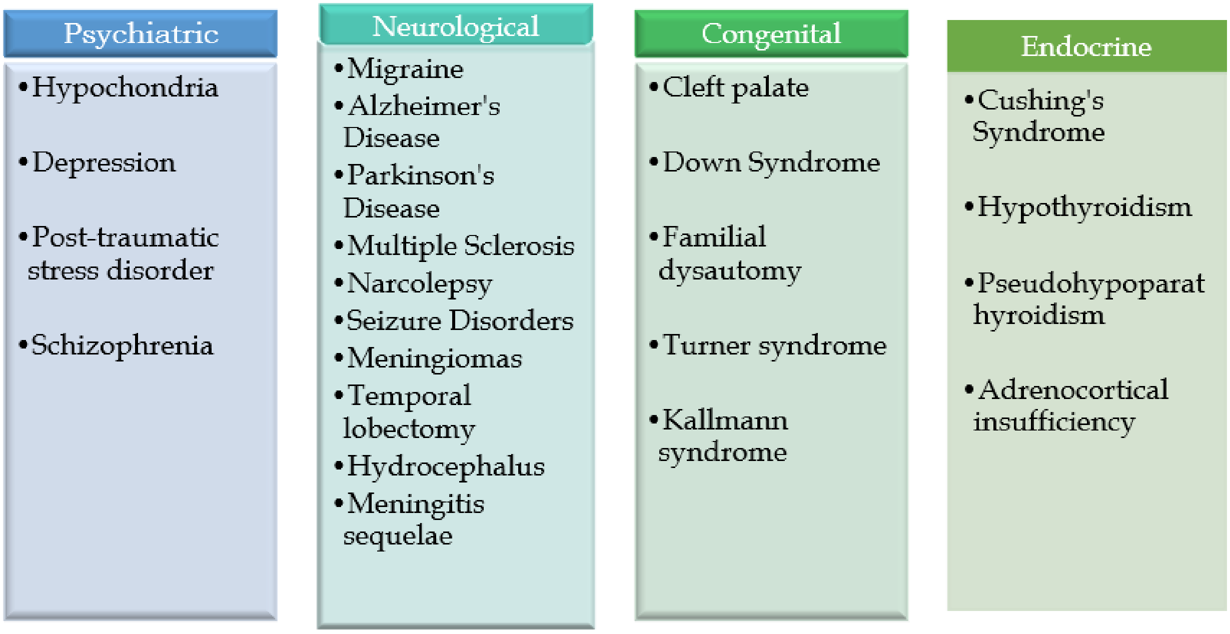
In a 2021 survey conducted in Iran, olfactory dysfunction was assessed in 50 patients with SARS-CoV-2 using the Iran Smell Identification Test (Iran-SIT). Participants, confirmed by PCR as infected, demonstrated significantly lower scores on the test, indicating more pronounced impairment of olfactory function compared to the general population. A negative correlation between age and olfactory performance was observed, signaling that olfactory acuity tends to decline with advancing age. These results highlight olfactory dysfunction as a common symptom in the SARS-CoV-2 infected population, suggesting its potential use in screening programs taking into consideration the age of the patient.[61].

In an analysis conducted at a large London hospital, it was found that 12.8% of patients previously hospitalized due to COVID-19 still experienced ongoing problems with smell or taste up to one year after infection. These symptoms persisted regardless of age, gender, ethnicity, smoking habits, C-reactive protein levels, use of intubation and ventilation or oxygen supplementation. Patients with impaired sense of smell or taste had a marked decline in quality of life, with a particularly strong impact on psychological well-being, which showed no improvement over time[62]. These results underscore the importance of extended holistic support, including psychological therapy and olfactory rehabilitation, for patients affected by these dysfunctions in the long term.

3.7 ETIOLOGY OF OLFACTORY DISORDERS

Olfactory disturbances can have many causes, including respiratory problems, tumors, nasal polyps, ethmoid sinusitis, alcoholism, drug use, chemical exposure, head and facial trauma, psychiatric, neurological and degenerative diseases, congenital and COVID-19[33,41,63]. Figure 6 shows some pathologies associated with olfaction disorders[31,33,64].

