World Journal of Clinical Cases

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.12998/wjcc.v2.i11.661

World J Clin Cases 2014 November 16; 2(11): 661-667
ISSN 2307-8960 (online)

MINIREVIEWS

Olfactory dysfunction in dementia

Jorge Alves, Agavni Petrosyan, Rosana Magalhães

Jorge Alves, Rosana Magalhães, Cognitive Rehabilitation Center, 4710-228 Braga, Portugal
Agavni Petrosyan, Department of Cognitive Sciences, University of California at Irvine, Irvine, CA 92717, United States
Author contributions: Alves J conceptualized the present work; Alves J and Magalhães R performed article search and data acquisition, and drafted the initial version of the manuscript; Petrosyan A contributed to data acquisition and further revisions of the paper; all authors read and approved the final version of the manuscript before submission.
Correspondence to: Jorge Alves, PhD, Cognitive Rehabilitation Center, Av. Central, 33, 3, S4, 4710-228 Braga, Portugal. jorge.alves@neuropsicologia.pt
Telephone: +351-25-3095648
Received: June 6, 2014 Revised: July 31, 2014
Accepted: September 6, 2014
Published online: November 16, 2014

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.

Alves J, Petrosyan A, Magalhães R. Olfactory dysfunction in dementia. *World J Clin Cases* 2014; 2(11): 661-667 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i11/661.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i11.661

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.

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 *et al*[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 *et al*[41] 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 *et al*[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 *et al*[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

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]
VD	Olfactory performance below normative scores; Unclear differential profile with other dementias	AD = PD[26]; mild DLB > MCI/AD[27] FTD < AD[54]
PD	Decreased odor identification, which may precede the development of clinical PD	FTD = AD[55] Legend: > more impaired; < less impaired; = similar
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]	http://sensonics.com/smell-products/smell-identification-test-international-versions-available.html
Brief Smell Identification Test[1]- 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

[1]Test available in multiple languages.

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].

REFERENCES

1 **Chu S**, Downes JJ. Odour-evoked autobiographical memories: psychological investigations of proustian phenomena. *Chem Senses* 2000; **25**: 111-116 [PMID: 10668001]

2 **Doty RL**, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: changes with age. *Science* 1984; **226**: 1441-1443 [PMID: 6505700]

3 **Duffy VB**, Backstrand JR, Ferris AM. Olfactory dysfunction and related nutritional risk in free-living, elderly women. *J Am Diet Assoc* 1995; **95**: 879-884; quiz 885-886 [PMID: 7636078 DOI: 10.1016/S0002-8223(95)00244-8]

4 **Murphy C**, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *JAMA* 2002; **288**: 2307-2312 [PMID: 12425708]

5 **Barresi M**, Ciurleo R, Giacoppo S, Foti Cuzzola V, Celi D, Bramanti P, Marino S. Evaluation of olfactory dysfunction in neurodegenerative diseases. *J Neurol Sci* 2012; **323**: 16-24 [PMID: 23010543 DOI: 10.1016/j.jns.2012.08.028]

6 **Duff K**, McCaffrey RJ, Solomon GS. The Pocket Smell Test: successfully discriminating probable Alzheimer's dementia from vascular dementia and major depression. *J Neuropsychiatry Clin Neurosci* 2002; **14**: 197-201 [PMID: 11983795]

7 **Doty RL**. Olfactory dysfunction in Parkinson disease. *Nat Rev Neurol* 2012; **8**: 329-339 [PMID: 22584158 DOI: 10.1038/nrneurol.2012.80]

8 **Pardini M**, Huey ED, Cavanagh AL, Grafman J. Olfactory function in corticobasal syndrome and frontotemporal dementia. *Arch Neurol* 2009; **66**: 92-96 [PMID: 19139305 DOI: 10.1001/archneurol.2008.521]

9 **Schubert CR**, Cruickshanks KJ, Fischer ME, Huang GH, Klein BE, Klein R, Pankow JS, Nondahl DM. Olfactory impairment in an adult population: the Beaver Dam Offspring Study. *Chem Senses* 2012; **37**: 325-334 [PMID: 22045704 DOI:

