The Journal of Laryngology & Otology (2017), ***131***, *572–579*.

doi:10.1017/S0022215117000858

REVIEW ARTICLE

Olfactory disturbances in ageing with and without dementia: towards new diagnostic tools

A GROS[1,3,5], V MANERA[3], C A DE MARCH[4,7], N GUEVARA[2], A KÖNIG[3], L FRIEDMAN[8,9], P ROBERT[1,3], J GOLEBIOWSKI[4,6], R DAVID[1,3]

[1]Ressource and Research Memory Center, [2]Department of Ear Nose Throat Surgery, Institut Universitaire de la Face et du Cou, Nice University Hospital, [3]CoBTek (Cognition – Behaviour – Technology), [4]Institute of Chemistry, University of Nice Sophia Antipolis, [5]Dijon Stroke Registry, EA4184, University Hospital and Medical School of Dijon, University of Burgundy, France, [6]Department of Brain & Cognitive Sciences, DGIST, Daegu Metropolitan City, Republic of Korea, [7]Department of Molecular Genetics and Microbiology, Duke University Medical Center, Durham, [8]Veterans Affairs Palo Alto Health Care System, Palo Alto, and [9]Department of Psychiatry and Behavioral Sciences, Stanford School of Medicine, Stanford University, Stanford, USA

Abstract

Background: Olfactory disorders increase with age and often affect elderly people who have pre-dementia or dementia. Despite the frequent occurrence of olfactory changes at the early stages of neurodegenerative disorders such as Alzheimer's disease, olfactory disorders are rarely assessed in daily clinical practice, mainly due to a lack of standardised assessment tools. The aims of this review were to (1) summarise the existing literature on olfactory disorders in ageing populations and patients with neurodegenerative disorders; (2) present the strengths and weaknesses of current olfactory disorder assessment tools; and (3) discuss the benefits of developing specific olfactory tests for neurodegenerative diseases.

Methods: A systematic review was performed of literature published between 2000 and 2015 addressing olfactory disorders in elderly people with or without Alzheimer's disease or other related disorders to identify the main tools currently used for olfactory disorder assessment.

Results: Olfactory disorder assessment is a promising method for improving both the early and differential diagnosis of Alzheimer's disease. However, the current lack of consensus on which tests should be used does not permit the consistent integration of olfactory disorder assessment into clinical settings.

Conclusion: Otolaryngologists are encouraged to use olfactory tests in older adults to help predict the development of neurodegenerative diseases. Olfactory tests should be specifically adapted to assess olfactory disorders in Alzheimer's disease patients.

Key words: Smell; Aging; Dementia; Alzheimer Disease; Early Diagnosis

Introduction

The risk of olfactory disorders increases with age and is higher in elderly people with pre-dementia and dementia.[1,2] The most common causes of olfactory disorders are chronic sinonasal diseases, acute rhinitis and post-traumatic conditions, as well as toxic chemicals, cancer and degenerative diseases. Although degenerative diseases are not the main cause of olfactory disorders, such disorders are often found in patients in the early stages of both Alzheimer's disease (before the appearance of other cognitive and behavioural symptoms) and Parkinson's disease (prior to motor symptoms). However, Alzheimer's disease and Parkinson's disease patients rarely undergo specific assessment for olfactory disorders in daily clinical practice.

At the histopathological level, olfactory disorders in Alzheimer's disease are caused by the presence of amyloid plaques in the olfactory epithelium, the olfactory bulb, the anterior olfactory nucleus and limbic regions associated with olfactory functions such as the uncus and amygdala. At the biochemical level, cholinergic deficits could contribute to the olfactory disorders found in Alzheimer's disease patients because acetylcholine plays a major role in the olfactory learning process.

Currently, Alzheimer's disease is diagnosed based on cognitive and imaging tests, even though olfactory disorder may be an early clinical marker of dementia due to Alzheimer's disease and could thus improve early clinical diagnosis.

