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**Olfactory dysfunction in dementia**

Alves J *et al.* Olfactory dysfunction in dementia

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**Abstract**

The natural aging process brings about some inevitable consequences, such as olfactory dysfunction, which is also frequently linked to numerous neurodegenerative disorders.

Many age-related dementia, such as Alzheimer’s disease, Vascular dementia, Parkinson’s disease, and Frontotemporal Dementia often display olfactory dysfunction. Despite the overwhelming evidence of above mentioned facts, the symptomatic relevance and potential clinical and pre-clinical value of olfactory dysfunction remains overlooked by many clinicians and public alike. Olfactory dysfunction has strong practical implications on daily activities and, although not as prominent as in other mammals, olfaction is still an evolutionarily relevant sense involved in human survival (*e.g.*, smelling gas; bad food). In this work, we provide a brief review of current research related to the olfactory dysfunction profiles in different types of dementia. Additionally, we present a compilation of accessible, easy to use olfaction assessment tools; and highlight future directions in terms of improving clinical diagnosis in patient care and research.

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**Key words**: Dementia; Aging; Olfaction; Olfactory dysfunction

**Core tip**: Olfactory dysfunction is often present as a symptom of a neurodegenerative disease. The potential clinical value (prodromal/pre-diagnostic, diagnostic, intervention target) of olfactory dysfunction still remains to be fully established. Standardized and easy to use tools are available and can be implemented to improve the definite differential profiles, through its widespread integration in clinical practice and research.

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**INTRODUCTION**

Although olfaction is a topic of scientific interest for both public and many professionals[1], awareness concerning olfactory dysfunction, both in healthy aging and dementia, remains limited even when considering the widespread prevalence of age-related olfactory decline. For example, half of the elderly population between 65 and 80 years of age have evident olfactory dysfunction[2-4].

Moreover, olfactory dysfunction has been acknowledged as a symptom present in dementias, such as Alzheimer's disease, vascular dementia, Parkinson and Frontotemporal Dementia (FTD)[5].

Indeed, olfactory dysfunction has a considerable prevalence in dementia, with estimated numbers as high as 100% in Alzheimer’s disease (AD)[6], 90% in Parkinson’s disease (PD)[7]; 96% in the frontal variant of FTD[8] and 15% in Vascular dementia (VD)[6].

In the next sections we will briefly review the main types of dementia in which olfactory dysfunction is present.

**RESEARCH**

The present study is a selective narrative review. The selected articles consisted of literature/articles previously known by the authors, complemented with a search on PubMed/MEDLINE focusing on olfactory dysfunction with the following search terms: olfaction (and related expressions - olfactory), Alzheimer’s disease, vascular dementia, Parkinson’s disease, frontotemporal dementia, Lewy body dementia, and dysfunction/impairment/deficit. Relevant articles were selected through abstract inspection. Both, reviews and clinical studies were included.

**OLFACTION IN HEALTHY AGING**

***Olfactory loss associated with normal aging***

Olfactory dysfunction has a considerable prevalence with recent estimates pointing to 3.8% in adults between 21 and 84 years of age, increasing prevalence with age (from 0.6% in those < 35 years to 13.9% among those ≥ 65 years), with higher prevalence in men[9]. Factors involved in age-related olfactory dysfunction include changes in non-olfactory elements of the nose (*e.g.*, airflow patterns and mucous composition), olfactory neuroepithelium, olfactory bulb, central brain regions involved in olfactory processing, and neurochemical changes in the brain (for a detailed review see Doty and Kamath[10]).

Measured with University of Pennsylvania Smell Identification Test UPSIT, Djordjevic[11] and Morgan[12] refer values of approximately 33-35 as a normal olfactory performance. Doty *et al*[2] also provide a prototypical progression of olfactory decline during normal aging. They report median UPSIT values of normal olfactory performance around 37, with olfactory decline starting in the 60 s, reaching around 34 in the 70 s, and 26 in the 80 s. Lower values than those of the observed normative scores would imply a loss of olfactory abilities (for further details please see Doty *et al*[2] or Doty and Kamath[10]) For a systematic review on normative and pathological values of olfactory performance in dementia please refer to Sun *et al*[13].

