

Smell, a widow to the mind

El olfato, una ventana a la mente

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Introduction

In the novel *Perfume: The Story of a Murderer*, German writer Patrick Süskind presents the peculiar case of Jean Baptiste Grenouille, endowed with an exceptional sense of smell but incapable of emitting an odor of his own. The author describes Grenouille's story from birth and childhood—when he endured multiple adversities—to adulthood, when he became a great perfumer whose passion for odors and female fragrances was so strong that he resorted to murdering women to obtain and preserve them. Thus, in this novel, the important role that smell can play in human life is highlighted. For this reason, olfactory disorders, whether of infectious or noninfectious origin, may predict the development of disease or be the result of the disease itself. Whatever their origin, these conditions undoubtedly affect the personal, behavioral, and social lives of affected individuals.

Among the senses, smell is the least explored and, at least in humans, is usually considered a more intuitive than informative sense. Perhaps for this reason there is little awareness of its importance and its indispensable character for well-being. Problems related to vision or hearing are the reason for systematic examinations, even from early ages, while olfactory disorders often go unnoticed.

Evolutionary biology has shown that the sense of smell is required for the survival of animals, including humans, in whom cultural disdain has considered it

merely a vestige of “animality” (since sniffing is a characteristic behavior of many animals). Smell enables us to identify nutrients, provides safety (by helping avoid potentially contaminated food), improves quality of life (self-esteem and mood), and directly influences behavior (personal hygiene, sexual life, etc.). This sense works with each respiratory cycle, allowing odor molecules to enter the nose and respiratory system with every inhalation, to be processed in primary and secondary brain areas. Among vertebrates, the types of olfactory receptors are common and structurally and functionally similar. However, unlike other vertebrates, in humans the perceived information is integrated in wide brain regions such as the archicortical region (entorhinal cortex) and neocortical areas (orbitofrontal and insular cortices), showing important interconnections with memory areas (explaining why we remember a smell and why we can associate a smell with a past event), language, and neurovegetative functions (particularly sleep). Thus, it participates in and influences behavior and emotions^{1,2}.

Anatomy of smell

In humans, the nasal cavity has about 2.5 cm² of surface area containing nearly 50 million receptor cells, each with 8 to 20 cilia, immersed in a mucus layer produced by the Bowman glands³. Binding of an odor particle to its olfactory receptor generates

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changes in the neuronal membrane potential, with axons projecting from the nasal epithelium through the cribriform plate to the olfactory bulb, which connects to primary olfactory structures such as the piriform cortex (including the limbic and paralimbic systems, which control instinctive and emotional responses), the anterior olfactory nucleus, the olfactory tubercle, the amygdala, and the entorhinal cortex, as well as secondary structures such as the hippocampus, thalamus, orbitofrontal cortex, and cerebellum⁴. Figure 1 illustrates these structures.

An important feature of the olfactory pathway in humans is the absence of the vomeronasal organ (an auxiliary olfactory structure specialized in pheromone perception), of which only a remnant remains, and the reduction in size of the turbinates vs other vertebrates such as dogs, which have a greater olfactory capacity than humans. The molecular mechanism of odor particle detection by receptors leads to the opening of ion channels and the subsequent activation of olfactory neurons.

The classical olfactory system is highly conserved across insects, reptiles, and mammals. In vertebrates, it is represented by a large family of genes encoding receptor proteins expressed in the cilia of olfactory receptor cells: 350 genes in humans, 1948 in elephants, 1767 in rats, 1391 in mice, 2129 in cows, and 1100 in dogs^{5,6}. This diversity shows that the number of genes involved in olfaction is not directly related to species size or evolutionary stage.

In humans, there is marked sexual dimorphism in olfaction: women have better odor perception and discrimination than men⁷, probably correlated with greater development of the orbitofrontal prefrontal area and possibly associated with the hormonal and reproductive system. Olfactory capacity also differs among racial groups; for example, African Americans and Hispanics experience functional loss earlier with aging compared with Caucasian populations,⁷ although the reason for this difference is unknown.

Classification of olfactory disorders

These disorders are classified as quantitative, characterized by an alteration in odor intensity rather than quality, ranging from hyposmia to anosmia, and qualitative, characterized by altered olfactory perception (dysosmia), such as distortion in odor quality (parosmia) or perception of an odor without an olfactory stimulus (olfactory hallucinations or phantosmia)⁸.

Why is smell so important in humans?