Accepted for publication 12 February 2017 First published online 20 April 2017

A problem faced by clinicians evaluating olfactory disorders in elderly people with cognitive impairment is that self-reported olfactory complaints may be inaccurate and can reflect a number of different smell and taste disturbances. To assess olfactory disorders objectively, clinicians should have access to sensitive, easy-to-use olfactory tests in their daily practice. Several tests have been developed for investigating different aspects of olfaction, ranging from odour sensitivity to odour identification. However, no 'gold standard' has been established and published studies have used assessment tools targeting different aspects of olfactory disorders and employing different odours (because odours are often culture and country specific), resulting in incomparable findings across studies and cultures. This review describes olfactory changes that occur during ageing and in patients with cognitive impairment, reports the tools currently available for assessing olfactory disorders, and offers new perspectives on how to improve current assessment methods for diagnosing olfactory disorders in elderly populations.

Method

To identify relevant articles published between January 2000 and October 2015, the following electronic databases were searched: PubMed (Medline), Cochrane Library, PsycINFO and Web of Science. The following keywords were used: 'olfaction' or 'olfactory disorders' or 'smell' combined with 'aging' or 'elderly' or 'dementia' or 'Alzheimer's disease'.

The titles and abstracts of retrieved articles were independently screened by two authors (AG and RD), and rated to assess their relevance to the research question. For the studies presented below, the age of participants is reported as the mean ± standard deviation.

Biology of olfactory disorders in ageing

Olfactory disorders in ageing

Olfactory disorders are frequently observed in ageing populations,[1] with prevalence rates of around 5 per cent for people aged 45–65 years and of more than 10 per cent for people aged over 65 years.[2] Olfactory disorders are usually first observed at the age of 60 years, with an earlier decline in men than in women,[3,4] and are estimated to affect more than 50 per cent of the population aged over 80 years old.[5] The definition of olfactory disorder includes both hyposmia (partial loss of olfactory function) and anosmia (complete loss of olfactory function).

Several age-related factors contribute to olfactory disturbance, for example structural changes in the olfactory epithelium and olfactory sensory neurons (including the olfactory bulb that mediates the neural response to olfactory stimuli[6]), pathways and processing regions.[7]

Olfactory disorders can affect odour signal analysis at different levels of the nervous system. Indeed, olfactory disorders at the peripheral level can result from alterations to the detection threshold (i.e. the molecular concentration of odorant that an individual can detect) due to impairments at the peripheral nervous system level.[8]

At the central level, olfactory disorders can result from alterations in discrimination ability (i.e. the ability to distinguish a specific odour from other odours) and identification ability (i.e. the ability to associate an odorant molecule with related words or images), both of which result from impairment at the central nervous system level.

Olfactory disorders in Alzheimer's disease

Olfactory disorders in Alzheimer's disease have been a focus of research since 2000. The first investigations studied alterations in the detection threshold, while more recent studies have focused on alterations in identification abilities. In addition, several biological and genetic markers related to Alzheimer's disease risk and pathogenesis have been associated with olfactory changes in ageing. For instance, in cognitively healthy elderly people, olfactory disorders have been associated with increased levels of cerebral amyloid lesions and apolipoprotein E ε4 status,[9–11] two well-known biomarkers of Alzheimer's disease.

Different types of olfactory disorders can be found in Alzheimer's disease, including quantitative disorders, which affect odour detection thresholds; and qualitative disorders, which affect odour identification.