Figure 6. Changes associated with olfaction disorders[30,33].



Traumas to the head and face represent one of the causes of olfactory dysfunction. A prospective study conducted at Santa Casa de Misericórdia de São Paulo between 2010 and 2012 investigated 24 cases of traumatic lesions of the olfactory nerve, revealing that trampling and falls from heights were the most frequent causes, followed by car and motorcycle accidents[3].

In addition to the previously mentioned causes, olfactory dysfunction can also be related to treatments such as **radiotherapy**. A 2017 study specifically investigated the relationship between olfactory dysfunction and radiotherapy in head and neck cancer patients, revealing a negative influence of radiotherapy on odor detection, identification, and discrimination[65].

Other causes of olfactory dysfunction involve biomechanical changes in the olfactory pathway, such as **ossification of the lamina cribriformis** of the ethmoid bone and lesions to the olfactory receptors due to viruses or chemical substances[15,33]. **Arrinia** or Arrinencephaly, another cause, is related to the absence of the olfactory bulb, occurring alone or together with other anomalies of the base of the brain and midline of the face. It is characterized by the absence of the nose, including nasal bones and lamina cribriformis.[66].

3.7.1 Airway obstruction and olfactory dysfunction in the pediatric population

Airway obstruction in the pediatric population is a common and serious clinical condition that affects quality of life and the ability to smell. The causes can be acute or chronic, and infectious or non-infectious, making it essential to identify the signs and symptoms of these conditions to ensure proper diagnosis and treatment[66].

Adenoid hypertrophy is the main cause of chronic upper airway obstruction in children and adolescents and is responsible for a large proportion of olfactory dysfunctions. In addition, recurrent infections of the respiratory system, such as **sinusitis** and **rhinitis**, can also contribute to airway obstruction and, consequently, olfactory dysfunction. Thus, it is essential that healthcare professionals be aware of the main causes and related symptoms to provide the best treatment and follow-up for pediatric patients[66].

In summary, a critical and individualized approach is important when diagnosing and treating the causes of nasal obstruction in children, taking into consideration the severity of symptoms, the impact on quality of life, and the need for more aggressive interventions when necessary.

3.8 INFLUENCE OF SUBLIMINAL ODORS ON THE HUMAN PHYSIOLOGICAL STATE

Odor memory is essential in cognition and can be divided into two processes: the identification (recognizing and recalling) of a previously smelled odor, and the odor evoked memory, which triggers autobiographical memories and personal associations. These memories are emotionally intense and affect mood and health due to the connection between the olfactory system and the brain areas responsible for emotional processing and associative learning.[67].

Delving into the fascinating world of smells leads us to unravel the intricate relationships between conscious, preconscious and subliminal processing that together shape our perception and have a significant impact on our behavior and daily experiences[68]. In this section, I briefly deal with subliminal odors as a way of illustrating the complexity of the topic at hand.

Smells, even when not consciously perceived, can exert substantial influence on the human physiological state. A notable example of this influence is the synchronization of menstrual cycles in women who maintain constant interaction and coexistence, a phenomenon triggered by **subliminal olfactory stimuli**. Evidence from studies using axillary sweat extracts collected during different phases of the menstrual cycle supports this correlation between menstrual synchronization and olfactory stimuli[28].

Furthermore, **subliminal smells**, those that are not consciously perceptible, have the power to shape our emotions, behavior, and physiological processes. These invisible stimuli can influence our moods, social preferences, and even brain function.[69,70]. This intricate connection emphasizes the importance of smell, not only as a sense that senses the world around us, but as a subtle, subliminal influencer of our behavior and well-being.

3.9 THE POWER OF SENSES IN SENSORY MARKETING: SENSORY HISTORY AND THE PROFESSIONS OF TASTE AND SMELL

Using our senses to evaluate and appreciate products is an ancient practice, rooted in traditions such as wine tasting and the production of essential oils and perfumes. This tradition has evolved and diversified over time, giving rise to professions such as oenologists, sommeliers[71]sommeliers, baristas, and perfumers. The knowledge accumulated throughout this historical evolution is now applied in varied areas such as the food industry, perfumery, interior design, and sensory marketing[72,73].