10.1093/chemse/bjr102]
10 **Doty RL**, Kamath V. The influences of age on olfaction: a review. *Front Psychol* 2014; **5**: 20 [PMID: 24570664 DOI: 10.3389/fpsyg.2014.00020]
11 **Djordjevic J**, Jones-Gotman M, De Sousa K, Chertkow H. Olfaction in patients with mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 2008; **29**: 693-706 [PMID: 17207898 DOI: 10.1016/j.neurobiolaging.2006.11.014]
12 **Morgan CD**, Murphy C. Olfactory event-related potentials in Alzheimer's disease. *J Int Neuropsychol Soc* 2002; **8**: 753-763 [PMID: 12240739]
13 **Sun GH**, Raji CA, Maceachern MP, Burke JF. Olfactory identification testing as a predictor of the development of Alzheimer's dementia: a systematic review. *Laryngoscope* 2012; **122**: 1455-1462 [PMID: 22552846 DOI: 10.1002/lary.23365]
14 **Yamagishi M**, Ishizuka Y, Seki K. Pathology of olfactory mucosa in patients with Alzheimer's disease. *Ann Otol Rhinol Laryngol* 1994; **103**: 421-427 [PMID: 8203807]
15 **Aliani M**, Udenigwe CC, Girgih AT, Pownall TL, Bugera JL, Eskin MN. Aroma and taste perceptions with Alzheimer disease and stroke. *Crit Rev Food Sci Nutr* 2013; **53**: 760-769 [PMID: 23638935 DOI: 10.1080/10408398.2011.559557]
16 **Larsson M**, Oberg C, Bäckman L. Recollective experience in odor recognition: influences of adult age and familiarity. *Psychol Res* 2006; **70**: 68-75 [PMID: 15480757 DOI: 10.1007/s00426-004-0190-9]
17 **McKhann GM**, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7**: 263-269 [PMID: 21514250 DOI: 10.1016/j.jalz.2011.03.005]
18 **Kovács T**, Cairns NJ, Lantos PL. Olfactory centres in Alzheimer's disease: olfactory bulb is involved in early Braak's stages. *Neuroreport* 2001; **12**: 285-288 [PMID: 11209936]
19 **Esiri MM**, Wilcock GK. The olfactory bulbs in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1984; **47**: 56-60 [PMID: 6693914]
20 **Wesson DW**, Levy E, Nixon RA, Wilson DA. Olfactory dysfunction correlates with amyloid-beta burden in an Alzheimer's disease mouse model. *J Neurosci* 2010; **30**: 505-514 [PMID: 20071513 DOI: 10.1523/JNEUROSCI.4622-09.2010]
21 **Attems J**, Jellinger KA. Olfactory tau pathology in Alzheimer disease and mild cognitive impairment. *Clin Neuropathol* 2006; **25**: 265-271 [PMID: 17140156]
22 **Rezek DL**. Olfactory deficits as a neurologic sign in dementia of the Alzheimer type. *Arch Neurol* 1987; **44**: 1030-1032 [PMID: 3632374]
23 **Motomura N,** Tomota Y. Olfactory dysfunction in dementia of Alzheimer's type and vascular dementia. *Psychogeriatrics* 2006; **6**: 19-20 [DOI: 10.1111/j.1479-8301.2006.00119.x]
24 **Fusetti M**, Fioretti AB, Silvagni F, Simaskou M, Sucapane P, Necozione S, Eibenstein A. Smell and preclinical Alzheimer disease: study of 29 patients with amnesic mild cognitive impairment. *J Otolaryngol Head Neck Surg* 2010; **39**: 175-181 [PMID: 20211105]
25 **Gray AJ**, Staples V, Murren K, Dhariwal A, Bentham P. Olfactory identification is impaired in clinic-based patients with vascular dementia and senile dementia of Alzheimer type. *Int J Geriatr Psychiatry* 2001; **16**: 513-517 [PMID: 11376468]
26 **Chou KL**, Bohnen NI. Performance on an Alzheimer-selective odor identification test in patients with Parkinson's disease and its relationship with cerebral dopamine transporter activity. *Parkinsonism Relat Disord* 2009; **15**: 640-643 [PMID: 19329351 DOI: 10.1016/j.parkreldis.2009.03.004]
