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RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

Olfactory Dysfunction in Neurodegenerative Diseases

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Abstract

Purpose of Review The sense of smell is today one of the focuses of interest in aging and neurodegenerative disease research. In several neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease, the olfactory dysfunction is one of the initial symptoms appearing years before motor symptoms and cognitive decline, being considered a clinical marker of these diseases' early stages and a marker of disease progression and cognitive decline. Overall and under the umbrella of precision medicine, attention to olfactory function may help to improve chances of success for neuroprotective and disease-modifying therapeutic strategies.

Recent Findings The use of olfaction, as clinical marker for neurodegenerative diseases is helpful in the characterization of prodromal stages of these diseases, early diagnostic strategies, differential diagnosis, and potentially prediction of treatment success. Understanding the mechanisms underlying olfactory dysfunction is central to determine its association with neurodegenerative disorders. Several anatomical systems and environmental factors may underlie or contribute to olfactory loss associated with neurological diseases, although the direct biological link to each disorder remains unclear and, thus, requires further investigation.

Summary In this review, we describe the neurobiology of olfaction, and the most common olfactory function measurements in neurodegenerative diseases. We also highlight the evidence for the presence of olfactory dysfunction in several neurodegenerative diseases, its value as a clinical marker for early stages of the diseases when combined with other clinical, biological, and neuroimage markers, and its role as a useful symptom for the differential diagnosis and follow-up of disease. The neuropathological correlations and the changes in neurotransmitter systems related with olfactory dysfunction in the neurodegenerative diseases are also described.

Keywords Olfaction · neurodegeneration · clinical marker · Parkinson's disease · Alzheimer's disease · olfactory bulbs · dopamine

This article is part of the Topical Collection on *Rhinosinusitis*

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Introduction

The sense of smell is important for functions such as feeding, ability to detect hazardous odors, and social relationships [1–3], having been hypothesized to be able to modify sexual behavior [4], and even determine various personality attributes based on body odor [5]. Olfaction is commonly defined by several distinct abilities, such as olfactory threshold detection, identification, discrimination, and odor memory [1, 6, 7]. Quantitative olfactory functioning can be categorized as a range of normal (normosmic) to diminished (hyposmia) and absent (anosmia) ability to detect and correctly label odors. Decreased olfactory function (hyposmia or anosmia) is estimated to afflict 3–20% of the population [6, 8]. Numerous factors influence the ability to smell, including physical activity, genetic factors, nutrition, smoking, sex, head trauma,

medical treatments, and exposure to viruses [9]. Even occupation involving specialized expertise and training can influence smell function, as shown by increased olfactory test scores in sommeliers [10, 11] and perfumers [12].

Impaired olfaction negatively affects quality of life, enjoyment of food, reducing challenges with maintaining personal hygiene, greater depressive symptoms, impacting on physical and mental well-being, and social relationships [2, 9, 13–15]. Decreased smell function impairs the ability to sense warning odors, increasing the risk of danger from fire, environmental toxins, leaking natural gas, and spoiled food [2, 14, 16]. Less than a quarter of individuals with olfactory dysfunction are conscious of their problem until tested [9]. Moreover, among adults 70 years and older, misidentification rates for warning odors were 20% for smoke, and 31% for natural gas [17], being a major public health concern [18, 19].

Risk of olfactory dysfunction increases with old age and may result from acute and chronic sinonasal disease, upper respiratory infections, toxic chemicals, head trauma, as well as degenerative diseases [6, 8, 20–22]. Over recent years, the link between olfactory dysfunction and neurodegenerative disorders has increasingly been recognized [14, 23–25]. The high prevalence, early manifestation, persistence throughout disease, and ease of olfactory testing have stimulated interest in the research of olfactory dysfunction as an early marker for neurodegenerative diseases, such as Parkinson's disease [24, 26–30], Alzheimer's disease [31–34], or dementia with Lewy bodies [35, 36]. Olfactory dysfunction has also been assessed in premotor stages of these diseases, such as in idiopathic rapid eye movement sleep behavior disorder [9, 37]. The use of olfaction, as biomarker for neurodegenerative diseases is helpful in the characterization of prodromal stages of the diseases, early diagnostic strategies, differential diagnosis, and prediction of clinical outcomes of neurodegenerative diseases. Overall, attention to olfactory function may help to improve chances of success for neuroprotective and disease-modifying therapeutical strategies [26, 28].

Understanding the mechanisms underlying olfactory dysfunction is central to determine its association with neurodegenerative disorders. Several anatomical systems and environmental factors may underlie or contribute to olfactory loss associated with neurological diseases [9], although the direct biological link to each disorder remains unclear and, thus, requires further investigation.

Neurobiology of Olfaction

The first step of odor perception starts at the nose. Olfactory information is transmitted from the olfactory epithelium (OE) to the olfactory bulbs (OBs), which in turn, projects to a variety of secondary olfactory structures including the anterior olfactory nucleus (AON), piriform cortex olfactory tubercle, the lateral entorhinal cortex, and para-amygdaloid complex [38, 39]. These olfactory structures are regarded as the primary olfactory cortex. Cells in the AON are responsive to odor stimulation [40] and the piriform cortex has a significant role in modifying the processing of odors based upon experience and learning [38, 41]. Neurons within these secondary olfactory structures project to tertiary olfactory structures, which include the orbitofrontal cortex, the insular cortex, and the dorsal hippocampus. In addition, thalamic regions receive olfactory information from several of the secondary olfactory structures, including the AON, piriform cortex, and olfactory tubercle [42].

In the nasal OE, the odorant molecules interact with olfactory receptor neurons (ORNs) via transmembrane G-protein-coupled olfactory receptors (ORs) [7, 43, 44]. Once the odorant interacts with the ORs, action potentials in the ORN axon may be generated relaying odorant information into OBs [45, 46]. In mammals, ORNs express only one OR type [47, 48]. ORNs expressing the same OR innervate two glomeruli per OB [49, 50]. In rodents, there are approximately 1000 genes involved in odor recognition, with approximately 350 of them coding for functional receptors in humans [27]. This enables humans to distinguish thousands to millions of odors [43, 51–53]. The olfactory mucosa, OE, and lamina propria include supporting or sustentacular cells for stability of the epithelium and basal cells that provide regenerative capacity. The supporting cells play an essential role in sustaining neurons for proper transduction of odorant stimuli into olfactory input [7, 27]. The OE is innervated not only by ORNs but also by fibers from the trigeminal nerve and autonomic fibers from the superior and cervical ganglion [2].