Besides the normal age-related olfactory decrements, sensory and central processing impairments in the components of olfaction, are observed in number of neurodegenerative conditions[14]. These impairments might influence appetite in people with dementia and lead to dietary restrictions with negative implications on nutrition and overall health[15].

It is important to note, however, that the performance in olfactory assessment tasks might also be influenced by the assessment method as well as other brain functions such as memory. For example, Larson *et al*[16] suggest that age-related difficulties in the activation of odor knowledge (*i.e.*, odor names) might contribute to the observed age differences.

**OLFACTION IN DEMENTIA**

***Alzheimer’s disease***

Alzheimer's disease is characterized by neuropathological changes, such as neurofibrillary tangles, neuritic plaques and atrophy, leading to progressively marked deficits in memory (amnestic presentation) and/or other domains such as language and visuospatial capacities (non-amnestic presentations)[17]. Olfactory bulbs are considered to be involved from the early stages of the disease and related to the neuropathological changes[18-20]. Indeed, there is evidence for considerable olfactory tau pathology in post-mortem confirmed AD, with tau pathology correlating with dementia severity[21]. Moreover, similar pathologic changes have been reported in the brain and olfactory mucosa of AD patients[14].

As expected due to the aforementioned lesional pattern, olfactory dysfunction, namely odor identification, is also a widely acknowledged, feature of Alzheimer’s[22] with patients showing overt deficits in odor identification[22,23].

Olfactory dysfunction may even be present during the amnestic mild cognitive impairment (MCI) stage of Alzheimer’s disease, mainly as an odor discrimination and identification difficulty and less of an odor detection deficit[24]. While cognitive and sensory characteristics associated with visuospatial, language and immediate memory skills are interconnected with olfactory discrimination, olfactory identification in itself is more related to delayed memory processing[24].

Although evidence is still limited, differential profiles between AD and other dementias have been observed which are evidently due to the underlying neurological decline characteristic of each dementia type. For example, smell identification seems to be more impaired in AD than in VD[23], however Gray *et al*[25] found impairment similarities. In the same way, AD and PD patients show equivalent levels of hyposmia (assessed through odor identification)[26]. On the other hand, there is evidence of more olfactory impairment in mild Dementia with Lewy Bodies (DLB) than in MCI or AD[27].

However, whether the available olfactory screening tests are well adjusted and specifically tailored for each of these dementias is still unclear.

***Vascular dementia***

Vascular dementia (VD) is characterized by cognitive decline, typically in a stepwise manner, compatible with dementia related to cerebrovascular disease[28].

VD is considered the second main cause of dementia[29] and is the topic of a considerable amount of research concerning its characterization and etiopathology. Research on olfactory dysfunction in VD is comparatively scarce. However, it has been found that VD patients score below normative performance in olfactory tests[25]. Nonetheless, when comparing VD and AD, there are mixed findings with Gray *et al*[25] reporting a similar degree of olfactory impairment between AD and VD while Duff *et al*[6] state lower performance in AD patients.

Interestingly, preliminary data, on people with history of stroke, identified them having within normal or slightly below normal olfactory performance[30].

From the aforementioned data it seems plausible to hypothesize that the presence or absence, the range/extent and type of olfactory deficit might depend on the location and extension of vascular pathology.

***Parkinson disease and other synucleinopathies***

Parkinson’s disease belongs to a group of neurological conditions named movement disorders, which occur due to a loss of nigrostriatal dopaminergic neurons in certain circuits of the brain[31].

Diagnosis usually occurs after the fifth decade of life typically with a slow progression of disease which is based on neurological examination and the patient’s clinical history[31]. Feature symptoms include tremor, trembling of hands, legs, jaw, and face; stiffness of the limbs and trunk; bradykinesia of movements; and postural instability, resulting in impaired balance and coordination. As expected, these symptoms interfere with several daily living activities[31].