Quantitative disorders. The olfactory epithelium of Alzheimer's disease patients undergoes several changes.[12] Psychophysical studies indicated that Alzheimer's disease patients have higher detection thresholds, and thus lower olfactory sensitivity, compared with cognitively healthy participants,[13,14] and that the degree of impairment correlates with disease severity.[13,15] A recent study ($n = 94$; age = 72.45 ± 9.4 years) showed asymmetry in olfactory thresholds depending on whether the odour was presented to the right or left nostril.[16] In this study, Alzheimer's disease patients detected odours from a closer distance when presented to the right nostril compared with the left nostril, suggesting that an important alteration had occurred in the left nostril. However, another recent study ($n = 35$, age = 71.05 ± 6.7 years) of Alzheimer's disease patients failed to replicate these results, finding no evidence of detection threshold asymmetry between the right and left nostrils.[1]

Qualitative disorders. Qualitative alterations or distortions in smell perception (known as dysosmias) are less well studied in dementia-related diseases. Dysosmia includes parosmia, which refers to a distorted perception of an odorant (odorants are described as smelling differently, often foul-smelling, from how the patient remembers), and phantosmia (smell perception in the complete absence of a physical odour). Some studies suggest that in Parkinson's disease,

https://doi.org/10.1017/S0022215117000858 Published online by Cambridge University Press

qualitative abnormalities of olfaction should be more carefully examined in the prodromal phase (i.e. the early stages) of Parkinson's disease, and have proposed phantosmia as a new premotor manifestation of Parkinson's disease.[17,18] However, a more recent study with a larger cohort concluded that idiopathic phantosmia is more likely to be a symptom than a reliable predictor of early Parkinson's disease or other neurodegenerative diseases.[19]

Qualitative disorders are mainly discovered when an accurate history is taken of a patient's ability to discriminate and identify odours.

Olfactory discrimination

Olfactory discrimination is the ability to recognise a smell that has been presented, and requires the original smell to be stored in the patient's memory. Studies into the odour discrimination abilities of Alzheimer's disease patients are scarce and have received more criticism than studies on odour sensitivity and identification. The main reason is that more cognitive components are required for olfactory discrimination than for odour identification. Indeed, the mnemonic component of these tests is intertwined with the semantic component.[20–22] However, despite these methodological constraints, altered discrimination ability is reported to be more predictive of cognitive decline compared with altered odour sensitivity or identification abilities.[23,24] A recent study investigated whether an olfactory discrimination test could discriminate between Alzheimer's disease and depression (participants with Alzheimer's disease, $n = 20$, age = 75.9 ± 9 years; participants with depression, $n = 20$, age = 73.4 ± 5.6 years).[25] The results showed that individuals with depression had impaired olfactory discrimination ability for both familiar and unknown odours, while individuals with Alzheimer's disease made mistakes in recognising only unknown odours, suggesting that emotional olfactory memory is somewhat preserved in individuals diagnosed with Alzheimer's disease.

Olfactory identification

Olfactory identification impairments have been reported in healthy elderly participants,[26] as well as in patients with mild cognitive impairment,[27] including both amnestic mild cognitive impairment (a cognitive state more commonly associated with conversion to Alzheimer's disease) and non-amnestic mild cognitive impairment.[28] Growdon *et al.* reported that diminished olfactory identification was associated with markers of neurodegeneration such as entorhinal cortex thickness and increased cortical amyloid burden.[26] Impaired odour identification is also a better predictor of cognitive decline than some memory disorders (e.g. deficits in episodic memory) among cognitively healthy participants.[29] Therefore, many studies have focused on the ability of patients to identify odours to aid the early diagnosis of Alzheimer's disease, and have suggested that olfactory identification may be more relevant than olfactory sensitivity for predicting conversion from mild cognitive impairment to Alzheimer's disease. In 2000, Devanand *et al.* assessed the predictive utility of an odour identification test for determining conversion from mild cognitive impairment to Alzheimer's disease.[30] This longitudinal study monitored 90 patients with mild cognitive impairment for over 3 years and found that patients with lower olfactory identification scores were more likely to develop Alzheimer's disease. These promising results suggest that inclusion of an olfactory identification test in the routine assessment might help predict conversion from mild cognitive impairment to Alzheimer's disease.[31] The University of Pennsylvania smell identification test is currently considered one of the top five predictors for assessing the conversion risk to Alzheimer's disease.[32] A recent study ($n = 148$, age = 67.9 ± 8.7 years) combined the University of Pennsylvania smell identification test with four other predictors: informant report of functioning, the selective reminding test – immediate recall (verbal memory), magnetic resonance imaging (MRI) hippocampal volume and MRI entorhinal cortex volume.[32] This combination of tests was strongly predictive of conversion to Alzheimer's disease and markedly superior to combining age and mini-mental state examination. As taste is heavily dependent on olfactory abilities, the study of taste disturbances may offer similar opportunities.[33] Impairments in olfactory identification could also be used to measure cognitive decline in patients with amnestic mild cognitive impairment.[34] Olfactory identification has been extensively documented in patients with amnestic mild cognitive impairment, but far less so in individuals with non-amnestic mild cognitive impairment. A recent study highlighted that olfactory identification was also impaired in individuals with non-amnestic mild cognitive impairment, although the degree of olfactory impairment did not correlate with cognitive performance.[35] An olfactory identification test was also a useful clinical marker for monitoring the effectiveness of symptomatic medications such as cholinesterase inhibitors in Alzheimer's disease patients,[36] and may contribute to the differential diagnosis with depression.[37]