At OB level, axons from ORNs synapse with the dendrites of secondary olfactory projection neurons, the mitral (MCs) and tufted cells (TCs), forming a structure called glomerulus [14]. MCs and TCs are the primary efferent projection neurons of the OB. They are excitatory glutamatergic neurons; their dendrites project to a single glomerulus and receive inputs form the olfactory sensory neurons. The incoming axons from the ORNs also synapse on local gamma-aminobutyric acid (GABA)ergic interneurons (periglomerular cells) that are activated by glutamate released from MCs and TCs, causing inhibition within the glomerulus [14]. *Glomeruli* are the first synaptic relay in the olfactory pathway and play a basic role in smell perception [14]. The cell bodies of MCs are located in the mitral cell layer of the OB, whereas the cell bodies of TCs reside in the external plexiform layer. While both cell types are similar in their reception of monosynaptic odor information form ORNs and their lateral dendrite arbors, they have different physiological responses to odors, including odor intensity coding [54].

The activity of MCs, TCs, and interneurons in the OB is subject to neuromodulation [55]. The OB receives dense

noradrenergic projections from the locus coeruleus, cholinergic input from the horizontal limb of diagonal band of Broca, and serotoninergic afferents from the medial and dorsal raphe nuclei [56, 57]. Dopamine is synthesized locally in the OB by dopaminergic interneurons of the periglomerular layer [58, 59]. Interestingly, a minor input to the OB from dopaminergic neurons from the midbrain substantia nigra has recently been described [60].

Additional major cell types in the OB are the granule cells that are found in the most central OB cell layer. The apical dendrites of granule cells synapse upon and are synapsed upon by MCs and TCs. Granule cells also receive centrifugal input from some secondary olfactory structures [7]. Granule cells (GABAergic and glutamatergic) are constantly renewed by neurogenesis during adulthood in many mammalian species, and they derive from neuroblasts originating from the subventricular zone of the anterior forebrain that migrate to the OB. There they differentiate and integrate into the granular and glomerular layers of the OB [61–63].

MC and TC axons project to the secondary olfactory structures [7, 64]. Neurons within secondary olfactory structures project into tertiary olfactory structures [42], and all these areas send projections back to the OB, terminating primarily in the granule cell layer. Hence, the olfactory system displays a complex system of associated connections, as well as reciprocal direct and indirect connections with other essential brain areas [24, 64].

Olfactory Testing in Neurodegenerative Diseases

Measurement of olfactory ability in the clinical setting typically consists of odor identification, odor discrimination, and odor detection threshold tasks [28]. Odor identification methods consist in the presentation of a suprathreshold concentration of an odor, and patients must make a choice from several items. In odor discrimination tasks, patients must differentiate between, but not identify, odors. Similarly, an odor discrimination/memory consists of smelling an odor, identifying that odor from a set of alternatives after various delay intervals. Odor detection thresholds are measured by presenting various concentrations of a given odor, usually in an ascending staircase series to determine the lowest concentration at which a subtle sensation can be perceived. In contrast, the lowest concentration at which an odor can be recognized is the recognition threshold and should be distinguished from the odor detection threshold [65].

Numerous tests have been used to measure olfactory function in neurodegenerative diseases with odor identification tests, such as the University of Pennsylvania Smell identification Test (UPSIT) [66, 67] and the Sniffin' Sticks Test [68–70], being the most common. UPSIT is a scratch and sniff test with 40 microencapsulated odorants, in which patients must choose among four descriptors for each odorant [65]. Since a number of odors are not universally recognized, the UPSIT has been adapted and validated for use in many different languages and cultures, and normative values for age and gender have been developed. Thus, the 12-item Brief Smell Identification Test (B-SIT) [71, 72], whose test items are derived from the UPSIT, were designed to be cross-cultural in familiarity [71]. In addition, cultural-specific tests have been developed as well. These tests include the Barcelona Smell Test-24 (BAST-24) for Spain [73], the Odor Stick Identification test for Japan (OSIT-J) [74], and the Italian olfactory identification test (IOIT) [75]. BAST-24 evaluates not only forced-choice identification but also detection and identification of odors [73]. The Sniffin' Sticks test includes a forced odor identification task for 16 odors performed by means of a list of four (multiple choice), and odor threshold test and an odor discrimination task [68, 69]. Like the UPSIT, it has been adapted and validated for use in many different languages and cultures, and normative values exist in relation to age and gender.

The usefulness of a fast and easy-to-use visual analogue scale (VAS) for the evaluation of the olfactory deficit has recently been evaluated in allergic rhinitis [76], trauma brain injury [22], and Parkinson's disease [77]. In Parkinson's disease, the VAS scores showed a significant correlation with the UPSIT and BAST-24 forced-choice identification scores [77]. According to these studies, the VAS test could be considered a quick and easy-to-use tool to screen and identify subjects with various degrees of smell loss.

Olfactory Dysfunction Associated with Normal Aging

Epidemiological studies show that the prevalence and severity of olfactory dysfunction increases with age [3, 6, 14, 25, 78, 79]. Thus, 10% of people older than 65 years have some form of olfactory dysfunction ranging from mild loss to anosmia [2, 9, 80, 81], affecting 62 to 80% of persons older than 80 years [14, 15, 25, 82]. In general, age-related olfactory dysfunction is more severe in men than in women [82, 83]. This is in agreement with the observation that overall women have a better olfaction function than men [6, 78]. This sex difference may be related to differences in the number of human OB cells in individuals. Thus, a study confirmed sex differences in the total number of OB cells in humans, showing that females had 40–50% more OB cells than males [84], which might explain the different olfactory function and decline in both sexes.

Olfactory disorders may underlie alterations at different levels of the nervous system [79]. Olfactory dsyfunction can result from alterations of the detection threshold due to impairments at the peripheral nervous system level. To some

degree, alterations in discrimination ability and identification ability are due to impairment at the central nervous system level requiring higher levels of cognitive control [25, 79, 85]. The question of how the age-related olfactory decline relates to degeneration of the peripheral and central olfactory nervous system is still unknown. In aging, odor threshold has been described to be impaired [86], suggesting that age-related changes in olfactory function may be due to damage of the OE. Odor identification and memory deficits have also been documented in elderly individuals [87]. Moreover, functional magnetic resonance imaging (fMRI) studies have found that activation in olfactory-related structures, such as the piriform cortex, the amygdala, the entorhinal cortex, and in olfactory-related regions of the cerebellum is decreased in aged individuals [88–90], suggesting that central olfactory system is also involved in aging-related olfactory dysfunction.