Researchers have recently directed their attention towards olfactory dysfunction in PD, as it is a prominent symptom, occurring in about 80%-90% of PD patients[32]. Moreover, olfactory dysfunction is usually prodromal to motor symptoms by several years[33,34]. Olfactory dysfunction also occurs alongside non-motor symptoms, such as in autonomic[35] (cardiovascular changes) and REM-sleep Behavior Disorders[36] (RBD), both during and at the premotor phases of PD.

Therefore, authors argue that deficits in the sense of smell may be used to assess the risk of developing PD in apparent asymptomatic patients[37].

In a population-based prospective study (longitudinal Honolulu-Asia Aging Study; HAAS), authors have demonstrated that odor identification deficits may precede the development of clinical PD in men by at least 4 years[34].

The fact that olfactory deficits appear even before confirmed PD diagnosis[38], while motor signs appear afterwards and gradually worsen, might explain the lack of relationship found between olfactory deficits and PD severity or disease duration[39].

Unsurprisingly, olfactory testing is quite sensitive and specific in distinguishing PD from other movement disorders[33,37,40]. In particular, considering that hyposmia is relatively rare in atypical Parkinson syndromes or in essential tremor, olfactory dysfunction presents added value due to its discriminatory power to differentiate neurodegenerative diseases[33]. Several tests are currently being used[10,41], some of them purposely adapted and implemented for assisting in Parkinson’s Disease diagnosis, presenting appropriate sensitivity and specificity indices[42].

Decreased odor identification in PD patients has been associated with older age, greater smoking habits, more coffee intake and lower performance in cognition tests[34]. Additionally, hyposmia was also found to be predictive of dementia installation in PD patients within 3 years of assessment[43]. Furthermore, patients with severe hyposmia at baseline, display more prominent cognitive decline in the follow-up assessment.

More recently, Lee and colleagues[44] divided non-demented PD participants into three groups according to their performance in an olfactory test (Cross-Cultural Smell Identification; CCSI[45]): PD-H (high score), PD-M (middle score) and PD-L (low score group). They further noted that the clinical dementia rating score was lower in the PD-H patients than in the PD-M or PD-L patients[44]. Moreover, the PD-L patients performance in the verbal memory tests was noted to be worse than that of the PD-H patients[44], which is in consonance with previous findings[34,43].

In terms of the neuropathological findings in olfactory bulb, depositions of α-Syn have been found in Lewy Body Diseases[33], with additional lesions extending to the olfactory epithelium as well as to the olfactory cortex and other olfactory-related structures[33,46]. Indeed, MRI studies confirmed that PD patients present greater Gray Matter (GM) loss in brain regions subserving primary and secondary olfactory processing, namely, bilateral piriform cortex (PC) and bilateral orbitofrontal cortex (OFC), when compared to controls (*e.g.,* Lee *et al*[47]). Additionally, right PC and left OFC volumes were correlated with the performance in olfactory tests (reduced performance correlated with lower GM volumes)[47].

These results foster the hypothesis that olfactory dysfunction is related with extranigral cortical involvement, which is consistent with the fact that the olfactory function does not improve with dopaminergic treatments[41]. Hence, other neurotransmitter systems are being considered to be involved in olfactory dysfunction (*e.g.,* cholinergic[48,49]).

Importantly, differences between studies may also be explained by the tested components such as odor threshold, discrimination and identification. Each of these olfactory components can be related to atrophy in different brain structures[47] therefore possibly contributing to the diverse smell deficits.

Finally, Takeda and colleagues highlight some considerations: there is actually no established standard odorants for the olfactory testing; environmental conditions such as humidity may interfere in olfactory stimulation; and sniffing (the act by one inhales air to be able to smell) may be impaired in PD patients due to motor deficits[41].

Since olfactory dysfunction is an evident feature of PD, which can be detected in early stages of the disease, to improve diagnostic precision, stronger efforts should be made to include olfactory assessment in the routine neurological examinations[41].

***Frontotemporal dementia***

Frontotemporal dementia is a clinical syndrome associated with shrinking/degeneration of the frontal and anterior temporal lobes of the brain[50], sometimes called frontotemporal lobar degeneration[51]. FTD was formerly known as Pick’s disease[50], however, currently, FTD groups several neurological designations such as Pick’s disease, primary progressive aphasia and semantic dementia[50,52].