When we perceive an odor, not only is the entorhinal cortex activated but also the orbitofrontal cortex. In fact, we have different representations for pleasant (rostromedial region, orbitofrontal cortex) and unpleasant odors (left lateral region, orbitofrontal cortex), which implies direct activation of areas of the limbic system that can interact with the endocrine system (without mediation of cortical structures) and the peripheral nervous system. The limbic system is a brain region that includes the hypothalamus, hippocampus, and amygdala, and is responsible for processing emotions and affect. Risk factors for olfactory disorders include smoking⁹⁻¹¹, inhaled drug use, and working in factories^{12,13}, among others¹⁴. As with visual and auditory alterations, olfactory disorders increase with age^{7,15}. Recently, in a cohort of 3503 American adults, the association of olfactory dysfunction with the 5-year all-cause mortality rate was investigated¹⁶. The authors observed that olfactory dysfunction in adults older than 65 years correlated with higher risk of death, but the underlying causes remain unknown and further research is required.

How do olfactory disorders affect quality of life and even mortality?

Beyond pure sensory function (perception and discrimination of odor molecules), which regulates eating behavior¹⁷ and social behavior^{15,18}, olfaction participates in emotional processing through connections with the amygdala and entorhinal cortex. Similarly, through its relationship with the orbitofrontal cortex, it plays a role in learning and memory. Smell is also considered an “emotional” sense *per se*, capable of assigning positive (pleasant) or negative (unpleasant) value to odors. Certain odors can induce emotional states. In *In Search of Lost Time*, Marcel Proust emphasized the importance of odors for memory and their associative power, such as when the smell and taste of a madeleine dipped in tea suddenly and vividly transported him to childhood memories. Indeed, olfactory stimuli modulate emotions and vice versa¹⁵.

Patients with olfactory (eg, anosmia, total loss of smell) and taste disorders present problems with self-esteem and mood¹⁹. They experience difficulties with food intake, meal preparation, self-confidence, personal hygiene, and sexual life. Nearly half report feelings of isolation, dissatisfaction with life, anxiety, or depression²⁰. Although the mechanisms involved in mood

