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Characteristics of olfactory function in a healthy geriatric population. Differences between physiological aging and pathology

Agnieszka Mydlikowska-Śmigórska[1,2], Krzysztof Śmigórski[2,3], Joanna Rymaszewska[3]

[1] Cardinal Henryk Gulbinowicz Scientific-Didactic Centre of Dementia-Related Diseases in Scinawa

[2] Neuropsychology Center "Neurona" in Wolow

[3] Wroclaw Medical University, Chair of Psychiatry

Summary

Changes in the olfactory ability are one of early symptoms of developing neurodegenerative diseases, especially Parkinson's disease and Alzheimer's disease. In a healthy population olfactory function is characterized by independence from an intelligence quotient and various cognitive functions, e.g., memory. The peak of the olfactory ability falls between 20 and 40 years of age. In the geriatric population the worsening of the olfactory ability is found. Because of it, the knowledge on differences between the changes associated with physiological aging and the symptoms indicating pathological changes in the brain is of clinical importance. In this article, neuroanatomical structures of the olfactory tract and their involutionary changes, which may contribute to age-related olfactory deterioration, are discussed. Data are presented on the frequency of olfactory dysfunction occurrence, sex differences in the olfactory ability, and characteristics of its worsening among the elderly. Furthermore, age-related changes in odor memory are reviewed. The authors suggest that the main criterion allowing for differentiation between a physiological and pathological smell loss is awareness/unawareness of the deficit in this domain.

Key words: smell, olfactory function, olfactory perception

Introduction

It is a well-documented fact that the olfactory ability deteriorates with age and in the case of some neurodegenerative diseases – for example, Alzheimer's disease and Parkinson's disease – characteristics of this deterioration are of diagnostic significance

[1, 2]. Taking into consideration a significant, although at first glance unobvious role of olfaction in human daily function, it is worth taking a closer look at what belongs to the normal and what may indicate a possibility of an underlying disorder. The aim of this article is to present olfactory function in a typical, physiological, non-pathological, process of aging.

Age-related olfactory function worsening in terms of neuroanatomical structures involved in olfactory perception

The first anatomical structure, which is encountered by inhaled air along with particles suspended in it, is a ridged surface of a nasal cavity, covered with a mucous membrane 150 μm thick. The mucous membrane contains two types of cells – respiratory cells and sensory cells. Sensory neurons are grouped in a small part of *area olfactoria*, which includes olfactory epithelium. It is located about 7 cm along nasal cavities and occupies around 1.5–2.5 cm^2 [3, 4]. It has been shown, that in its basal layer (and within the limits of lamina propria) a contains a population of proliferating stem cells which are able to form neurons and supporting cells. Thanks to them the olfactory epithelium cells are continuously renewed and olfactory nerves regenerate throughout one's life [5].

Sensory cells are grouped into clusters, which bilaterally penetrate the cribriform plate situated in the anterior cranial fossa. Their axons reach both olfactory bulbs located under the frontal lobes, precisely speaking – under the olfactory sulcus, which separates gyrus rectus from medial orbitofrontal gyrus in both brain hemispheres [6, 4].

The first processing station of the olfactory tract is the olfactory bulb (OB). The olfactory bulb is small and delicate (on average: 6–14mm in length and 3.7mm in width). In healthy individuals, the olfactory bulb volume varies depending on: (1) sex – it is larger in men than in women; (2) age – it decreases with age; (3) the olfactory ability – a distinct decrease of the olfactory ability is noticed in individuals >55 years old, which is accompanied by a reduction of the bulb volume [5, 7, 8]. The olfactory bulb is ipsilaterally (i.e., on the same side of the body) connected to olfactory nerves – based on the same ipsilateral rule, neuronal projections are sent out from olfactory bulbs to subsequent central brain structures.

In vertebrates, the olfactory bulb consists of seven layers. The external layer (the olfactory nerve layer) includes receptor neurons and glial cells. These neuron axons project to one of the deepest layers of the bulb, the so-called glomerular layer. In it, and in the granular layer, the majority of input synapses end. The deepest olfactory bulb layer is called subependymal. In its area around 25 thousand receptor neurons are synaptically connected to cell groupings, which are called glomerulae. The exact number of glomerulae in humans is unknown – but it is estimated at around 90 [4, 6].