FTD accounts for up to 10% to 20% of presenile dementia cases and its onset tends to occur between the ages of 45 and 65 years[52,53]. The main feature in FTD is a marked change in the behavior, usually characterized by either impulsive, disinhibited or apathetic behaviors; accompanied by inappropriate social interaction, lack of social skills, lack of empathy, distractibility and compulsive behavior. Regarding language disturbances, patients may present difficulties in producing or understanding speech[50,52].

Concerning other cognitive abilities, such as spatial skills and memory, they tend to remain intact. For a careful characterization of this clinical syndrome, core features and cognitive changes in FTD, refer to the works of Snowden *et al*[52] and Neary and colleagues[51].

Regarding its neuropathology, FTD is mostly characterized by cortical loss of pyramidal cells, and spongiform degeneration. In fewer cases, neuron swellings or inclusions are observed, that is, accumulation of tau proteins in neurons, visible as silver-staining aggregations (Pick bodies)[50,52].

Despite being less frequent than in Parkinson’s Disease, olfactory dysfunction has been reported in FTD as well[54]. Considering the neuroanatomy of the olfactory system (involving parahippocampal gyrus and entorhinal area) and the existing compromise of the temporal cortex in FTD, olfactory dysfunction should be expected as well. One of the first studies comparing several dementia types, concluded that, when compared with AD and Semantic Dementia (SD) FTD patients do present olfactory impairment but at a lesser degree[54]. Namely, FTD patients demonstrate preserved odor discrimination abilities, whereas impairment surfaced in tasks of odor naming and odor–picture matching[54]. Additionally, the authors found a correlation between odor identification performance and measures of executive functioning[54].

In the same line of findings, McLaughlin and Westervelt[55] compared groups of FTD, AD patients and controls in an odor identification test (BSIT). The authors found that the FTD performed significantly worse than the controls, but very similar to the AD group[55]. Additionally, a tendency towards correlation between FTD severity and olfactory identification ability was observed.

In another study[8] patients with the frontal variant of FTD presented olfactory recognition deficits. The authors highlight the need to assess olfactory function in FTD patients more often, since initially these patients are commonly misdiagnosed as having depressive disorder. Considering the fact that depressive patients are expected to have better olfactory function, olfactory testing could be used to distinguish depression in elderly from a FTD diagnosis[8].

When comparing variants of FTD in an odor identification test, Omar and colleagues[56] did not find differences between the subgroups, even when compared in a flavor identification task. Interestingly, these authors also found that the odor identification performance paralleled the flavor identification and both performances were correlated in clinical groups[56].

**CONCLUSION**

***General conclusions and future directions***

In the present review, in hopes of providing a primer of the topic, we summarized the main findings regarding olfactory dysfunction in aging and the main types of dementia (please refer to Table 1 for a summary of main findings in different dementias).

While there is still no solid olfactory profile for each type of dementia, olfactory assessment might prove to be a valuable tool in assisting diagnosis, as a biomarker for disease progression and a surrogate marker for disease-modifying drug efficacy[33,57]. Easy to use tests/assessments (Table 2 for an exemplifying list of standardized tests) are available and can be easily implemented from a practice-research integrative perspective, leading into an improved evidence-based profiling. However, a clear definition of the evaluated component (identification, recognition, retrieval, choice) must be regarded carefully since the discrepancies in the results reported throughout this work might have the contribution of confounding variables such as memory and naming difficulties.

Regarding these procedural issues, computerized odor systems might provide a more accurate disposal of odorants and determination of potential differential olfactory thresholds in early stages of different types of dementia. Although, functional neuroimaging studies, concerning the present topic, are scarce, if implemented more often they may assist in the clarification of the existence of different in vivo neural signatures related to differential olfactory impairments (*e.g.,* naming identification, confrontation identification, retrieval).

In the context of neuroimaging, despite the costs associated with sophisticated olfactometer apparatus, simpler alternatives, such as odorant saturated cotton can be implemented as well (although with less reliability). Also, semi-automatic olfactometers/odor dispensers for imaging setting can be built on a rather reasonable budget[58].