3.9.1 The insertion of olfaction in the consumer experience and sensory branding

The human senses play a vital role in our daily interactions and perceptions of the world around us. While sight allows us to distinguish objects, smell enriches visual experiences, adding a layer of depth and emotion. Similarly, the combination of smell and taste guides our food choices, social interactions, and is even used in marketing strategies. Therefore, sensory analysis of products becomes essential, especially for those professionals whose main working tools are taste and smell, such as perfumers, baristas, sommeliers, and automotive odors specialists[73].

Within the marketing field, a concept known as "*Brand Sense*" or "Sensory *Branding*" has emerged to emphasize the relevance of sensory stimulation in the process of forming and strengthening brand identity. In this strategy, olfaction appears as a key element to generate memorable experiences and establish emotional bonds with consumers[74,75].

This approach includes investments in the "store atmosphere", where sensory resources - olfactory, visual and auditory - are used to evoke memories and influence consumer behavior, stimulating their interest and influencing their purchasing decisions[76-79].

In the specific sphere of smell, this strategy translates into "olfactory marketing," in which companies associate specific smells with a product or brand to evoke individual memories and emotions. This feature arouses sensations, feelings, and thoughts that influence consumer behavior, including the purchase decision. In addition, the identification of a similar odor in another environment can trigger memories of the store or product brand, encouraging the promotion of the company when the consumer shares this experience[80,81].

In summary, Sensory *Branding* aims to engage the five senses to make the brand more recognizable and appreciated by consumers, providing unique and emotionally engaging experiences. This strategy makes the brand stand out in the market and strengthens its presence in the consumers' minds[74,75].

3.9.2 Olfactive Brands: The aromatic signature in the construction of brand identity

Olfactive brands are those that incorporate the sense of smell into their *branding* strategies, creating a unique signature that becomes a distinctive element of their identity. This approach demonstrates how companies can leverage the senses to create deeper emotional connections with consumers[81].

The physiological connection between smell and memory is intrinsic and long-lasting, thanks to the neural proximity of both in the limbic system. This connection manifests itself in the incredible durability of memory and the ability of smell to evoke detailed autobiographical memories. Environmental and product scents significantly influence brand recall and product choices, making olfaction an effective tool in *branding*[72].

The consumer experience is enriched by an olfactory brand strategy that reflects the brand identity: *Abercrombie & Fitch* creates a distinctive atmosphere with *Fierce* perfume in its stores[81]*Singapore Airlines* provides a consistent experience through the exclusive fragrance *Stefan Floridian Waters*; *The Ritz-Carlton* hotel chain relies on *Essence of Ritz-Carlton* for a sophisticated and memorable stay; Nike uses specific fragrances in its stores to foster an energetic atmosphere; *Victoria's Secret* evokes sensuality and mystery with the signature scent in its stores; Zara creates a pleasant and inviting atmosphere with subtle fragrances in its stores; and Puma strengthens the brand image by creating exclusive fragrances in partnership with artists and celebrities. Through these initiatives, the brands establish lasting emotional bonds and increase their brand recognition.

4 CONCLUSION

Based on the comprehensive review of the literature, it is concluded that a detailed understanding of the anatomy, physiology, and semiology of the olfactory system is critical for accurate diagnosis and proper prognosis of olfactory disorders. This knowledge allows the identification of specific signs and symptoms, as well as the use of advanced diagnostic techniques to accurately assess olfactory function.

In addition, understanding the mechanisms underlying olfactory disorders is essential for the development of personalized and effective therapeutic strategies. The integration of clinical approaches, such as olfactory assessment tests, with imaging methods and genetic studies allows for a comprehensive evaluation of the patient, considering genetic, environmental, and behavioral factors.

However, it is important to recognize that there is still much to be discovered and explored in this field. Future research should continue to deepen our understanding of the pathophysiology of olfactory disorders, seeking to identify new biomarkers, more effective therapies, and rehabilitation approaches to improve the quality of life of affected patients. Collaboration between researchers, clinicians, and healthcare professionals plays a crucial role in this advancement, promoting an integrated and multidisciplinary approach to address olfactory disorders and their impact on the health and well-being of individuals.

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