The mechanisms underlying olfactory dysfunction with advancing age are still unclear [3, 91]. However, several factors may contribute to olfactory dysfunction in aging including increased propensity for nasal disease, nasal engorgement, reduction in the width of foramina in the cribriform plate, loss of selectivity of receptor cells to odorants, reduction in mucosal metabolizing enzymes, decrease in mucosal blood flow, changes in neurotransmitter and neuromodulator systems, as well as structural and functional abnormalities in the olfactory system [2, 7, 14, 15, 25, 79, 92].

Age-related changes in the OE include a thinning of the epithelium, and a decline of ORNs that generally starts after 65 years of age [3, 4, 7, 14, 93], with the OE gradually being replaced by respiratory epithelia [94, 95]. These changes in the OE may be partly due to the reduced regenerative capacity of the ORNs [96]. Thus, it has been suggested that in the absence of efficient ORN regeneration, damage due to insults (e.g., exposure to toxins, respiratory tract infections) may accumulate to form permanent damage [25].

The size of the OB and the number of its laminae decreases with age, reflecting generalized atrophy and loss of neuronal elements secondary to OE damage [14]. In line with ORN damage, in patients with olfactory deficit, a reduction in the OB volume has been shown [25, 97–100]. However, in our, and others, previous studies, a lack of correlation of specific components of the sense of smell, such as odor threshold, odor discrimination, and odor identification and OB volume has been shown [101, 102••].

Age-dependent alterations also include a reduction in the volume of the hippocampus, amygdala, piriform cortex, and AON [15, 103]. Changes in the number, volume, and localization of islands of Calleja within the olfactory tubercle, a cortical structure receiving monosynaptic input from the OB, have been also shown and may be a contributor to pathological changes in the olfactory cortex function and olfactory perception [104]. In cognitively normal older individuals, worse odor identification has been associated with increased cortical amyloid, and with neurofibrillary pathology in the entorhinal cortex and hippocampus [32, 105]. Thus, olfactory functioning may be a valid indicator of the integrity of the aging brain [14].

A relevant observation is that impaired odor identification is associated with increased mortality risk in aged adults [14, 105–107]. The exact cause of this association is not known, but olfactory deficits may lead to an increase in accidents in the home, because of the inability to smell and taste food that is unsafe or not smelling a gas leak or fire, and this may increase mortality risk. It has also been suggested that the association of olfactory dysfunction with increased mortality in older individuals may be mediated by cognitive impairment [106, 107]. Lastly, it appears as if olfactory function is a good indicator of general health [108, 109].

Several studies indicate that odor identification deficits are associated with future cognitive decline [81, 110, 111]. In addition, olfactory dysfunction in cognitive normal persons could represent preclinical neurodegenerative disorders [2, 9, 14, 15, 24], being useful as part of a preclinical detection strategy and for enrollment in neuroprotective therapeutic strategies.

Olfactory Dysfunction in Neurodegenerative Diseases

An impaired sense of smell is associated with many neurodegenerative diseases [72, 79, 112–114]. Olfactory dysfunction is regarded as a clinical correlate of incidental Lewy body disease (iLBD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), idiopathic rapid eye movement (REM) sleep behavior (iRBD), mild cognitive impairment (MCI), and Alzheimer's disease (AD) [9, 115–119].

Olfactory dysfunction can appear early, frequently preceding the motor and cognitive symptoms, being considered a prodromal symptom of some neurodegenerative diseases such as PD and AD [24, 120, 121]. Furthermore, pathological protein aggregates seem to affect olfactory regions prior to other regions, suggesting that the olfactory system might be particularly vulnerable to neurodegenerative diseases [7, 9]. Indeed, OB pathology is prevalent in the early stages of some neurological disorders [122, 123]. The reason why these disorders affect the olfactory system early is still unknown. It has been suggested that given the ubiquitous but varying degrees of olfactory dysfunction among such diseases, a differential disruption of a common primordial neuropathological substrate might cause these differences in olfactory function [9].

Several anatomical systems and environmental factors may underlie olfactory loss associated with neurodegenerative diseases, although the biological link to each disorder remains unclear [9]. One hypothesis claims that pathogenic agents enter in the OE. This so-called vector hypothesis

suggests that the OE and OB allow pathogen and toxin penetration into the brain [7, 124, 125]. Identifying the mechanisms whereby neurodegenerative disorders progress throughout the brain is of critical importance both for the development of early diagnostic methods and for possible modulation of disease progression [7].

The high prevalence, the early presence, persistence throughout disease, and ease of olfactory testing have increased the interest in the use of olfaction dysfunction as biomarker for early diagnostic strategies, differential diagnostic, and prediction of clinical outcomes of neurodegenerative diseases.

Incidental Lewy Body Disease

iLBD describes autopsied individuals who have abnormal alpha-synuclein (α-synuclein) aggregates in the central nervous system, the so-called Lewy bodies and Lewy neuritis, without clinical findings of parkinsonism or cognitive decline [117, 126, 127]. Up to 30% of autopsied individuals over age 65 have iLBD in some neuropathological series [128, 129]. Lewy type-α-synucleopathy has been found in OBs and olfactory tracts in iLBD patients, and it has been hypothesized that iLBD may represent preclinical PD or DLB [117, 126, 127]. A marked decrease in the UPSIT scores in the iLBD patients has been described, although the number of cases in these studies was very low [117, 126, 130].

REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is a parasomnia characterized by a dream-enacting behavior and the loss of atonia during the phase REM of sleep [131, 132]. iRBD is increasingly recognized as a prodromal stage of neurodegenerative diseases, most frequently PD and DLB [131]. Odor identification deficits in iRBD patients have been repeatedly shown [37, 119, 133]. Moreover, the baseline of olfactory performance of those iRBD patients who convert to a synucleopathy in less than 5 years is in the range of performance of patients with PD, whereas non-converters have significantly better smell function [37].

