

# Olfaction in Neurologic and Neurodegenerative Diseases: A Literature Review

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## Abstract

### Keywords

- olfactory mucosa
- cerebrum
- dementia
- olfaction disorders
- aging

**Introduction** Loss of smell is involved in various neurologic and neurodegenerative diseases, such as Parkinson disease and Alzheimer disease. However, the olfactory test is usually neglected by physicians at large.

**Objective** The aim of this study was to review the current literature about the relationship between olfactory dysfunction and neurologic and neurodegenerative diseases.

**Data Synthesis** Twenty-seven studies were selected for analysis, and the olfactory system, olfaction, and the association between the olfactory dysfunction and dementias were reviewed. Furthermore, is described an up to date in olfaction.

**Conclusion** Otolaryngologist should remember the importance of olfaction evaluation in daily practice. Furthermore, neurologists and physicians in general should include olfactory tests in the screening of those at higher risk of dementia.

## Introduction

Olfaction is usually neglected by physicians at large, even though it monitors the intake of airborne agents into the human respiratory system, including dangerous substances, and warns of spoiled foods. Furthermore, this primary sensory system enhances quality of life by adding to flavor and palatability of foods and beverages.<sup>1</sup> Most complaints of decreased “taste” function actually reflect decreased smell function.<sup>1,2</sup> In addition, loss of smell is involved in various neurologic and neurodegenerative diseases, such as Parkinson disease (PD), Alzheimer disease (AD), multiple sclerosis, and Huntington disease.<sup>3</sup>

The aim of this study was to review the current literature about the relationship between olfactory dysfunction and neurologic and neurodegenerative diseases.

## Review of the Olfactory System

### Olfactory Mucosa Cellular Composition and Neurogenesis

Human olfactory mucosa is a pseudostratified columnar epithelium resting on a highly cellular lamina propria. Four types of cells are present at the epithelium: ciliated bipolar olfactory receptors, sustentacular cells, microvillar cells, and basal cells, beyond the Bowman gland.<sup>1,4–6</sup>

The olfactory system is composed by peripheral structures of ~6 million bipolar receptor cells located within the olfactory neuroepithelium.<sup>4,7</sup> This ciliated bipolar olfactory receptor cell is a true bipolar neuron, projecting a single dendrite to the surface of the olfactory neuroepithelium and a single axon to the olfactory bulb. The dendrite extends to the epithelial surface and has nonmotile cilia with membrane receptors,

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where odor molecules bind.<sup>4</sup> The axons form into bundles, called the *olfactory fila*, and project through the cribriform plate of the ethmoid bone and synapse at the olfactory bulb. In humans, the surface area of the cilia is ~25 mm.<sup>1,8</sup>

Olfactory receptor neurons are surrounded by the sustentacular cells, which probably contribute to regulation and conservation of the appropriate ionic environment around the receptor neurons for adequate olfactory transduction.<sup>1,4</sup>

Microvillar cells presumably act as a second morphologically distinct class of chemoreceptor, first described in 1982. However, their precise role in olfaction has not yet been clearly demonstrated.<sup>4,9</sup>

The Bowman gland is a serous-producing tubuloalveolar gland, another component of the lamina propria, composed of secretory acini with a duct that passes through the olfactory epithelium.<sup>4,10</sup> This secretion probably is essential for olfactory transduction.<sup>4</sup>

Recent studies have shown that the olfactory system displays robust and functional neurogenesis throughout life,<sup>6</sup> by containing cells with very broad developmental potency. Human olfactory mucosa yield neurospheres that could be propagated as secondary and tertiary neurospheres.<sup>11</sup> They are the basal cells, a well-recognized distinct population of stem cells of the olfactory epithelium, capable of continuously regenerating olfactory receptor neurons throughout the life span.<sup>4,11,12</sup> The basal cells have multipotency and self-renewal characteristics and are able to give rise experimentally to other neural and non-neural cells.<sup>4,6,13</sup>

### Olfactory Bulb and Primary Olfactory Cortex

As described previously, the single axons of the 10 to 20 million olfactory receptor neurons join together into fascicles and nerves, which pass through the 15 to 20 foramina of each cribriform plate to synapse within the olfactory bulb.<sup>4,14</sup>

The olfactory bulb continues to the olfactory tract and arrives at the primary olfactory cortex areas, such as anterior olfactory nucleus, entorhinal cortex, and amygdale.<sup>15,16</sup>