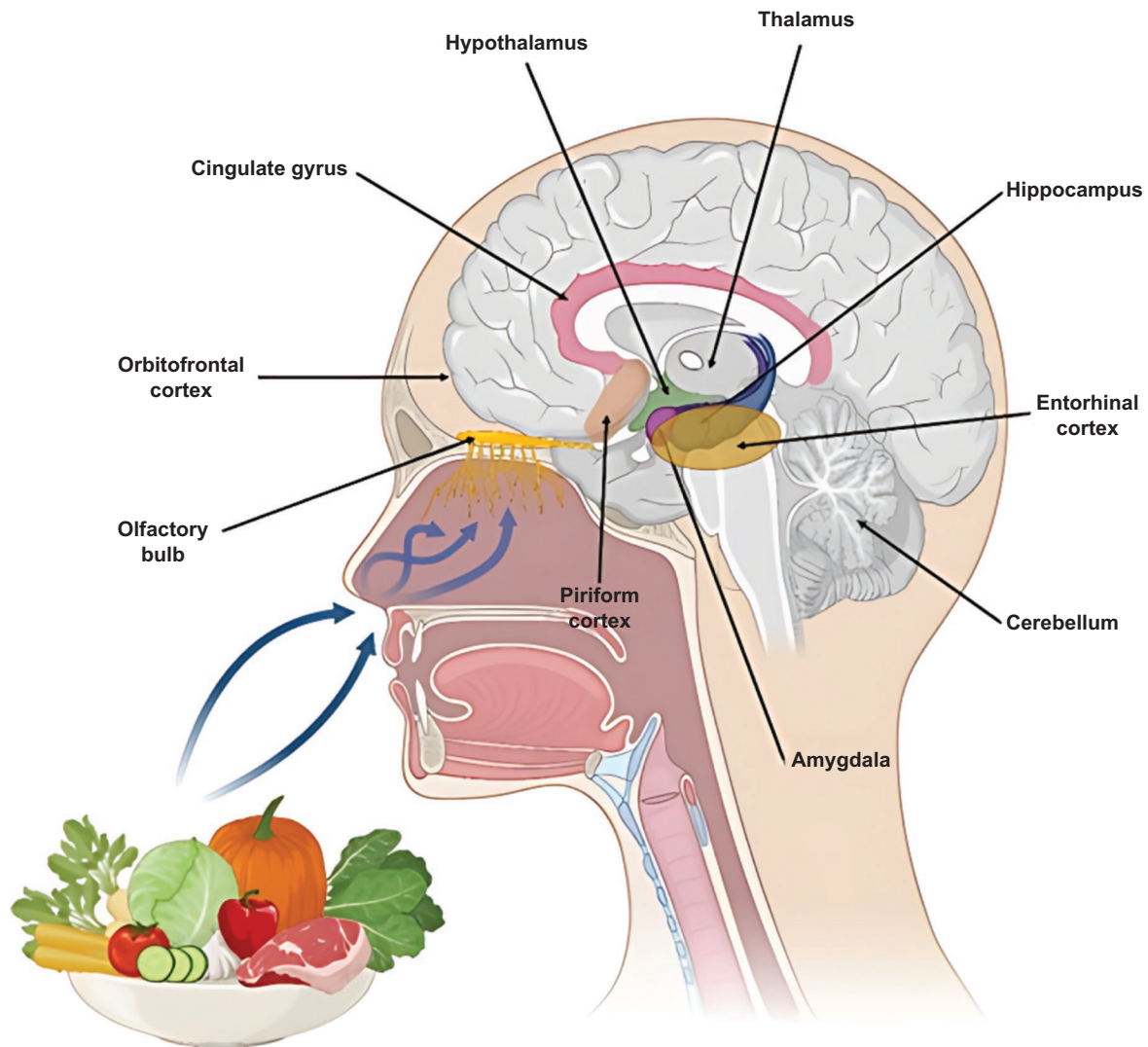


Figure 1. Primary and secondary brain structures related to smell. The binding of an odorant particle to its olfactory receptor generates changes in the neuron's membrane. This information is carried to the olfactory bulb and, from there, to primary structures (piriform cortex, site of limbic system structures [cingulate cortex, amygdala] that participate in instinctive and emotional responses) and secondary structures (orbitofrontal cortex, cerebellum, etc.) that also participate in integrating the stimulus.

disorders are not fully understood, it is thought that they are influenced not only by limitations in activities of daily living (due to olfactory dysfunction) but also by dysregulation of the limbic and hormonal systems^{21,22}.

Significant differences have been reported in depression scales (eg, Beck Depression Inventory scores) between patients with normal olfactory function (normosmia) and those with some degree of dysfunction (quantitative: hyposmia vs anosmia). In that study, the authors concluded that patients with depression had reduced olfactory performance and that patients with olfactory dysfunction had depressive symptoms related to the severity of olfactory loss²³. These signs appear associated with limitations in

activities of daily living, such as reduced afferent input to the limbic system⁹.

In various neurodegenerative diseases (eg, Alzheimer disease and Parkinson disease), as well as in neuropsychiatric disorders (depression, anxiety, and autism), olfactory signs have been reported among the prodromal symptoms (initial signs preceding the development of disease)^{24,25}. Certain infectious processes can also induce olfactory disorders. The most recent and perhaps most widely recognized example, due to its global impact, is SARS-CoV-2 infection. One of the earliest reported signs was quantitative compromise of olfactory function (hyposmia or anosmia), particularly with the wild strain, with an incidence rate of 73% vs

Table 1. Infectious causes of olfactory disorders

Infectious agents causing olfactory dysfunction	Infectious agents using the olfactory pathway to invade the nervous system
Viruses (influenza, parainfluenza, rhinovirus, coronavirus)	Bacteria (<i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i>)
Bacteria (<i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i>)	Viruses (coronavirus, influenza) Protozoa (<i>Naegleria fowleri</i> , <i>Balamuthia mandrillaris</i> , <i>Acanthamoeba spp.</i>)

the alpha (41%) and delta (48%) variants²⁶. Although the long-term scope and severity of COVID-19 sequelae remain unknown, the development of severe cognitive effects and dementia is a concern. Follow-up studies in convalescent patients have shown that, 6 months after infection, individuals who had COVID-19 presented with headaches and cognitive decline correlated with the severity of olfactory impairment²⁷⁻³⁰. Furthermore, there is the possibility that these olfactory disorders may increase the risk of long-term neurological sequelae or neurodegenerative diseases^{27,31}. Table 1 illustrates the main infectious agents that use the olfactory pathway to access the central nervous system or compromise its function.

Conclusions

Despite the wide variety of infectious and non-infectious causes of olfactory dysfunction, which makes its understanding and treatment complex, it is necessary to establish educational and clinical programs focused on preventing olfactory disorders, as well as identifying high-risk populations to provide counseling and reduce negative consequences on health and quality of life.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data and does not require ethical approval. The SAGER guidelines are not applicable.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

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