Parkinson's Disease

PD is the second most common neurodegenerative disorder affecting about 1% of the population over 60 years of age [134]. The diagnosis of PD is based on the presence of motor symptoms such as bradykinesia, rigidity, tremor, and postural instability, usually manifesting unilaterally or asymmetrically [135]. Motor features in PD are predominantly a consequence of the loss of dopamineergic neurons in the substantia nigra *pars compacta*, and the symptomatic therapy used currently focuses on dopamine replacement strategies [135]. The main pathologic hallmark of PD is the presence of abnormal intraneuronal aggregates of the protein α-synuclein, termed Lewy bodies and Lewy neuritis in several structures of the central nervous system [123, 136]. In addition to parkinsonism, several non-motor symptoms are also part of the clinical spectrum of PD, including hyposmia, sleep disturbances, autonomic abnormalities, apathy, pain, and cognitive impairment [135, 137, 138]. These non-motor symptoms reflect the involvement of other brain regions beyond the substantia nigra [123].

Olfactory Dysfunction in PD

Among the most salient non-motor symptoms of PD is olfactory dysfunction [2, 24, 28, 139], present both in familial [140–142], and sporadic PD [24, 28, 143], with a prevalence ranging between 50 and 96% [24, 139, 144–146]. Anosmia occurs only in a minority of PD patients while hyposmia is more common [7, 66]. PD-associated olfactory dysfunction involves several domains of odor perception [147]. Detection threshold that requires a lower level of perceptual processing is impaired in PD patients. In addition, odor detection, discrimination, and identification that are considered be dependent on central processing, are severely affected in PD [24, 47, 65, 148]. Up to 72% of PD patients with olfactory dysfunction have been found to be unaware of their olfactory deficit [66], being frequently difficult to quantify the loss of smell since subjective symptoms do not always correspond to the real degree of olfactory dysfunction [134].

It has been suggested that detection of certain odors might be selectively compromised in PD [149]. However, when comparing studies using different tests, a set of odorants specific to PD has not been found [30, 150]. The lack of specificity to PD may also reflect the absence of specific damage to/lack of different receptor types, either at the OE or OB levels [30]. Moreover, it must be taken in consideration that most odorants used in the olfactory tests are composed of multiple chemicals, and different combinations of chemicals can produce the same smell [30].

Epidemiological studies have indicated an inverse association between smoking and PD [151–153]. PD risk is lowest among subjects with the longest duration of smoking, the greatest lifetime dose of smoking, the most cigarettes smoked per day, and, in past smokers, the fewest years since quitting [153]. On the other hand, olfactory function was less attenuated in current cigarette smokers with PD than in past or never smokers with PD [153, 154]. This observation is in agreement with recent findings on general population showing that smoking habit is associated with a better smell recognition/memory [6].

The use of complementary measures of the olfactory system in PD has been explored, such as biopsies of the OE,

measurements of OB volume, and functional neuroimaging, as potential biomarkers in PD. No specific pathological changes in the OE biopsies of PD patients compared with non-PD patients have been found [155–157]. When using structural magnetic resonance imaging (MRI), mixed results have been found. On a structural level, a reduced OB volume in PD patients compared with healthy controls has been described, suggesting that morphological abnormalities of the OB may contribute to the olfactory dysfunction in PD [158–161]. Moreover, the volume of the OBs and tracts was significantly smaller in patients with PD than in other PD-related disorders, suggesting that OB volumes allow to not only distinguish PD patients from healthy individuals but also potentially differentiate PD from atypical parkinsonian syndromes [162]. However, most studies have shown no difference in OB volumes between PD and controls, as well as no correlation between volume and disease characteristics, such as duration, motor symptom scores, or severity of olfactory impairment [100, 163–165]. Although methodological differences in the studies may be taken in account for the controversial results, it has been proposed that OB volumes cannot be used as a screening test to diagnose presymptomatic PD patients [164]. By using voxelwise analysis of diffusion-weighted imaging (DWI), an increased diffusivity in the olfactory tract of early PD patients has been observed [166]. In addition, PD patients with anosmia had reduced fractional anisotropy (FA) values, in contrast with the PD patients without severe olfactory dysfunction and the healthy controls [167]. All these studies suggest an abnormal structural integrity in the central olfactory structures in PD patients [167, 168].

Based on functional fMRI studies, a reduced neuronal activity in the amygdala and hippocampus has been reported in PD patients in the presence of olfactory stimuli inside the scanner [169] and a decreased functional connectivity in the primary olfactory cortices as well as the secondary olfactory structures compared with controls [170].

Olfactory Dysfunction as a Biomarker for Early PD and Disease Progression

PD has a premotor period of several years [171, 172]. Olfactory dysfunction is often one of the first manifestations of the disease, preceding the appearance of the classical motor symptoms by at least 5 years [9, 14, 28, 135, 143, 173–175] and may be considered a biomarker for the diagnosis of PD in its early premotor stages, as well as for the prediction of symptom progression [26, 27, 173, 174]. Earlier detection of PD would enable testing of potential disease-modifying treatment strategies when pathology is less advanced and treatments may be more effective [28, 135].

Many studies have demonstrated an association between olfactory dysfunction and an increased risk to develop PD [33, 143, 171, 173, 174, 176]. These findings are supported by clinic-pathologic studies demonstrating higher odds of incidental Lewy body pathology on autopsy for hyposmic patients without clinical symptoms of PD compared with normosmic participants [126, 177]. Further, a reduced intrinsic integrity of the substantia nigra in patients with unexplained smell loss support the PD at-risk status of these patients [178]. Due to many other causes of hyposmia in other disorders and the general population [28], combining olfaction with other markers of premotor PD improves the positive predictive values [176, 179, 180].

Dopaminergic imaging with single-photon emission computed tomography (SPECT) is highly specific for the dopaminergic deficit seen in parkinsonian disorders and can be used to identify a high-risk group for PD since it has been demonstrated that dopamine transporter imaging deficit precedes a PD diagnosis by several years [132, 181]. Moreover, using olfactory testing in clinically unaffected first-degree relatives of PD patients with a 5-year follow-up showed that all of the hyposmic individuals who went on to develop PD had an abnormal dopamine transporter imaging at baseline [180]. In addition, the combination of hyposmia and dopamine transporter imaging deficits may be highly predictive of conversion to PD within 4 years of clinical follow-up, as recently shown [182].

In addition to serving as a marker of early PD, olfactory function has also been studied as a potential marker of disease progression [28]. Early studies suggested that olfactory dysfunction in PD remains stable over time, appearing independent of disease severity, disease duration, or dopamine transporter abnormalities [66, 183]. However, more recent longitudinal studies have shown that olfactory impairment was not stable, although it did not deteriorate in a linear fashion [174, 184, 185] and that marked changes in olfactory threshold and odor discrimination alterations correlate with more rapid disease progression [185–187] and dopamine transporter imaging [179, 188].

