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Alterations in Olfaction during Alzheimer Disease, Parkinson Disease and Lewy Body Disease

Patrick Manckoundia[1,2,*], Alain Putot[1], Rachid Mahmoudi[3,4], Mélanie Dipanda[1], Sophie Putot[1], Sanaa Asgassou[1], Anne-Julie Bianchi[5] and Hélène Sordet-Guepet[1]

[1]*Elderly Persons Pole, Hospital of Champmaillot, University Hospital, BP 87 909, 2 rue Jules Violle 21 079 Dijon Cedex, France*
[2]*INSERM U1093 Cognition Action Plasticite Sensorimotrice. Universite of Bourgogne Franche Comte BP 27877 F-21078 Dijon Cedex, France*
[3]*Department of Internal Medicine and Gerontology, University Hospital, Maison Blanche Hospital, Reims, F-51092, France*
[4]*University of Reims Champagne-Ardenne, Faculty of Medicine, E.A 3797, Reims, F-51092, France*
[5]*Department of Geriatric Rehabilitation, Hospital of Beaune, BP 40104, Avenue Guigone of Salins, 21203 Beaune Cedex, France*

Abstract

Increasing interest is being shown in the link between olfaction, a complex sensory system, and cognition, particularly in the elderly. Olfaction is known to affect cognitive abilities and mood. In this article, we consider the impairment of olfactory function due to Alzheimer disease (AD), Parkinson disease (PD) and Lewy body disease (LBD), through pathological changes in the peripheral and central olfactory structures. The high frequency of these olfactory disorders as well as their early occurrence in AD, PD and LBD suggest that they should be screened for in subjects suffering from these three neurodegenerative diseases.

Keywords: Alzheimer disease; Lewy body disease; Olfaction; Parkinson disease

Abbreviations: AD: Alzheimer's Disease; LB: Lewy Bodies; LBD: Lewy Body Disease; PD: Parkinson Disease

Introduction

The loss of olfaction is not often reported by those who suffer from it, especially the elderly. It therefore deserves to be screened for by caregivers so that it can be recognized [1,2]. As well as its major role in social behaviour of many species and its interest in terms of safety, the olfactory system affects the quality of life of individuals because of its strong emotional component [1,2]. Long ignored by the medical community, the sense of smell is now considered precious, and involved in memory processes. Olfaction disorders are seen at a very early stage of certain neurodegenerative diseases including Alzheimer disease (AD), Parkinson disease (PD) or Lewy body disease (LBD) [1-16]. The risk of cognitive deterioration in persons with impaired olfaction could be 4 to 5 times greater than that in normosmic individuals [2]. The aim of this work is to review what is known about impaired olfaction in AD, PD and LBD.

Reminder about Olfactory Memory

The coding of olfactory memory is both verbal and sensory, and dependent on the context of the exposure [1,17]. Olfactory memory is characterized by its durability over time and its emotional nature [1,2,9,18-20]. Explicit olfactory memory, linked to repeated or long-standing memories of odours, allows the identification of smells whereas implicit olfactory memory, based on sensations, does not allow the individual to put a name to an odour because of the impairment of semantic memory, the latter being culturally shared [21]. The importance of the subconscious perception of an odour, which can be memorized and associated with places and experiences, particularly distressing ones, has been shown, thus confirming the existence of implicit memory [21].

Olfaction is evaluated using three types of tests: psychophysical tests, which need a conscious response of the patient, electrophysiological tests and psychophysiological tests [22]. Identification tests are the most commonly used psychophysical tests. Familiar odorants are presented to the person, who is asked to identify the name of the odour or in some cases to choose a picture that illustrates the source of the odour. Furthermore, some identification tests are able to provide an absolute determination of olfactory function (i.e., normal, mild, moderate, severe or total loss). Finally, sex-and age-related normative data are available for some of these tests [22]. Among the psychophysical tests, there are also suprathreshold odour discrimination tests, which consist in asking subjects to distinguish among sets of odorants or odorant mixtures at suprathreshold levels. Measurements of the perceived strength of odours an also be assessed using rating scales and magnitude estimates [22]. In electrophysiological tests, which measure fluctuations in olfactory event-related potentials [23], odour-induced recordings are obtained from electrodes positioned near or on the olfactory epithelium, producing a summated negative potential termed the electro-olfactogram [22]. The psychophysiological tests principally quantity the responses of the autonomic nervous system to stimuli, in this case odour [22].