It should be emphasized that the olfactory bulb is not just a relay station, with activity limited to transmitting olfactory information to more centrally-located centers. According to current findings, it actively processes olfactory information and

conducts complex neuronal computations similar to those performed by the primary cortex centers [9]. It is assumed that in the olfactory bulb the stimulation of olfactory receptors by odorant particles is transformed into olfactory maps. The term 'map' is abstract here, because it refers to a temporal pattern sequence of electric spikes, which is decoded by more centrally-located centers, although the nature of these processes is unclear. A recent finding, that spatial localization of each glomerulus is rigidly embedded in the bulb structure and invariable for each animal, suggests that odors identity may be coded as spatial patterns of the glomeruli activity within the bulb [10].

The next stop on the route of olfactory processing is the primary olfactory cortex (POC). The name does not refer to a single region, but it includes various, spatially scattered structures. The centers forming the primary olfactory cortex have been given such a name due to the large number of connections from the olfactory bulb, which are directed straight to them [11]. The secondary olfactory cortex (SOC) is also a conglomerate of dispersed cortical and subcortical structures, which obtain connections from the primary olfactory cortex. It is worth noting that 9 out 22 olfactory cortex centers which are involved in olfactory information processing, receive direct connections from the primary olfactory cortex, skipping the thalamus [12]. Research findings suggest that identification, categorization and differentiation of olfactory stimuli is a result of processes of forming and modulating olfactory objects, which are performed by the piriform cortex. Studies on both animals and humans indicate that dispersed patterns of olfactory traits and categories generated by the piriform cortex play a critical role in maintaining perceptual continuity of ecologically-discrete stimuli [13].

Much is known of the peripheral olfactory system structures, however, neurophysiology and information processing occurring in the tertiary olfactory cortex requires further research. Temporal structures, which co-form the tertiary olfactory cortex, seem to be more associated with odors memory rather than their perception *per se*. By contrast, the isle and the orbitofrontal cortex are the regions which engagement in olfactory perception processes has been consistently confirmed in various studies employing neuroimaging techniques [14]. So far neurophysiological and neuroanatomical studies have not born fruits in terms of unequivocal conclusions concerning structural and functional differences in brain constitution which could clarify various individual differences concerning the olfactory ability.

A few possible mechanisms referring to particular neuroanatomical structures have been offered in order to explain age-related deterioration of the olfactory ability:

1. In terms of the peripheral structures level – changes occurring in the mucus composition and in its movement dynamics. A different blood circulation in the mucus membrane or changes in the thickness of the olfactory epithelium may influence the effectiveness of transportation of olfactory particles to olfactory receptors [15].
2. In terms of the olfactory epithelium – weakening of the olfactory receptor neurons regeneration [16], reduction of the olfactory epithelium area and reduction of density and complexity of the adrenergic innervation within the lamina propria [5].

3. In terms of the olfactory bulb – a decrease in the number of mitral cells and glomeruli, as well as a thinning of the glomerulal layer and a decrease in the size and concentration of the mitral cells (from 60 thousand at the age of 25 to 14.5 thousand at the age of 95) [17]. It is important to note that the mitral cell number decreases at a stable rate of 10% per decade [18]. In addition, about 86% of the healthy population the presence of neurofibrylar deposits in the olfactory bulb has been confirmed and one third of them reveal the presence of amyloid [19]. Coupled with aging disturbances develop in the olfactory bulb structure. They consist in penetrating of olfactory nerve fibers in deeper areas of the bulb and forming the glomeruli outside the glomerulal layer. These changes influence the synaptic organization and consequently – olfactory information processing [19, 20].
4. In terms of central olfactory structures – brain damage because of chronic ischemia or of systemic diseases may be a potential cause of age-related olfactory dysfunctions. Another reason may be the presence of neurodegenerative changes (amyloid tangles and plaques, Tau proteins pathology,), which are found in one third of the elderly without dementia [19].

It should be emphasized that olfactory sensitivity, which is based on the peripheral structures, deteriorates with age more than the ability to identify and discriminate between smells [8, 21], what suggests that age-related deterioration of the olfactory ability is caused, at least partially, by the olfactory epithelium damage or changes in the physiology of the mucus secreted by the nasal cavity mucous membrane.