Olfactory Deficit and Cognitive Decline in PD

Cognitive decline is frequent in PD, especially in the later years of the disease, and they are often present in people with PD aged over 70 years regardless of the age at disease onset [135]. Cognitive decline in PD presents usually as several specific cognitive domains, including episodic verbal learning and verbal memory, attention, and executive function [26, 135, 173, 189–191].

The correlation between olfactory dysfunction and cognitive decline in PD has been examined in both cross-sectional and longitudinal studies, suggesting that olfactory dysfunction may serve as a predictor of cognitive decline [7, 28, 192]. In newly diagnosed PD patients, it has been reported that olfactory dysfunction increases the risk of dementia up to 10 years

after PD diagnosis regardless of baseline cognitive function, age, gender, and motor dysfunction decline [192, 193] although several studies have suggested that only PD patients with severe hyposmia and mild cognitive impairments developed severe dementia after 3 years [194, 195]. On the other hand, being normosmic with normal cognition at baseline is a good predictor of a stable cognitive function up to 10 years after diagnosis [192].

Because it is a marker of high sensitivity, olfaction may be used in combination with other putative biomarkers in order to increase specificity as a predictor of cognitive decline in PD [190]. Cerebrospinal fluid (CSF) biomarkers, including tau and Aβ1-42 have been associated with cognitive impairment in PD and DLB [196, 197] and reduced CSF Aβ1-42 being an independent predictor of cognitive decline in two mixed stage PD cohorts [198, 199].

Olfactory Dysfunction and PD Differential Diagnosis

Olfactory dysfunction has been suggested to be useful in distinguishing PD from other neurodegenerative diseases. Several studies have focused at olfactory function in parkinsonian syndromes, suggesting olfactory dysfunction as a clinical marker to distinguish PD from other parkinsonisms [200–202]. A preserved or only mildly impaired olfactory function in a parkinsonian patient is more likely to be related to atypical parkinsonism such as MSA, PSP, or CBD, whereas markedly reduced olfaction is more suggestive of PD [200–203].

In addition, patients with tauopathies associated with parkinsonism, such as CBD and PSP, tend to have fairly normal olfactory function, frequently indistinguishable from healthy controls [201, 204, 205], helping to differentiate these disorders from PD and MSA [29, 205]. MSA patients may experience olfactory dysfunction although the severity of the smell loss is less pronounced than in PD patients, tending to have olfactory impairment intermediate between PD and the tauopathies [202–205].

Olfactory function may be used to differentiate PD from other forms of parkinsonism, such as drug-induced parkinsonism (DIP) and vascular parkinsonism [28]. DIP patients usually had normal or close to normal olfaction that facilitates the identification of patients with “unmasked” PD [26, 206]. Similarly, when comparing olfactory function in patients with vascular parkinsonism and PD, the patients with PD showed lower olfactory scores, whereas those with vascular parkinsonism are not different from healthy controls [207].

Olfactory Dysfunction in Genetic PD

Olfactory dysfunction in genetic forms of PD shows heterogeneity depending on the affected gene [24, 208]. The most common cause of inherited parkinsonism are the mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene that account for a relevant proportion of familial and sporadic PD cases [141, 142, 209, 210]. Several causal mutations have been found in the *LRRK2* gene, being the G2019S mutation the most common worlwide [211]. Hyposmia has been reported to be approximately 30% less frequent in *LRRK2*-PD patients than in idiopathic PD [212–215]. In addition, olfactory function presents better UPSIT scores in *LRRK2* G2019S PD than in idiopathic PD patients [77, 141, 142, 212, 216]. The causes for the differences in olfactory function between *LRRK2*-PD and idiopathic PD remain unknown. Less-severe involvement of olfactory structures or a more heterogeneous pathology in *LRRK2*-PD has been suggested to account for such differences [217, 218]. Olfactory function seems to be particularly preserved in females with the G2019S mutation, suggesting a gender effect in the expression of some *LRRK2*-PD symptoms [212]. Several studies suggested that asymptomatic carriers of the *LRRK2* G2019S mutation are not more hyposmic than healthy controls [183, 215, 219], suggesting that olfactory dysfunction is not a common symptom at the prodromal phase of *LRRK2* G2019S-associated PD, being not a good predictor of conversion to PD at the premotor stage [219].

Other cause of genetic PD is that linked to α-synuclein gene alterations. Patients carrying the A53T mutation of the α-synuclein gene presented with hyposmia, while no olfactory deficits were observed in carriers of the α-synuclein E46K mutation [220–222]. The most-frequent form of genetic PD with autosomal recessive inheritance is that associated to mutations in the *Parkin* gene. In these patients, the absence of olfactory dysfunction is common [223, 224]. In patients with mutations in the *PINK1* gene, other less-frequent form of recessive PD, olfactory abnormalities have been described [225].

PD patient carriers of a mutation in the *glucocerebrosidase* (*GBA*) gene, the most common risk factor for PD, seems to have impaired olfaction after the appearance of motor symptoms [226–228].

Mechanisms Involved in Olfactory Dysfunction in PD

The origin of olfactory dysfunction in PD remains currently unknown, but it is believed to relate both peripheral and central olfactory impairments [7]. The mechanisms involved in the loss of smell in PD may involve neuropathological alterations and/or dysfunction caused by changes in neurotransmitter levels in the olfactory system [28].

Neuropathological Correlates of Olfactory Dysfunction in PD

The olfactory system is among the earliest brain regions involved in PD before involvement of the nigrostriatal pathway [123, 143]. According to Braak staging of the disease, Lewy pathology begins in the OB and dorsal

motor nucleus of the vagus, consistent with the early onset of olfactory dysfunction [7, 9, 123, 153, 192, 229].

It has been hypothesized that one of the initial events in PD is a pathogenic access to the brain through the nasopharynx, resulting in olfactory dysfunction [154]. This "vector hypothesis" has also been discussed for the pathogenesis of other neurodegenerative diseases associated with hyposmia such as AD [124]. It has been suggested that α-synuclein pathology may spread from peripheral to central olfactory structures [124]. This is supported by the observation that in PD cases and controls with incidental Lewy bodies, α-synuclein pathology in the OB and associated structures is found [230]. Recent work in rodents using microinjections of α-synuclein fibrils into the OB demonstrate that the olfactory route can be a vector of pathology spreading into the substantia nigra and other regions involved in later stages of PD [7, 231••, 232]. Specifically, they found that α-synuclein aggregates progressively spread from the OB to a total of over 40 different brain subregions bilaterally over the course of 12 months, and that the progressive development of synucleopathy was coupled to the emergence of specific olfactory deficits [231••].