The Physiological Ageing of Olfaction

The physiological ageing of olfaction or presbyosmia is progressive. In most cases, it consists of a diminished sense of smell, hyposmia, rather than a complete loss, anosmia [2,3,24]. This ageing of olfaction affects 50% or more of persons aged from 65 to 80 years and 62 to 80% of those aged 80 years and older; it is the leading cause of olfaction disorders [2,3,24,25]. The origins of diminished olfaction due to ageing are sensory and probably cognitive [2,24]. Hyposmia is notably

***Corresponding author:** Patrick Manckoundia, Elderly Persons Pole, Hospital of Champmaillot, University Hospital, BP87909, 2rueJules Violle 21 079 Dijon Cedex, France Tel: 0380293970; E-mail: patrick.manckoundia@chu-dijon.fr

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related to architectural and functional modifications of the olfactory neuroepithelium especially a decrease in lymphatic elements, in cytochrome P450, in mucociliary transport and in nasal blood flow as well as modifications of the septal cartilage. This deterioration in olfaction is aggravated by atrophy of the olfactory bulb, a decrease in the number of neurons, the deterioration of central olfactory structures, abnormalities of basic olfactory circuitry, related to the neuronal expression of aberrant proteins in these zones, and various insults, including viral, to the olfactory receptors [2,3,23-25]. These pathological features are also found in neurodegenerative diseases [23,25].

Ageing-related alterations of olfactory performance include increased olfactory thresholds, a deterioration in recognition memory, diminished perceived intensity and diminished ability to discriminate between and identify odours [2,24,26]. However, with ageing, olfactory thresholds are more strongly impaired than odour identification [27]. This is explained by the fact that odour identification and recognition are thought to involve high-level cognitive processes and thus to rely on additional cerebral resources [28-31], while detection thresholds rather rely on low-level perceptual processes [32,33].

Several factors contribute to the loss of olfactory function due to ageing. These include nasal engorgement, damage to the olfactory epithelium from environmental stresses, a decrease in levels of mucosal metabolizing enzymes, the loss of odorant receptor cells, and changes in neurotransmitter and neuromodulator systems [25].

Alzheimer Disease and Olfactory Disorders

Olfactory disorders are found in 85 to 90% of persons with AD [2]. This is so high that the absence of olfactory disorders could have a negative predictive value in AD [2]. Olfactory disorders seem to occur early in AD, even before the onset of cognitive disorders [2,4-11,14]. According to certain authors, they could predict the onset of AD, and it has been suggested that olfaction disorders could play a major role in screening for the disease [2,5,11]. Once they have appeared, olfactory disorders worsen progressively throughout the AD, in parallel with other symptoms of the disease [2]. The deterioration in olfaction is both peripheral and central with the collapse of test scores for odour detection, odour discrimination, recognition memory and odour identification, but the preservation of intensity judgements, hedonic and edibility assessments of odours [2,3,5].

The literature suggests that AD affects odour identification and recognition more strongly than it does odour detection. One explanation is that the greater deficits found in odour identification and recognition may be analysed as the summation of cognitive and perceptual deficits, while detection threshold deficits might be less dependent on cognition. Olfactory disorders found in AD could therefore be the result of impairments on these two levels. Indeed, in view of the results of a principal component analysis, it has been suggested that odour threshold tests on the one hand, and odour identification or discrimination tests on the other hand are relatively independent measurements of olfactory function [34,35]. Furthermore, in AD, higher order olfactory functions seem to be more strongly affected than other functions [35].