Independence of the olfactory ability from cognitive and personality-related aspects of human functioning

Olfactory function is independent of fluid intelligence, short-term memory and episodic memory [22]. It has been shown that the olfactory ability is independent from other cognitive outcome measures (WAIS-R, *Randt Memory Test*, Digit Crossing Test, tapping) [23]. Based on available research data, it can be stated that individual cognitive differences are not associated with differences in the quality of the olfactory function. Nor is mere olfactory discrimination a predictor of cognitive functioning in healthy individuals [24]. The olfactory ability assessment is independent of individual's socio-economical background and it allows one to estimate the risk of dementia progression at the preclinical and prodromal stages with higher reliability. At these stages standard cognitive outcome measures are of limited usefulness because of the cognitive reserve and the neuronal compensation phenomena. Based on these mechanisms, well-educated individuals of a higher socio-economic status are able to compensate cognitive deficits up to a certain stage of the cognitive deterioration process, what makes an early diagnosis significantly more difficult [25].

Despite numerous studies being conducted, no clear, stable, personality-related differences associated with the olfactory ability have been determined. It has been stated

that there were some relationships between personality traits and the olfactory ability [26]: (1) neurotic individuals are able to better detect various smells (they give more correct responses to test questions); (2) both impulsiveness and a lack of assertiveness are associated with some weakening of the smell identification ability. According to the study authors, the findings can be explained in terms of strong associations of the olfactory functions with the limbic structures, which are excessively active in individuals characterized with increased anxiety trait.

Characteristics of olfactory ability in physiological aging

An age-related drop in the olfactory ability is well documented in the professional literature. Even a specific term has been coined – presbyosmia – to describe normal, age-related changes in olfactory ability [22]. The first scientific investigations into this matter were published by Douglas in 1901 (he noticed nasal tissue atrophy in the elderly) and by Vaschide in1904, who stated that sensitivity to camphor worsened with age and this reduction was especially strong among males [27].

Olfactory function peaks between 20 and 40 years of age [19]. As per the researchers, the rate of objectively confirmed olfactory impairment increases from 11–24% in the middle age group to 37–70% in the elderly [28, 29]. By the age of 80, 80% of the population exhibit deterioration of the sense of smell. Estimates pertaining to the frequency of olfactory impairment occurrence indicate that it is a common phenomenon and the level of olfactory ability may be a good indicator of brain function integrity [30].

The quality of feminine perception is better than that of the masculine. Sex differences are already noticeable at early stages of ontogenetic development, as even 4-year-old girls show superior performance in recognizing peers by smell compared with their male counterparts. Additionally, female infants prefer their mother's smell much more than male infants do [27]. Paradoxically, scientific confirmation of these seemingly obvious differences took more than half a century because a global picture of sex differences, in terms of the olfactory function, is much more complicated. The first accounts from the end of the 19th century and the beginning of the 20th century were contradictory. For example, Bailey and Nichols stated in 1884 that men were more sensitive to smells than women. In contrast, Toulouse and Vaschide in 1899 proved that women were more sensitive to the smell of camphor than men. Since the 1950s, evidence has started to be collected which indicates the superiority of women over men in the olfactory ability domain – in accordance with results of the studies of that time women showed higher sensitivity to smell of exaltolid (a musk odor derived from garden angelica) and citrus [27]. Nowadays, it is empirically verified that women are better than men in recognizing both familiar and unfamiliar smells. [31].

Studies of the life-span olfactory ability changes in both sexes did not find any distinct differences in terms of detection and identification, although a noticeable trend

was observed which indicates that women perform slightly better in smell identification tasks [26]. With the development of standardized methods of smell assessment in the 1980s and later, results appeared which were characterized by higher consistency and unambiguously demonstration of women's superiority in all aspects of the measured olfactory functions – detection threshold, identification and recognition of smells. This superior performance seems to be independent from cultural factors [26, 31, 32] and is observed both in cross-sectional and longitudinal studies [33]. Based on these completed longitudinal studies, it has been stated that the olfactory ability worsens significantly with age and the rate of deterioration is the fastest in the case of free, un-cued smell recognition. Moreover, women's ability worsens more slowly than that of men's ability [28]. Women are more sensitive to and, in general, more oriented towards smells than men are [34].