Although olfactory symptoms are a feature of dementia, which is regarded as such with a relative consensus, diagnostic guidelines seldom highlight its role or presence as a supportive feature. In this regard, screening pocket olfactory tests could be recommended in healthcare and diagnostic guidelines as a supportive test for improving differential diagnosis through fast data collection and prior screening for the purposes of a more extensive olfactory assessment. Although one may argue that these tests are not exempt of costs, there are alternatives, such as the Smell Diskettes, which can be reused for several months.

The use of olfactory baseline measurements, similar to the neuropsychological baseline assessments used in some countries, should be implemented worldwide. However, as in neuropsychological assessments, baseline olfactory results are seldom available.

As noted recently, olfactory assessments could also be included in other routine sensory assessments, such as in eye or hearing tests[59]. Routine olfactory tests, assessing several olfaction components[54], could assist not only in the detection and the discovery of causes for olfactory dysfunctions, but also aid longitudinal studies aiming to understand olfaction, and more immediately in the detection of common causes of olfactory dysfunctions, such as airway disorders and viral or bacterial infections.

In order to improve and generalize these baseline assessment practices, it is important to increase awareness of its clinical and research relevance not only among the researchers, but also among the physicians and the psychologists. Concerted informative action for generating awareness among governmental and legislative health bodies should be implemented by researchers and clinicians in all the fields of olfactory dysfunction. The absence of baseline assessments will continue to minimize accuracy in studies and clinical practices, since comparisons of patient values exclusively to group results, and not to individual levels of olfactory functioning, will only yield approximate results.

In sum, we hope that the potential of utilizing the olfactory dysfunction for diagnosis and perhaps even as intervention outcome, together with an awareness of available inexpensive and easy to implement assessment tools, can lead to its wider clinical use (integrated with research efforts). The latter mentioned proposal may very well improve dementia diagnosis and allow an establishment of differential profiles. Implementation of olfactory tests in standard neuropsychological screening and diagnostic batteries, from preclinical and early stages of dementia, will clarify if olfactory dysfunction holds any potential for aiding research progress in the field of dementia[13,24].

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**Table 1 Table of main findings (comparing findings in different dementias)**

|  |  |  |
| --- | --- | --- |
| Type of dementia | Profile/main findings | Differences between dementias (extent/degree/severity of impairment) |
| Alzheimer | Odor identification deficit, is a widely acknowledged feature of Alzheimer’s | Mixed findings:AD > VD[6,23]; AD = VD[25]AD = PD[26]; mild DLB > MCI/AD[27]FTD < AD[54] FTD = AD[55]Legend: > more impaired ; < less impaired; = similar |
| VD | Olfactory performance below normative scores; Unclear differential profile with other dementias |
| PD | Decreased odor identification, which may precede the development of clinical PD |
| FTD | FTD patients demonstrate preserved odor discrimination abilities, Impairments in odor naming and odor-picture |

AD: Alzheimer’s disease; VD: Vascular dementia; PD: Parkinson’s disease; FTD: Frontotemporal Dementia; DLB: Dementia with Lewy Bodies; MCI: Mild cognitive impairment.

**Table 2 Easy to use common olfaction tests**

|  |  |
| --- | --- |
| Test name | Internet address |
| **Smell Identification Test (UPSIT)1**[60]Commercially known as the Smell Identification Test | http://sensonics.com/smell-products/smell-identification-test-international-versions-available.html |
| **Brief Smell Identification Test1-** also known as the Cross-Cultural Smell Identification Test[61] | http://sensonics.com/smell-products/brief-smell-identification-test.html |
| **Pocket Smell Test**[62] | http://sensonics.com/smell-products/pocket-smell-test.html |
| **Smell Diskettes**[63] | http://www.smelldiskettes.com/ |
| **Screening 12 Test (Sniffin' Sticks)**[64] | http://www.usneurologicals.com/index.php?app=ecom&ns=prodshow&ref=ST\_SniffinSticks |

1Test available in multiple languages.