As for the pathological features, the senile plaques and the neurofibrillary tangles are seen in all olfactory structures, both peripheral and central [2,4-8,11,12,36,37]. The first neurodegenerative modifications affect the entorhinal cortex, corresponding to Braak stages I and II. Then the transentorhinal cortex, the hippocampus and the amygdala are affected, corresponding to Braak stages III and IV. Involvement of the cerebral cortex corresponds to stages V and VI [2,37]. The alteration of these structures is crucial, as they play a critical role in the processing of olfactory signals, notably the entorhinal cortex and the hippocampus, which are involved in odour memory and recognition [2,5,36]. The entorhinal cortex is the gateway for olfactory input to the hippocampus, and there is seamless synchronization between olfactory function and the activity of hippocampus [38]. In addition, olfactory deficits are associated with the ε4 allele of Apo-lipoprotein E (ApoE ε4), whose implication as a risk factor for AD has been shown [2,5,7,11]. Persons with AD who carry ApoE ε4 present impaired odour sensitivity, odour identification and odour memory recognition [2,5]. In elderly persons with ApoE ε4, but no clinical expression of AD, or mild cognitive impairment, the olfactory deficit is related to the presence of neurofibrillary tangles in olfactory centres (hippocampus and entorhinal cortex) [11], thus underlining the interest of screening for olfactory disorders at the same time as conducting neuropsychological tests and performing magnetic nuclear resonance imaging to analyse the hippocampus and entorhinal cortex so as to predict the conversion of Mild Cognitive Impairment into AD. This strategy has a sensitivity of 85.2%, a specificity of 90% and only 10% of false positives [12]. In addition, there appears to be a relationship between the number of ε4 alleles and the deficit in neurons containing acetylcholine in the brains of patients with AD, which is important given that acetylcholine plays a major role in olfactory learning [2,5,11,14]. These data strongly suggest that olfactory tests, in association with other tools, would improve the early detection of AD, even in persons with no identified cognitive deficit. In addition, for certain authors, an improvement in olfactory function could attenuate cognitive neuropathology in AD [38].

Olfaction and Parkinson Disease

Up to 90% of persons with PD suffer from olfactory disorders, even though they may not complain about this olfactory deficit [2,13,15,16]. As in AD, the early impairment of olfactory pathways is both peripheral and central. Moreover, these disorders precede motor signs by several years and could thus constitute a preclinical or premotor marker of PD [2,13-16]. Usually, this hyposmia is unrelated to any specific odours [2,13,15]. It is often latent, stable over time, not proportional to either the stage of the PD, or its duration and improves with treatments for motor symptoms [2,13-15]. The olfactory disorders described in PD include increased detection thresholds, impaired discrimination tasks, which reflect the severity of the disease, and impaired odour identification [2,13].

However, other authors suggest that, as in AD, PD affects odour identification more strongly than it does odour detection. The explanation is the same as that given for the disease [34,35]. Furthermore, in contrast to AD, PD seems to have an equal impact on all olfactory functions, independent of their cognitive level [35]. In very advanced stages of PD, motor disorders of sniffing exacerbate the olfactory disorders by hampering the penetration of odorous molecules into the nasal passages [2,13,15].

Concerning the pathological and pathophysiological features, the Lewy bodies (LB) associated with PD, are observed in the olfactory system very early on, notably in the olfactory bulb, the anterior olfactory nucleus, the dorsal motor nucleus of the vagal and glossopharyngeal nerves, the amygdala and the cerebral cortex. This explains the earliness of olfactory deficits in this disease [2,13-15,39]. Nonetheless, LB are not found in the neurons of olfactory receptors [13,15]. Olfactory disorders have been described before death in PD patients who harbour the LRRK2 (leucine-rich repeat kinase 2) gene mutation, in whom LB can be found in the frontal cortex, as well as the temporal, parietal, cingulate

and transentorhinal cortex [15]. The loss of neurons in the anterior olfactory nucleus correlates with the quantity of LB and the duration of the PD [15]. However, the olfactory deficit cannot be attributed to LB because LB does not cause neural damage. To us, it seems appropriate to study the hypothesis of this relationship of causality. For example, there is neither an olfactory deficit (clinical), nor LB (pathological lesions) in persons presenting parkinsonian syndrome of vascular origin or induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. These parkinsonian syndromes are not neurodegenerative and are characterized by the preservation of olfactory regions [13,15]. Moreover, olfaction is better in PD associated with the Parkin gene, which is characterized by the absence of LB, than in idiopathic PD [2,13]. The nucleus basalis (the cholinergic nucleus), which has projections to the cerebral centres of olfaction, undergoes degeneration in PD [15]. The α4 and α7 sub-units of the nicotinic acetylcholine receptors appear to decrease in number in the cerebral cortex of patients with PD [15]. Dopamine seems to be implicated in olfactory dysfunction in PD via tyrosine hydroxylase, which is increased in the periglomerular region of the olfactory bulb [15]. This increase is associated with a rise in the number of dopaminergic periglomerular cells [15]. Degeneration of the nucleus basalis as well as dysfunction of the α4 et α7 sub-units of the nicotinic acetylcholine receptors and the dopaminergic system are also found in AD [15]. However, this mechanism is still unclear [15]. Other neurotransmitters, notably norepinephrine or serotonin, could also be implicated in olfactory dysfunction in PD [15]. Finally, it has been shown that olfactory dysfunction is associated with parasympathetic dysautonomia, independent of parkinsonism and striatal dopaminergic denervation, whereas selective olfactory disorders seen in PD are associated with nigrostriatal dopaminergic denervation, cholinergic denervation of the limbic archicortex, and cardiac sympathetic denervation [23].