Interesting data is available on age – and race-related individual differences [22]. It has been stated that within the age range of 57–85 years: (1) men's olfactory performance is worse than women's; (2) Afro-Americans' olfactory function is less effective compared with Caucasian race representatives. The researchers conducted a 5-year long longitudinal study and found that during that study 31% of the participants showed worsening of the olfactory identification and – intriguingly – 20% showed improvement. Participants at the age of 75–85 years presented the most pronounced deterioration, whereas younger participants at the age of 57–74 years – milder reduction of the olfactory ability. Nonetheless, despite these differences and fluctuations, there was a noticeable trend observed in the data consisting of an increase of age and speed of the olfactory loss, especially among men. According to the researchers, at the age of 85 a risk of loss of the ability to identify a specific smell increases within the subsequent 5 years from 0.29 to 0.45. What is essential from the point of view of treating olfaction as an objective measure of the brain functional integrity, it has not been confirmed that factors such as: the cognitive ability, other diseases, smoking tobacco, drinking alcohol, and mental health quality, affect the olfactory ability.

Based on the other cross-sectional studies, age-related differences in olfactory function changes have been described [35] – e.g., protraction of the time needed to complete smell differentiation task, especially in men. According to the authors, it stems from the idea that the elderly are more susceptible to olfactory adaptation and that they need more time to regain the primary threshold of the olfactory sensitivity after being exposed to the same smell.

Age-related loss of the ability to recognize and identify smells cannot be explained exclusively in terms of sensory deficits [36]. The most important factor contributing to olfactory memory and its age-related differences is semantic knowledge of the smells. The second factor is the kind and quality of a smell name – it affects smell memory. Regression analyses indicate that chronological age and the smell naming ability are the strongest variables affecting the episodic memory of smells [37]. What is interesting, the smell intensity is weakly related to memory of this smell and it

does not influence its retention – only a very mild, not age-related relationship with the identification ability has been found. There are three potential explanations for the decrease in smell naming ability, which plays a key role in the ability to store these names in episodic memory: (1) erroneous perception of a smell; (2) impaired semantic memory of a smell (e.g., damage of a concept denoting an object which is a source of a smell); (3) age-related impairment of the lexical access – an individual may have access to semantic knowledge, although he or she may not be able to retrieve the pertinent verbal label [37].

Women remember smells better than men, even though age-related memory deterioration is observed. It is a result of the fact that women are more prone than men to use semantic strategies of smells coding. Interestingly, better memory of smells in women has been confirmed only when they were presented known smells – whereas when unknown smells were presented, the sex-related differences disappeared [38].

The elderly have serious problems with recognizing smells presented to them: only after two weeks the accuracy of their responses is completely random. Young individuals experience such difficulties not sooner than 6–7 months [27]. Generally, the olfactory identification ability in the elderly is similar to children's ability – they obtain equally poor results in tests assessing this function [39, 40]. Most probably it results from a children's vocabulary deficiency and an impairment of the lexical access in the elderly, which are accountable for similar test outcomes [37].

A relationship between short-term memory efficiency and the ability to discriminate and identify odors has been investigated in various age groups [41]. The authors assumed, based on the literature review, that odor identification depends to a large degree on perceptual properties of a stimulus. According to them, they are more important than in other cognitive functions. Short-term memory plays an important role because a cognitive representation of at least one odor has to be maintained in it, in order to make it possible to compare it with another odor that is currently being smelled. Perceptual attributes of an odor may engage in interactions with other cognitive representations held in this memory storage. If a smell is unfamiliar to participants, they may maintain a less-detailed, more unstable representation, which leads to a decrease of the identification accuracy. It has been found, that participants' age correlated negatively with their performance on an olfactory discrimination task. Smaller burden of the short-term memory improved the tasks completion in the youngest and the oldest participants. No changes in terms of the olfactory identification ability were found – according to the authors, it results from the fact that the olfactory identification is more cognitively burdensome than discrimination and manipulating the short-term memory burden does not bring significant effects.