Despite clinical interest in developing olfactory measures for identifying patients with Alzheimer's disease and related disorders, a recent review highlighted contradictory results in this area. This finding may be explained by the use of different tests and different methodologies among studies; thus, the lack of generally applicable instruments prevents olfactory testing being integrated into the routine clinical evaluation of Alzheimer's disease.[38] For acceptance by the scientific and medical communities, new olfactory tests should be both reliable for research use and suitable for assessing Alzheimer's disease patients in daily clinical practice.

Indeed, since the discovery that olfactory regions are affected in Alzheimer's disease, numerous studies have

https://doi.org/10.1017/S0022215117000858 Published online by Cambridge University Press

aimed to identify an olfactory test that can predict disease development or help with diagnosis. Nevertheless, at more than 10 years after the first published study, no gold standard method of measurement has yet been developed for general clinic application.

Currently available psychophysical tests

Olfactory tests differ depending on whether the aim is to explore the odour detection threshold or to identify or characterise the odour.

Most sniffing tests use odorant stimulations comprising a mixture of familiar compounds such as essential oils, raw materials or flavours. Their familiarity is designed to enable rapid completion of the description task. Most are related to odours generated by various foods, such as orange, clove, fish and vanilla.[4] Alternatively, non-food smells generally include woody or flower smells; odours are chosen to be culture specific, although efforts have been made to set up internationally applicable tests.[39]

These tests are insufficient for a standalone diagnosis and were not initially designed for use by ENT specialists or neurologists. However, the identification of olfactory disorders can help to establish a diagnosis for, and can even represent an early marker of, neurodegenerative diseases. It is necessary to use olfactory tests to assess olfactory disorders because patients rarely report these. Table I shows the tests currently used and their levels (peripheral and/or central nervous system) of assessment, the pathological conditions for which they were developed and for which they are currently used, their sensitivity and specificity in diagnosing Parkinson's and Alzheimer's disease patients, and their strengths and weaknesses.

Towards a new diagnostic tool?

This review highlighted the important points that olfactory disorders (1) are qualitatively different in cognitively healthy and Alzheimer's disease individuals and (2) may predict conversion from mild cognitive impairment to Alzheimer's disease. However, no gold standard olfactory assessment instrument is currently available for diagnosing or monitoring Alzheimer's disease in daily clinical practice. This is primarily due to a lack of consensus on the validity of existing olfactory tests for clinical practice and research purposes. At least one study tried to compare different olfactory tests to identify the most reliable one, but it failed to identify a reference tool independent of the population and pathology of interest.[75]