As concerns the association between olfactory disorders and the clinical symptoms of PD, hyposmia may be one of the first signs of synucleinopathy, which occurs a few years before the motor symptoms [40]. Some studies have suggested a correlation between hyposmia on the one hand and cognitive disorders, especially specific cognitive domains, such as measurements of episodic verbal learning or verbal memory, and neuropsychiatric manifestations on the other hand [23,29,30,40]. However, the correlation between olfactory disorders and Mini-Mental State Examination (MMSE) scores is not established; it is borderline at best and non-existent at worst [4,29]. It has been also found that the future incidence of visual hallucinations was higher in patients with worse baseline scores in olfactory tests [41].

In sporadic forms of PD, risk factors for olfactory impairment, such as old age, male sex or head trauma, have been reported [15]. Several environmental agents, including certain viruses, metal ions, solvents, herbicides and pesticides, can directly damage the olfactory system in PD [14,15].

Several authors have suggested that olfactory disorders, especially hyposmia, might be used on the one hand as a biomarker to predict clinical outcomes of PD, i.e. the evolution of motor dysfunction or the occurrence of other late signs [40,41] and on the other hand to assess the effects of disease-modifying drugs [23]. Thus, olfactory tests combined with dopamine transporter imaging may be used as a biomarker for the early detection of PD [23]. However, electrophysiological tests do not seem to predict the course of PD [23].

Olfaction and Lewy Body Disease

As in PD, olfactory disorders are also observed in LBD. Given the similarities between LBD and PD, this section will be brief. LB is found in the olfactory bulb, the anterior olfactory nucleus and the cortex of persons suffering from LBD [13]. These structures are involved in olfaction [13].

Olfactory impairment in LBD is severe and may be complete [2,10]. Furthermore, olfaction disorders seem to occur even earlier in LBD than in AD, appearing at a mild stage of the disease. This has been demonstrated by Williams and colleague who found that patients with mild LBD fared significantly worse on an identification test than did those with mild AD. Thus, the smell identification score predicted a diagnosis of mild DLB rather than mild AD independently of the effects of age, sex and cognitive function [42]. This result is contrary to the findings of Wilson et al., who found no relationship between LBD and olfaction disorders. However, the Wilson et al. study was limited, since only 15 of the 77 participants in the study had major neurocognitive disorder (formerly dementia) [43].

Consequences of Olfactory Disorders

Olfactory deficits expose elderly persons with or without neurodegenerative disease to potentially serious safety risks by increasing the risk of food poisoning. They also affect quality of life, i.e., they may lead to depression syndromes and eating behaviour disorders, resulting in protein-energy malnutrition because of the loss of eating pleasure, all of which significantly influence physical well-being, and increase mortality [1-3,25,26]. The impaired perception of body odours, whether personal or of others, may affect social interactions and sexual behaviour notably by causing a loss of pleasure [1-3,26]. These repercussions compound other disorders associated with AD, PD or LBD.

Conclusion

Despite being undervalued, the sense of smell is an essential sense given its plasticity and its emotional dimension. Impaired olfaction is frequently reported in the early and even very early stages of neurodegenerative diseases in elderly patients. Olfactory deficits, in association with other markers, seem to predict the onset of AD and PD and occur long before the cognitive or motor disorders specific to these diseases. However, screening for these deficits, which would be useful to diagnose these diseases as early as possible, is difficult in clinical practice. Moreover, their specificity in neurodegenerative diseases is low.

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