Until now, however, there is little information about possible PD-specific changes at the peripheral level of the olfactory system. The involvement of OE on olfactory loss, have not yet been defined. While it has been suggested that the OE may offer a diagnostic target, several studies have shown no significant differences in immunohistochemical markers, including different α-synuclein subtypes, of OE in PD patients when compared with controls [155, 233]. These observations suggested that the alterations in olfaction in PD may be not to be directly associated with specific changes in the OE but with processes associated with Lewy body formation in central olfactory areas [135, 144, 230]. In addition, the study of the EEG components in PD patients has provided evidence for a decline of central brain networks as a causal factor for olfactory loss in PD [168].

At the OB level, it has been described that the synucleopathy density scores are correlated with UPDRS motor scores, suggesting that α-synuclein pathology develops early and continues to accumulate [127]. α-Synuclein inclusions are found in interneurons, in the internal plexiform layer, and less frequently in MCs and TCs, which raises the possibility that these relay neurons might be more resistant to developing α-synuclein aggregates than other neurons [24, 230]. A role of MCs and TCs in the propagation of pathology to connected regions is, however, not excluded [7]. PD patients also showed a loss of MCs, but dopaminergic are rarely affected in either the OB or associated nuclei [234]. Moreover, an increase in periglomerular dopaminergic neurons [235–237] and a direct axonal dopaminergic projection from the substantia nigra to the OB have been described [60], suggesting a relevant role of dopamine in olfactory dysfunction [102••]. α-Synuclein pathology has been found across the central olfactory system, including the AON, cortical nucleus of the amygdala, piriform cortex, olfactory tubercle, entorhinal cortex, and orbitofrontal cortex [230, 238, 239]. The cortical nucleus of amygdala receives the primary OB projections showing more α-synuclein pathology and neuronal loss than other nuclei in the amygdala [240]. As a result, the volume of the amygdala is reduced by 20% [240]. The loss of volume in the amygdala and the piriform cortex inversely correlates with olfactory deficits suggesting that cell loss in these regions could contribute to the functional deficits [189, 241].

In addition to α-synuclein pathology, tau pathology has also been found in the AON in PD [237, 242]. Interestingly, patients with CBD and PSP, parkinsonian disorders with little or no olfactory loss, did not demonstrate tau pathology in the AON, suggesting that tau pathology may contribute to olfactory impairment in PD [237, 242].

Neurotransmitter Systems in Olfactory Dysfunctions in PD In addition to the dopaminergic system, progressive degeneration of the cholinergic and serotoninergic neuromodulatory systems innervating olfactory structures has been suggested to correlate with olfactory loss [24, 102••, 134, 243].

Dopamine Dopamine has long been known to play a major role in the pathogenesis of PD, but more recently, its association with olfactory loss has been investigated. The OBs contain a population of approximately 10% of dopaminergic interneurons within the glomerular layer and dopamine receptors are expressed in the OB, specifically D2-like receptor in the periphery and D1-like receptor in the cores and in the external plexiform layer [244, 245]. Dopaminergic interneurons participate in olfactory processing, and determine olfactory abilities, such as perception, discrimination, and olfactory social interactions [58, 60, 102••, 246–248]. In addition, a high plasticity of the OB dopaminergic neurons in response to manipulation of the olfactory pathway has been reported. Thus, odor deprivation by naris occlusion selectively reduces the number of adult-generated dopaminergic cells [249, 250], which recover after naris reopening [250]. Moreover, in preclinical studies, the administration of a selective dopamine D2 receptor agonist either systemically or locally to the OB decreases odor detection performance [247], whereas a dopamine D1 receptor agonist has the opposite effect [247, 251]. These findings suggest that the dopaminergic neurons inhibit olfactory perception via D2 receptors and stimulate it via D1 receptors

Whether alterations in dopamine activity are directly associated with olfactory dysfunctions in PD is still unknown. Several studies have demonstrated correlations between olfactory tests and a decrease in dopamine transporter activity in the substantia nigra and striatum in PD patients [188, 252, 253]. However, olfaction has not been found to be responsive to dopaminergic replacement therapy [183]. On the other

hand, the fact that the number of striatal dopaminergic neurons is generally decreased in PD [158, 254] is confronted with a 100% increase of tyrosine hydroxylase-positive (TH, the key enzyme of the dopamine pathway) cell numbers at the level of the OB that has been described in PD patients [235]. In addition, it has been reported that increasing inhibitory action of dopaminergic interneurons would account for hyposmia in these patients [184]. In a more recent study, however, investigating approximately twice as many subjects, the same authors found similar number of OB TH-positive cells in male controls and male PD patients, suggesting that hyposmia in PD patients may be not explained by an increase in BO dopaminergic neurons [235]. Despite these controversial results regarding the number of BO TH-positive cells in PD patients, a role of dopamine in olfactory dysfunction in PD must be considered. Moreover, the recently described direct dopaminergic projection from the substantia nigra to the OB provides a new neuroanatomical basis for altered dopaminergic neurotransmission in hyposmia in PD

Acetylcholine Cholinergic innervation of the OBs arises from the horizontal limb of the diagonal band of Broca to the glomerular layer and moderately in the subglomerular layers [56, 255]. The OBs express both muscarinic and nicotinic acetylcholine receptors [256–258]. Several studies have demonstrated that acetylcholine release and activation of acetylcholine receptors facilitate olfactory learning, memory, and odor discrimination [259–262]. The cholinergic system has been associated with olfactory dysfunction in PD since Lewy bodies and neuronal loss in the substantia nigra occurs concurrently with accumulation of α-synuclein deposition in cholinergic neurons of the basal forebrain [24, 123, 263, 264].

The protective effect of smoking on odor recognition that has been described in PD patients [153, 154] could reflect the agonist effect of nicotine on the cholinergic system. However, the association between changes in acetylcholine levels and olfactory impairment has been described as not specific for PD [9].