Pathology-specific tests

No test has been developed and used specifically for neurodegenerative diseases: tests developed for ENT diseases are usually extended to neurodegenerative diseases, and vice versa. Although the European test of olfactory capabilities, the 'Sniffin' Sticks' test and the quick smell identification test were designed specifically for Alzheimer's disease, they are preferentially used for other types of ENT diseases.[53–55,70,74] This may be because lack of a single, reliable test makes it difficult to compare results among different studies. Therefore, clinicians working on Alzheimer's disease have no reliable evidence to support the use of olfactory testing of Alzheimer's disease patients. Consistent with this hypothesis, a recent review highlighted the importance of developing a single, reliable test for routine clinical use in Alzheimer's disease patients.[38] It is unlikely that a single all-purpose test will ever be developed because of the large number of pathologies in which olfaction is affected, such as ENT, psychiatric and neurodegenerative diseases, which all have different aetiologies and effects on olfaction. Therefore, efforts should instead be made to develop tests specific to a single pathology and culture or country.

Culture-specific tests

Olfaction is strongly affected by culture, with familiar and unfamiliar odours varying among countries and regions, making a single test unlikely to have general utility. This explains why researchers in different countries have modified existing tests or developed their own tests. However, the human odorant receptor gene repertoire is also highly variable, suggesting that most people will not have the same response to odorant stimulation.[76] Genetic effects on the olfactory perception of single compounds are only beginning to be understood. For example, the perception of methanthiol is affected by genetic variation only in Caucasian people: no correlation has been demonstrated for African people.[77] As these variations are likely to be highly complex for mixtures of odorants, olfactory stimulation by single odorant compounds appears preferable.

Test composition

Testing stimulation using pure compounds might be simpler for several reasons. Quality control is more straightforward for a pure compound than for a mixture that may contain tens of chemicals. In addition, the chemical composition of the blend used in these tools may be unknown to the user and also depends on the commercial constraints of the supplier, which are likely to change over time (for example, because of economical or safety concerns). Even if the olfactory response triggered by a single compound is not simpler than that of a complex mixture, it seems intuitively better to make olfactory tests using pure odorants. As a comparison, visual or auditory tests use simple stimuli (rather than complex) to identify dysfunction.[78,79] Monitoring olfaction with a complex blend is similar to monitoring the auditory response using a symphony rather than using reproducible sounds at defined frequencies. Even single odorants can trigger responses corresponding to familiar stimulants with a single descriptor, at least for people of the same cultural background.

https://doi.org/10.1017/S0022215117000858 Published online by Cambridge University Press

TABLE I
CHARACTERISTICS OF EXISTING PSYCHOPHYSICAL OLFACTORY DISORDER TESTS

Characteristic	UPSIT	'Sniffin Sticks' olfactory test	B-SIT	Biolfa®	ETOC
Assessment	Central level; identification task	Central and peripheral level; odour threshold. discrimination and identification	Central level; identification task	Central and peripheral level; odour threshold and identification	Central and peripheral level; supra-threshold detection task and an identification task
Specifically developed for	Clinical otolaryngologists	Assess olfactory threshold, discrimination, and identification	Detect AD	Find causal origin of the disorder of smell[40]	Measure the decline in olfactory performance with ageing
Used for	Type 3 von Willebrand disease[41], schizophrenia[42], psychosis[43], PD[44–46], migraine[47], cognitive decline[28,32] and AD severity[48]	Neurodegenerative disorders[49], amnestic MCI patients and AD patients[50,51], and apathy[52]; Sniffin Test was used in four studies related to AD since the test was created	Chronic rhinosinusitis[53–55], Korsakoff syndrome[56], multiple sclerosis[57], obsessive–compulsive disorders[58], spinal anaesthesia[59], PD[60–63]	AD and olfactory impairment	AD and olfactory impairment
Culture	British, Chinese, French, German, Italian, Korean and Spanish adaptations[64]	Developed in Germany, designed for Europe and adapted by other countries[65,66]	US culture	French culture[67]	European culture (cross-cultural)
Sensitivity/ specificity in PD and AD	In PD: sensitivity, 90%; specificity, 86%[68] In AD: sensitivity, 89%; specificity, 83%[69]	In PD: sensitivity, 83.3%; specificity, 82.0%[70]	In PD: sensitivity, 82%; specificity, 77%	–	–
Strengths	Reliability ($r = 0.94$)[71] and practicality	More adapted to dementia populations than the UPSIT[72]	Short version; only 5 of the 12 B-SIT odours (banana, cinnamon, petrol, pineapple, smoke) are needed to detect PD	Culture specific	Recent development of an application to detect AD
Weaknesses	Test results vary depending on demographic features (e.g. age, sex and smoking history) and have often been criticised for being culturally biased[73]; the short version (Q-SIT) is less sensitive and reliable compared with the UPSIT and B-SIT in the context of AD; the UPSIT had to take several factors into account to achieve good sensitivity	No study on its sensitivity and the specificity for AD patients	B-SIT test was developed specifically for detecting AD, but is currently used more often for ENT diseases; only one study on AD patients since 2010[38]	Only one study into the ability of Biolfa to differentiate perception and identification thresholds in AD	Only one study emphasised the use of ETOC in AD research[74]