The source memory in regard to odors has been investigated as well [42]. The participants were presented with 16 odors – 8 of them were introduced by a man and the other 8 by a woman. The source memory was tested by asking if an odor was presented by a man or a woman. The memory of odors was tested by presenting them in pairs, a known smell paired with a new one, and asking which of them had

already been presented. The source memory was worse in the elderly (>65), but no significant differences were found in the odor memory in comparison with young participants.

Doty and Kamth [29] carried out a comprehensive literature review concerning the olfactory ability in the elderly. Their ascertainment can be summarized in the following way:

1. Impairment of the olfactory identification ability is observed in the elderly. This weakening is less pronounced in healthy individuals, who are characterized by higher sensitivity to odors compared to individuals who are ill.
2. The elderly have more difficulties with smells discrimination (e.g., evaluating a few smells presented simultaneously, when a participant is supposed to distinguish which odor is different compared to the rest; a similar challenge is matching odor samples with other samples presented after different time intervals).
3. An ability to assess intensity of at least some odors, such as: mercaptan or amyl acetate, gets worse with age. The other odors, such as: rose, eugenol, androstenone – pose no challenge. It is worth to emphasize that the research results suggest that the ability to assess odors intensity starts to deteriorate in men who are at least 20 years old and in women who are at least 40 years old.
4. ERP and EEG studies usually draw a distinction that the elderly reveal longer N1 latencies and smaller N1 and P2 amplitudes.

Classification of olfactory disorders

Humans can discriminate between odors which structurally differ by only one particle [43]. Contemporaneously, around 24 million Americans suffer from chronic olfactory disorders and as many as 200,000 medical consultations annually in the USA concern smell loss. In general, olfactory perception disorders can be divided into quantitative (loss of smell) and qualitative (olfactory perception distortions). Another criterion of the smell disorders classification pertains to their intensity: partial loss of the olfactory ability is called hyposmia, and complete loss – anosmia. Patients with partial loss of smell often suffer from olfactory perception distortions, which may be divided into: parosmias (distorted olfactory experiences in response to an odor present in the air) and phantosmias (distorted olfactory experiences in response to an odor which is actually absent). Olfactory disorders occur relatively frequently – they afflict between 4 and 25% of the general population and men are more susceptible than women [44]. 10–60% of patients with the olfactory dysfunction suffer from parosmia [45]. The other risk factors are: smoking, working in a factory, low education, and low income. The perception distortion occurs most frequently in severe loss of smell. From the medical point of view, the three most common causes of olfactory dysfunctions are: (1) sinusitis; (2) upper-respiratory tract infection; (3) head trauma. Daulatzai [46] provides a more detailed list of causes of decline in olfactory ability: (1) air pollution (exposure to city air causes neuro-inflamation in humans); (2) aging and changes

associated with it (e.g., a change in the olfactory bulb volume); (3) ApoE4 allele (its carriers perform much worse on olfactory tests); (4) sinusitis; (5) infections, poisoning and their influence on neuronal transmission; (6) diabetes; (7) sleep apnea, and (8) alcohol abuse. However, it is noteworthy to mention that not all cases of olfactory disorders are irreversible. A partial improvement has been observed in younger patients and it may occur spontaneously many years after the onset of symptoms, although its likelihood decreases with the duration of the disease.

Awareness of the olfactory deficits as the criterion for distinguishing between physiological aging and pathological aging

Unawareness of disorders is an inability to recognize deficits and assign to them meaning and their functional implications [47]. Confirmation of olfactory deficits does not constitute a compelling argument in favor of dementia diagnosis. As it has been mentioned earlier, reduction in the olfactory ability in the old age is a common phenomenon, which is caused by the natural processes of involution. The difference between physiological and pathological aging lies in the severity of the deficits and degree of their awareness. Studies indicate that awareness of the deficit is of significant diagnostic and predictive importance. Patients unaware of the olfactory dysfunction perform worse in tests of learning, verbal memory, and attention/processing speed compared to individuals aware of it [28]. It should be emphasized that the discussed role of the olfactory deficits unawareness is of importance in differentiation between the health standard and the prodromal stage of neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease, when cognitive (in the case of AD) or motor deficits (in the case of PD) are minimal, whereas olfactory deficits are pronounced.