Serotonin Serotonin arises from the raphe nuclei, which send projections to the OB [57, 265]. Serotonergic fibers are densest in the glomerular layer, which is innervated by the median raphe nucleus [266]. Fibers from the dorsal raphe, however, target the mitral and granule cell layers of the OB, as well as the piriform cortex and the amygdala [265].

The major effect of serotonin in the OB is the modulation of MC activity, being predominantly excitatory although inhibition was observed to a lesser frequency at the accessory olfactory bulb level [57, 267]. Neuromodulation of olfactory circuits by acetylcholine plays an important role in odor discrimination and learning [265].

In patients with PD, Lewy pathology is found in the raphe nuclei [123], along with marked depletion of serotonin in the OB and other areas of the olfactory system [268, 269], whereas a preservation of serotonin was found in disorders with normal or close to normal olfaction, such as PSP [270]. Although the evidence is still far from conclusive, these observations suggest that alterations in serotonin levels may have a role in the olfactory dysfunction in PD [269].

Dementia with Lewy bodies

DLB is diagnosed when cognitive impairment precedes parkinsonian motor signs or begins within 1 year from its onset [271]. In DLB, olfactory deficits are similar to PD being often apparent in early stages of the disease and considered part of the emerging concept of prodromal DLB [271, 272]. Similar to those with iLBD, patients with DLB frequently exhibit severe pathology in the OB; however, studying the olfactory mucosa α-synuclein pathology has been found only in the cribrifrom plate [273].

Similarly as that which occurs in PD, in addition to α-synuclein pathology, DLB also displays tau and Aβ pathology [274], suggesting, as already mentioned, a role for aggregated tau in the olfactory dysfunction of synucleopathies.

Alzheimer's Disease

AD is the most common neurodegenerative disorder in older individuals, clinically characterized by progressive deterioration in cognitive functions and dementia [275]. AD accounts for 60–80% of all cases of dementia [276], with an annual incidence of 1% in persons aged 60–70 years and 6–8% in those aged 85 years or more [277]. The prevalence of AD will continue to increase alongside the longevity of the population [276]. The pathological hallmarks of AD are neuronal loss, the accumulation of amyloid-β plaques, and phosphorylated tau protein neurofibrillary tangles (NFTs), which may contribute to the neurodegenerative processes [275, 276].

Olfactory Dysfunction in AD

One of the earliest brain regions affected by AD is the olfactory system showing amyloid plaques and NFTs, with olfactory dysfunction being an early symptom of AD [276, 278, 279]. Approximately 85% of patients with early-stage AD exhibit olfactory dysfunction [276], being developed prior to the appearance of cognitive dysfunction [280, 281].

Deficits in odor detection, identification ability, recognition, discrimination, and long-term odor recognition memory have been reported in AD [80, 147, 280]. However, odor identification, defined as the ability to identify and name specific odorants, and discrimination are more severely impaired than odor detection [7, 148]. Studies involving odor discrimination abilities in AD patients have been more criticized than studies on odor identification [79]. The main reason is that—

possibly—olfactory discrimination requires recomplex processing than odor identification [79, 282].

The overall severity of olfactory dysfunction in AD is similar to that in PD; however, PD patients present more severe impairment of detection threshold [7]. These findings suggest that the neuroanatomical pathology underlying olfactory impairment in AD versus PD are to some extent different [7]. Since low odor identification scores have been associated with higher levels of AD pathology in central olfactory structures [283], this suggests that AD patients are more affected in higher-order olfactory tasks than to the inability of odor information to enter the brain [7, 148].

Olfactory dysfunction in AD is often unnoticed. Only 6% of AD patients complain at an early stage about a decrease in olfactory function whereas 90% of these patients demonstrated a significant impairment in the olfactory test [284, 285]. It has ben proposed that MCI patients with a low olfactory function score are considered more likely to develop AD, especially those with a low olfactory function score who are not aware of their problems in the sense of smell [284].

In longitudinal studies, reduced olfactory identification performance predicts faster cognitive decline in older controls and persons with mild cognitive impairment or AD dementia [33, 105, 286].

Olfactory Dysfunction as a Predictor for MCI to AD Conversion

The gradual onset and slow progression of AD poses a challenge for early differentiation of AD from other causes of cognitive decline, including healthy aging and MCI [276]. After initial studies establishing the presence of olfactory dysfunction in AD patients compared with cognitively intact subjects [287], subsequent research has focused on the use of odor identification impairments for predicting the conversion from MCI to AD [286].

Thus, prospective cohort studies established that olfactory deficit infers risk for development of cognitive impairment [110]. A clear increase in odor identification deficits predicting conversion from cognitively intact individuals to MCI and to AD has been reported [34, 284, 286]. In MCI patients, baseline odor identification deficits were associated with a fourfold increased risk of conversion to AD [34, 284, 286]. Thus, results of a 2-year follow-up showed that 47% of MCI patients with olfactory impairment and 11% of MCI patients with a normal sense of smell eventually developed AD [288]. Olfactory deficit defined as UPSIT score equal or lower than 34 out of 40 in participants with MCI predicted conversion to AD at 2-year follow-up [284]. Impairment in odor discrimination also occurs in patients with MCI and AD but is slightly less robust than odor identification in distinguishing patient groups [282].

A meta-analysis suggested that the combination of odor identification tests with clinical/neuropsychological assessment and imaging biomarkers could be the most useful tool to detect subclinical AD and predict the conversion from MCI to AD [148]. In this line, a 3-year follow-up showed that a combination of olfactory function impairment, verbal memory, hippocampus volume, and entorhinal cortex volume had a strong predictive value (90% specificity and 85.2% sensitivity) for AD converting from MCI [289].

Based on currently available knowledge, the importance of olfactory assessment in daily clinical practice should be recognized. In addition, olfactory function tests should be incorporated in the assessment of high-risk populations for dementia to screen systematically for subclinical AD [114].

Mechanisms Involved in Olfactory Dysfunction in AD

Neurodegeneration and Olfactory Dysfunction in AD The precise mechanisms underlying olfactory dysfunction in AD are still largely unknown. Diminished olfactory identification has been associated with markers of neurodegeneration, such as reduced entorhinal cortical thickness, hippocampus, and amygdala volumes [32, 289]. Additionally, loss of left hippocampal volume has been associated with the performance of odor recognition tasks in AD patients [290]. Moreover, using fMRI, it has been shown that the blood oxygenation level-dependent signal in the primary olfactory cortex was weaker in patients with early-stage AD than in healthy controls [291].