27 **Williams SS**, Williams J, Combrinck M, Christie S, Smith AD, McShane R. Olfactory impairment is more marked in patients with mild dementia with Lewy bodies than those with mild Alzheimer disease. *J Neurol Neurosurg Psychiatry* 2009; **80**: 667-670 [PMID: 19448090 DOI: 10.1136/jnnp.2008.155895]
28 **Wiederkehr S**, Simard M, Fortin C, van Reekum R. Validity of the clinical diagnostic criteria for vascular dementia: a critical review. Part II. *J Neuropsychiatry Clin Neurosci* 2008; **20**: 162-177 [PMID: 18451187 DOI: 10.1176/appi.neuropsych.20.2.162]
29 **Albert MS**, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7**: 270-279 [PMID: 21514249 DOI: 10.1016/j.jalz.2011.03.008]
30 **Cecchini MP**, Bojanowski V, Bodechtel U, Hummel T, Hähner A. Olfactory function in patients with ischemic stroke: a pilot study. *Eur Arch Otorhinolaryngol* 2012; **269**: 1149-1153 [PMID: 22042242 DOI: 10.1007/s00405-011-1819-0]
31 **Hall WC.** Movement and Its Central Control. In: Purves D, Augustine GJ, Fitzpatrick D, Hall WC, Lamantia AS, Mcnamara JO, Williams SM, editors. Neuroscience. 3rd ed. Sunderland, MA, USA: Sinauer Asociates Inc., 2004
32 **Hawkes CH**, Shephard BC, Daniel SE. Is Parkinson's disease a primary olfactory disorder? *QJM* 1999; **92**: 473-480 [PMID: 10627864]
33 **Attems J**, Walker L, Jellinger KA. Olfactory bulb involvement in neurodegenerative diseases. *Acta Neuropathol* 2014; **127**: 459-475 [PMID: 24554308 DOI: 10.1007/s00401-014-1261-7]
34 **Ross GW**, Petrovitch H, Abbott RD, Tanner CM, Popper J, Masaki K, Launer L, White LR. Association of olfactory dysfunction with risk for future Parkinson's disease. *Ann Neurol* 2008; **63**: 167-173 [PMID: 18067173 DOI: 10.1002/ana.21291]
35 **Mizutani Y**, Nakamura T, Okada A, Suzuki J, Watanabe H, Hirayama M, Sobue G. Hyposmia and cardiovascular dysautonomia correlatively appear in early-stage Parkinson's disease. *Parkinsonism Relat Disord* 2014; **20**: 520-524 [PMID: 24637128 DOI: 10.1016/j.parkreldis.2014.02.010]
36 **Slow EJ**, Postuma RB, Lang AE. Implications of nocturnal symptoms towards the early diagnosis of Parkinson's disease. *J Neural Transm* 2014; **121** Suppl 1: 49-57 [PMID: 24500032 DOI: 10.1007/s00702-014-1168-4]
37 **Haehner A**, Hummel T, Reichmann H. A clinical approach towards smell loss in Parkinson's disease. *J Parkinsons Dis* 2014; **4**: 189-195 [PMID: 24322062 DOI: 10.3233/JPD-130278]
38 **Müller A**, Reichmann H, Livermore A, Hummel T. Olfactory function in idiopathic Parkinson's disease (IPD): results from cross-sectional studies in IPD patients and long-term follow-up of de-novo IPD patients. *J Neural Transm* 2002; **109**: 805-811 [PMID: 12111470 DOI: 10.1007/s007020200067]
39 **Doty RL**, Deems DA, Stellar S. Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology* 1988; **38**: 1237-1244 [PMID: 3399075]
40 **Duda JE**. Olfactory system pathology as a model of Lewy neurodegenerative disease. *J Neurol Sci* 2010; **289**: 49-54 [PMID: 19783257 DOI: 10.1016/j.jns.2009.08.042]
41 **Takeda A**, Saito N, Baba T, Kikuchi A, Sugeno N, Kobayashi M, Hasegawa T, Itoyama Y. Functional imaging studies of hyposmia in Parkinson's disease. *J Neurol Sci* 2010; **289**: 36-39 [PMID: 19720385 DOI: 10.1016/j.jns.2009.08.041]
42 **Antsov E**, Silveira-Moriyama L, Kilk S, Kadastik-Eerme L, Toomsoo T, Lees A, Taba P. Adapting the Sniffin' Sticks olfactory test to diagnose Parkinson's disease in Estonia. *Parkinsonism Relat Disord* 2014; **20**: 830-833 [PMID: 24792992 DOI: 10.1016/j.parkreldis.2014.04.012]
43 **Baba T**, Kikuchi A, Hirayama K, Nishio Y, Hosokai Y, Kanno S, Hasegawa T, Sugeno N, Konno M, Suzuki K,