Hampered insight in the olfactory ability has been described in the professional literature many times. In the healthy population subjectively experienced dysfunction is reported by: (1) 2% of individuals at the age of 55–64 years; (2) 2.7% of individuals at the age of 65–74 years; and (3) 4.6% of individuals at the age of 75 years and older. In another study, it has been stated that 9.4% of the group aged 55–97 years old endorsed subjectively experienced olfactory disorders, whereas olfactory identification tests indicated an olfactory disorders rate of 24.5% [48]. In contrast, Nordin et al. [49] proved that 70% of the elderly denying any olfactory disorders were actually hyposmic [49]. In a study by White and Kurz [40], 43% of participants could not recognize olfactory dysfunctions in themselves. No differences were found between older and younger participants. The authors assumed that specific meta-cognitive errors were related to the speed of the olfactory disorders development. According to them, unawareness of the olfactory dysfunction may stem from: (1) slow pace of the smell loss, typical of aging, because of which people do not notice these changes; (2) fast pace of the smell loss, which makes participants underestimate the severity of the changes – this is typical of Alzheimer's disease. It should be emphasized that

in healthy individuals insight in the olfactory deficits may be only partially reduced – they are aware of smell worsening, they only underestimate it. By contrast patients with the pathological smell loss portending development of dementia in future, show much more spectacular reduction in insight, basically its complete loss.

Despite the aforementioned frequent difficulties in independent self-evaluation of the olfactory ability, many authors have pointed to unawareness of the olfactory impairment as a prognostic factor of dementia development. Olfactory dysfunction accompanied by its unawareness is a predictor of Alzheimer's disease [50] and Parkinson's disease development. Around 80% of patients with PD is not aware of the smell loss or they heavily underestimate it [51]. The lack of hiposmia awareness is closely associated with occurrence of mild cognitive impairment in the course of PD [52]. Based on longitudinal studies, it has been stated that unawareness of functional deficits is a predictor of dementia development in individuals with diagnosed cognitive impairment [53]. Other studies suggest that the olfactory ability itself is a good predictor of episodic memory deterioration and worsening of cognitive processing speed [54]. The lack of awareness of olfactory dysfunctions distinguishes also individuals losing smell due to peripheral pathology (e.g., nose damage, cold, sinusitis) from those suffering from changes due to central pathology (e.g., in the progression of dementia). In one study, two populations suffering from olfactory disorders were compared – individuals suffering from sinusitis and from Alzheimer's disease. It was found, that characteristic of people with AD was that – unlike people suffering from sinusitis – they were not aware of worsening of the olfactory ability [55].

Healthy individuals sometimes may not be aware of worsening of the olfactory ability. However, people suffering from neurodegenerative disorders virtually never realize that they are afflicted with this dysfunction. Confirmation of the olfactory ability worsening which is accompanied by a patient's lack of insight in the observed deficits should make a clinician more sensitive to the possibility of developing dementia within the next one–two years, especially, if the patient has been already diagnosed with mild cognitive impairment.

Recapitulation

It is a common phenomenon that among people older than 55–65 years olfactory ability deterioration is found both in men and women, regardless of their intelligence quotient, education or profession. The peek olfactory performance falls on the age range of 20–40 years. The elderly may have some problems with odors identification and differentiation. Evaluation of some odors intensity may pose a challenge, especially for elderly men. Noteworthy, patients' self-evaluation of their olfactory ability is usually in some degree over-estimated compared with their actual level of performance. The difference between healthy and pathological smell loss lies in the deficits awareness degree. In the prodromal and even preclinical stage of AD or PD clinicians'

attention should be brought by the lack of insight in undeniable olfactory deficits. In such cases it pays to conduct a comprehensive neuropsychological assessment and consider cerebral-spinal fluid biomarkers evaluation.

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Address: Agnieszka Mydlikowska-Śmigórska
Cardinal Henryk Gulbinowicz Scientific-Didactic
Centre of Dementia-Related Diseases in Scinawa
59-330 Ścinawa, Jana Pawła II Street 12
e-mail: a.mydlikowska@gmail.com