### Olfactory Mucosa Localization

Theoretically, the human olfactory mucosa constitutes 1.25% of the nasal mucosa, corresponding to an area of ~2 cm<sup>2</sup>. The number and density of bipolar olfactory neurons are probably ~6 × 10<sup>6</sup> and 30,000/mm<sup>2</sup>, respectively.<sup>4,17</sup>

The olfactory epithelium in the human fetus is uniformly distributed without interruption by respiratory epithelium in a continuous pattern.<sup>18</sup> Féron and other authors have observed that the distribution of the olfactory epithelium in adult humans is frequently disrupted with interspersed patches of respiratory epithelium.<sup>18–20</sup> Comparison of fetal and adult samples suggests that invasion of respiratory tissue into olfactory epithelium increases with age, as suggested in a previous study of adult olfactory epithelium.<sup>18</sup> This probably occurs because this mucosa is a dynamic structure with features reflecting innate and environmental as well as developmental influences. Thus, it can be assumed that the precise location and the overall dimension of the neuroepithelium may be different among individuals and may change over time.<sup>4</sup>

Recent anatomical studies modified the previous concept of distribution area of the olfactory mucosa. It was assumed that the neuroepithelium was restricted to the area of the cribriform plate, superior turbinate, and the opposite superior nasal septum.<sup>4</sup> Leopold and other authors demonstrated that the olfactory mucosa extends within the medial and anterior surface of the middle turbinate, either in the lateral or in the medial wall of the nasal cavity.<sup>21,22</sup> This would not be in conflict with the work of Biedlingmaier and Whelan<sup>23</sup>, since they looked at much more inferior middle turbinate tissue and did not find olfactory tissue.<sup>21</sup>

## Discussion

### Olfactory Deficit in Elderly People

A decay of the smell function occurs in old age. In fact, age is the strongest correlate of olfactory decline in healthy adult humans and has a much larger impact than even cigarette smoking.<sup>1</sup> These data are confirmed by cross-sectional and longitudinal studies.<sup>24</sup>

Generally, olfactory impairment related to age is more severe for men than for women, although individual differences are present. This deficit often goes unnoticed and is rarely investigated by physicians, unlike alterations in hearing and vision. About 2% of the population under 65 years of age has olfactory impairment. This rises dramatically between 65 and 80 years, with about half of the population complaining of loss of smell. Over 80 years, smelling problems are noticed by 75% of elderly.<sup>1</sup>

Possible reasons for smell changes related to age include ossification and closure of the foramina of the cribriform plate, age-related degenerative processes occurring in the brain,<sup>1,24</sup> and cumulative damage to the olfactory receptors from different types of insults throughout life.<sup>1</sup>

### Olfactory Deficit and Dementia

Recently, the olfactory neuroepithelium has attracted the renewed interest of scientists, because the olfactory mucosa has the potential to be an early marker of neurodegenerative conditions, such as schizophrenia, AD, multiple sclerosis, and PD.<sup>4</sup>

There is considerable variation in the prevalence and magnitude of olfactory dysfunction among neurodegenerative diseases. In AD, PD, and Parkinson–dementia complex of Guam, olfactory dysfunction is severe (University of Pennsylvania Smell Inventory Test [UPSIT] scores under 20), whereas that of Huntington disease, multi-infarct dementia, amyotrophic lateral sclerosis, and schizophrenia is more moderate. Progressive supranuclear palsy is associated with minor changes in olfactory function, even though it shares major clinical features with PD. These data suggest that olfactory testing could help in differential diagnosis of several neurodegenerative diseases.<sup>1</sup>

Olfactory deficit can be noticed in the ability to detect, recognize, and remember odorants in the elderly, particularly in patients with AD.<sup>25</sup> In the case of AD, smell problems occur in the beginning of the disease,<sup>26</sup> and this pattern can reflect an “preclinical” period of disease development by preceding

the onset of classic disease symptoms.<sup>1</sup> Moreover, olfactory impairment is mostly found in individuals at risk for AD, including subjects with mild cognitive impairment who eventually develop AD, those with another potential risk factor for AD (namely subjective memory complaints),<sup>25,27</sup> and relatives of AD patients.<sup>7,27,28</sup> Olfactory dysfunction in AD is associated with disease progression, can be helpful in the differential diagnosis of major depression and AD, and may have clinical value as an early diagnostic marker in predicting incident AD in high-risk individuals.<sup>25</sup> The presence of apolipoprotein E-4 allele in an anosmic normal individual increases the risk of having cognitive decline in the future by 4.9-fold.<sup>1</sup>