Takahashi S, Fukuda H, Aoki M, Itoyama Y, Mori E, Takeda A. Severe olfactory dysfunction is a prodromal symptom of dementia associated with Parkinson's disease: a 3 year longitudinal study. *Brain* 2012; **135**: 161-169 [PMID: 22287381 DOI: 10.1093/brain/awr321]

44 **Lee JE**, Cho KH, Ham JH, Song SK, Sohn YH, Lee PH. Olfactory performance acts as a cognitive reserve in non-demented patients with Parkinson's disease. *Parkinsonism Relat Disord* 2014; **20**: 186-191 [PMID: 24262869 DOI: 10.1016/j.parkreldis.2013.10.024]

45 **Double KL**, Rowe DB, Hayes M, Chan DK, Blackie J, Corbett A, Joffe R, Fung VS, Morris J, Halliday GM. Identifying the pattern of olfactory deficits in Parkinson disease using the brief smell identification test. *Arch Neurol* 2003; **60**: 545-549 [PMID: 12707068 DOI: 10.1001/archneur.60.4.545]

46 **Braak H**, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003; **24**: 197-211 [PMID: 12498954]

47 **Lee EY**, Eslinger PJ, Du G, Kong L, Lewis MM, Huang X. Olfactory-related cortical atrophy is associated with olfactory dysfunction in Parkinson's disease. *Mov Disord* 2014; **29**: 1205-1208 [PMID: 24482154 DOI: 10.1002/mds.25829]

48 **Müller ML**, Bohnen NI. Cholinergic dysfunction in Parkinson's disease. *Curr Neurol Neurosci Rep* 2013; **13**: 377 [PMID: 23943367 DOI: 10.1007/s11910-013-0377-9]

49 **Bohnen NI**, Müller ML, Kotagal V, Koeppe RA, Kilbourn MA, Albin RL, Frey KA. Olfactory dysfunction, central cholinergic integrity and cognitive impairment in Parkinson' s disease. *Brain* 2010; **133**: 1747-1754 [PMID: 20413575 DOI: 10.1093/brain/awq079]

50 **NINDS.** NINDS Frontotemporal Dementia Information Page [Internet] 2014. Available from: URL: http: //www.ninds.nih.gov/disorders/picks/picks.htm

51 **Neary D**, Snowden J, Mann D. Frontotemporal dementia. *Lancet Neurol* 2005; **4**: 771-780 [PMID: 16239184 DOI: 10.1016/S1474-4422(05)70223-4]

52 **Snowden JS**, Neary D, Mann DM. Frontotemporal dementia. *Br J Psychiatry* 2002; **180**: 140-143 [PMID: 11823324]

53 **Manji H,** Wills A, Kitchen N, Dorward N, Connelly S, Mehta A. Oxford Handbook of Neurology. Oxford: Oxford University Press. *Physiotherapy* 2009; **95:** 326 [DOI: 10.1016/j.physio.2007.10.003]

54 **Luzzi S**, Snowden JS, Neary D, Coccia M, Provinciali L, Lambon Ralph MA. Distinct patterns of olfactory impairment in Alzheimer's disease, semantic dementia, frontotemporal dementia, and corticobasal degeneration. *Neuropsychologia* 2007; **45**: 1823-1831 [PMID: 17270222 DOI: 10.1016/j.neuropsychologia.2006.12.008]

55 **McLaughlin NC**, Westervelt HJ. Odor identification deficits in frontotemporal dementia: a preliminary study. *Arch Clin Neuropsychol* 2008; **23**: 119-123 [PMID: 17875380 DOI: 10.1016/j.acn.2007.07.008]

56 **Omar R**, Mahoney CJ, Buckley AH, Warren JD. Flavour identification in frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry* 2013; **84**: 88-93 [PMID: 23138765 DOI: 10.1136/jnnp-2012-303853]

57 **Takeda A**, Baba T, Kikuchi A, Hasegawa T, Sugeno N, Konno M, Miura E, Mori E. Olfactory dysfunction and dementia in Parkinson's disease. *J Parkinsons Dis* 2014; **4**: 181-187 [PMID: 24625830 DOI: 10.3233/JPD-130277]

58 **Vigouroux M**, Bertrand B, Farget V, Plailly J, Royet JP. A stimulation method using odors suitable for PET and fMRI studies with recording of physiological and behavioral signals. *J Neurosci Methods* 2005; **142**: 35-44 [PMID: 15652615 DOI: 10.1016/j.jneumeth.2004.07.010]

59 **Fox M.** Worried You May Be Developing Alzheimer's? Check Your Eyes. NBCNews [Internet]. 2014 July 12. Available from: URL: http: //www.nbcnews.com/health/aging/worried-you-may-be-developing-alzheimers-check-your-eyes-n153226

60 **Doty RL**, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav* 1984; **32**: 489-502 [PMID: 6463130]

61 **Doty RL**, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). *Laryngoscope* 1996; **106**: 353-356 [PMID: 8614203]

62 **Solomon GS**, Petrie WM, Hart JR, Brackin HB. Olfactory dysfunction discriminates Alzheimer's dementia from major depression. *J Neuropsychiatry Clin Neurosci* 1998; **10**: 64-67 [PMID: 9547468]

63 **Briner HR**, Simmen D. Smell diskettes as screening test of olfaction. *Rhinology* 1999; **37**: 145-148 [PMID: 10670026]

64 **Hummel T**, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem Senses* 1997; **22**: 39-52 [PMID: 9056084]

P- Reviewer: Altamura C, Carter WG **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com