Neuropathological Correlates of Olfactory Dysfunction in AD At the neuropathological level, in AD patients, amyloid and tau deposits have been found throughout the olfactory pathways, including temporal piriform cortex [79, 105, 116]. In the OBs, a minimal number of amyloid plaques have been also found, although the NFTs with abnormally phosphorylated tau protein are typically higher [242, 292].

Although the local mechanisms related to Aβ-associated pathophysiology in olfactory regions are still unknown, several studies have implicated a close relationship between the spatial and temporal patterns of Aβ and olfactory dysfunction in AD [293, 294]. Aβ is present in the OE of 71% of AD cases but only in 22% of normal control cases [279]. The increased expression of presenilin proteins (PS1 and PS2), the catalytic components of protease complexes that directly cleave the amyloid precursor protein, exclusively occurring in the OE enlighted the possibility for a feasible biomarker in the preclinical stages, since it can be observed at early stages of AD [279]. However, the progression of Aβ plaques in the brain is less predictable than that of NFTs [7]. Thus, the involvement of Aβ plaques in the olfactory function might be subject to a lot of variance [7]. Moreover, in vivo imaging studies have shown weak associations

between amyloid and olfactory impairments [15, 32, 278]. In spite of a recent study showing that Aβ disturbs local GABAergic neuron circuits through both presynaptic and postsynaptic mechanisms that might affect the odorant information process resulting in abnormal outputs form MCs [295], previous data suggest that AD-related odor identification deficits are not directly related to fibrillar Aβ burden, ascribing olfactory deficits to other neuropathologic features such as NFTs [296••].

All together suggests that impairments in odor identification tests could be more associated with tau deposition and neurodegeneration in regions involved in olfactory processing. In this line, odor identification deficits in early AD has been associated with NFTs in the OB, and olfactory projection areas [105, 277, 297], especially in the entorhinal cortex, and hippocampus CA1 region [105, 278, 296••]. According to Braak and Braak staging of the neuropathology in AD [122], as the disease progresses, three main stages can be distinguished based on the distribution of neurofibrillary tangles: trans-entorhinal, limbic, and neocortical stages [14, 242]. Tau aggregates that make up the NFTs in AD and other tauopathies have been shown to be capable of undergoing cell-to-cell transfer and propagate aggregate pathology in a prion-like fashion in experimental models of disease [298]. Despite all these studies, further research on the cellular and molecular mechanisms underlying olfactory dysfunction in AD is required.

Genetic Factors in Olfactory Dysfunction in AD The possible contribution of genetic factors to the olfactory dysfunction in AD, such as the presence of one or two copies of the ε4 allele of apolipoprotein E (Apoε4), an established risk factor for AD, has been suggested [33, 299]. Volumetric MRI studies have shown that Apoε4 is associated with the degree of atrophy in the entorhinal cortex in early AD patients [300]. Moreover, it has been suggested that people with anosmia and one Apoε4 allele have an approximate fivefold increased risk of later AD [301]. However, in a large multi-ethnic older community cohort, no significant associations between the UPSIT score and the presence of the Apoε4 allele has been shown [302].

Neurotransmitter Systems in Olfactory Dysfunction in AD Neuromodulatory systems are early affected in AD, with 30-90% cholinergic cell loss in the nucleus of Meynert [303]. Cholinergic deficits could contribute to the olfactory dysfunction in AD patients, because acetylcholine plays a major role in the olfactory learning process [304]. Moreover, in a small, non-blinded, uncontrolled study, it has been demonstrated that the treatment response of the cholinesterase inhibitor, donepezil, was associated with an improvement in olfactory function of AD patients. This result suggested that olfactory recognition might be used to predict therapeutic effects in AD patients [281].

Other Neurodegenerative Disorders

The classic clinical features of the progressive supranuclear palsy (PSP) include supranuclear vertical ophtalmoplegia, severe postural instability with early falls, and subcortical dementia [201], most commonly developing in the seventh decade of life. PSP shares many common features with PD; however, several studies have suggested that hyposmia, which is a common and early feature of PD, is not present in PSP [204]. However, mild deficits in odor identification have been described in PSP [201, 242].

Corticobasal degeneration (CBD) is a tauopathy that may present with bradykinesia, which may be misdiagnosed as PSP. Regarding the olfactory deficit in CBD, several studies have found no alterations in olfactory function [204] or only slight alterations [205].

Clinical studies have shown mild deficits in odor identification in multiple-system atrophy (MSA) [204, 205], although a study failed to confirm this previously reported hyposmia [203]. Among the diseases that have mild or no olfactory deficits, MSA is the only one with pathological inclusions in olfactory regions [242], being tau accumulation present in the OB in one third of PSP cases [242].

Olfactory dysfunction in amyotrophic lateral scleroris (ALS) has not been deeply studied. Hyposmia has been reported in idiopathic ALS and in Guamanian ALS patients [305, 306], although, in several studies, hyposmia has been found only in patients with bulbar symptoms [307], or in a subgroup of ALS patients with cognitive impairment [308]. A neuropathology study suggested that TDP-43 inclusions might be involved in the olfactory dysfunction since these inclusions have ben observed in the olfactory system [309]. In a recent report, ALS patients showed a decreased odor threshold; however, they did not show impaired performance in identification and discrimination tests, resembling the pattern of olfactory dysfunction occurring in sinonasal diseases that results from impeded odorant transmission to the olfactory cleft [306]. In addition, ALS patients with alterations of respiratory function performed worse in the olfactory tests than the ALS patients with preserved respiratory function [306], suggesting that olfactory dysfunction in ALS patients might be partly a consequence of impaired respiratory function.

Conclusions

Epidemiological studies show that the prevalence and severity of olfactory dysfunction increases with age, although the mechanisms underlying olfactory dysfunction with advancing age are still unclear. In addition, olfactory dysfunction in cognitive normal persons could represent preclinical neurodegenerative disorders.

In the neurodegenerative diseases, olfactory dysfunction can appear early, frequently preceding the motor and cognitive symptoms, being considered a prodromal symptom of some diseases, such as PD and AD. The measure of olfactory function in association with other clinical, biological, or neuroimaging markers is a useful tool for preclinical detection strategy, differential diagnosis, and for enrollment in neuroprotective therapeutic strategies.

Although several neuropathological mechanisms have been associated with the olfactory dysfunction in neurodegenerative diseases, further preclinical and clinical research on cellular and molecular mechanisms underlying olfactory dysfunction in neurodegenerative diseases is required.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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