Surprisingly, most patients with AD and PD are unaware of their olfactory loss before taking the test; 85 to 90% of patients in the early stages present olfactory impairment, and this deficit is associated with decreased activation of central odor processing structures (as measured by functional imaging).<sup>1,15</sup>

In AD, neuropathologic changes within olfaction-related brain regions usually accompany these olfactory changes. One of the pathologic hallmarks of AD, the neurofibrillary tangles (NFTs), have been identified within the olfactory bulb, olfactory tract, transentorhinal and entorhinal cortex, anterior olfactory nucleus, and amygdale.<sup>25</sup> The number of NFTs within such regions has been correlated with the severity of dementia.<sup>15</sup> Recent neuropathologic studies suggest that AD-related pathology may begin within olfactory central cortex and then spread to multiple areas of the brain.<sup>15</sup> These neuropathologic changes have been associated with impaired olfaction around the time of death in those without dementia or with mild cognitive impairment.<sup>24,27</sup>

As seen, olfactory impairment has been significantly associated with the AD neuropathology burden in the brain and the risk of future AD. Some animal models of AD-related neuropathologic changes have indicated a strong association between NFT in the olfactory system and cognitive decline and a negative association between amyloid- $\beta$  burden in the brain, another hallmark of AD disease, and olfaction. Moreover, oxidative damage in the olfactory epithelium is present in the early stages of AD.<sup>27</sup>

### Functional Magnetic Resonance Imaging in Patients with AD

Wang demonstrated that functional magnetic resonance imaging (fMRI) is sensitive to changes in olfactory function due to AD. Patients with AD have reduced BOLD (blood-oxygen-level dependent) signals in the hippocampus and insula regions when compared with healthy control subjects of similar age. Such alterations are significantly correlated with UPSIT, Mini-Mental State Examination, and CDR (clinical dementia rating) scores, proposing the significance of olfactory fMRI in patients with AD.<sup>15</sup>

Furthermore, when the odorant concentration is increased 10-fold, only slightly more activation is induced in some brain regions. These data about additional recruitment of activity suggest that total anosmia in AD is not the rule but rather the exception, and they indicate that at least some residual capacity is available.<sup>15,26</sup> Experimental results indicate the

feasibility for using olfactory fMRI as a marker for diagnosis and evaluation of AD.<sup>15</sup>

### Olfactory Epithelium Biopsy

Because the olfactory mucosa contains the only surface neural cells of the body, the olfactory receptor neurons, some authors call the neuroepithelium the “window to the brain.” Therefore, an olfactory biopsy could potentially help to understand what occurs in the brain with neurologic and neurodegenerative disease.<sup>4</sup> Olfactory epithelium is accessible for low-risk biopsy, allowing examination of the neurogenesis process,<sup>6,18</sup> as shown by neuropathologic studies on neurodegenerative diseases like AD and PD.<sup>18</sup>

### Gender Differences in Human Olfactory Bulb

Recent studies indicate the existence of differences in human olfactory bulb related to gender. Oliveira-Pinto et al demonstrate a sex-related difference in the absolute number of total, neuronal and non-neuronal cells, favoring women by 40-50%, which may have olfactory functional impact.<sup>29</sup>

### Conclusions

Olfactory dysfunction can manifest in various degrees and difficulties in discrimination, odor identification, and olfactory memory. Neurologic and neurodegenerative diseases, particularly AD and PD, are major causes of dysosmia. There is much evidence that olfactory tests can be used to differentiate diagnosis between PD and other types of parkinsonism.

This review shows that olfactory tests can be a useful tool in differential diagnosis of dementia and other diseases, as well as among the various types of dementia, and indicates that impairment in olfactory discrimination can predict future cognitive decline.

However, some questions remain unanswered: ‘What is the boundary between the olfactory changes related to aging and those caused by disease?’; ‘Is it possible to differentiate them through the olfactory tests?’; ‘In which time the pathological changes of AD are installed in the olfactory structures?’ More studies are necessary to clarify these issues.

Based on current knowledge of the association between smell and dementias, the authors suggest that the otolaryngologist should remember the importance of olfaction evaluation in daily practice. Furthermore, neurologists and physicians in general should all include olfactory tests in the screening those at higher risk of dementia.

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