UPSIT = University of Pennsylvania smell identification test; B-SIT = brief smell identification test; ETOC = European test of olfactory capabilities; AD = Alzheimer's disease; PD = Parkinson's disease; MCI = mild cognitive impairment; US = United States (of America); Q-SIT = quick smell identification test

Above all, the use of pure compounds would enable odour perception to be linked to the pharmacology of the olfactory system, a task that is difficult to perform with complex mixtures. Human beings perceive odours through the stimulation of odorant receptors expressed by olfactory sensory neurons located in the nasal epithelium.[80] Humans possess close to 400 different functional odorant receptor genes,[81] and the differential activation of these receptors encodes the olfactory signal within our brain. The current consensus is that a given odour is associated with a 'combinatorial code' of odorant receptor activation. Thus, the pharmacology of odorant receptors and their role in the perception of pure compounds are beginning to be uncovered.[82]

Conclusion

Olfactory disorders may predict the conversion from mild cognitive impairment to Alzheimer's disease. Currently, no gold standard olfactory test is available for diagnosing or monitoring Alzheimer's disease in clinical practice. The development of a single, reliable assessment tool for Alzheimer's disease populations is thus critical. This tool should be specific to the pathology and culture of interest, and should use pure odorants (to simplify the analysis and to determine genetic factors and psycho-physiological effects). Future efforts should aim to understand why olfactory tests developed specifically for memory centres are not used. For example, clinicians may not be accustomed to the olfactory system, be unable to store odorant correctly, have insufficient time and may not be convinced by the available evidence. The objective is to develop a test that will account for all clinical, cultural and molecular factors mentioned in this review.

Acknowledgements

The authors thank K W Zhu and H Matsunami for their comments and revisions. This work was supported by grants from the Gen Foundation (to CAdM) and from the Centre National de la Recherche Scientifique (défi AUTON 2016) to JG. Thanks also go to Giract for providing a PhD bursary.

References

1 Doty RL, Bayona EA, Leon-Ariza DS, Cuadros J, Chung I, Vazquez B, *et al*. The lateralized smell test for detecting Alzheimer's disease: failure to replicate. *J Neurol Sci* 2014; **340**:170–3
2 Murphy C, Gilmore M, Seery C, Salmon D, Lasker B. Olfactory thresholds are associated with degree of dementia in Alzheimer's disease. *Neurobiol Aging* 1990;**11**:465–9
3 Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: changes with age. *Science* 1984;**226**:1441–3
4 Choudhury ES, Moberg P, Doty RL. Influences of age and sex on a microencapsulated odor memory test. *Chem Senses* 2003; **28**:799–805
5 Lafreniere D, Mann N. Anosmia: loss of smell in the elderly. *Otolaryngol Clin North Am* 2009;**42**:123–31
6 Enwere E. Aging results in reduced epidermal growth factor receptor signaling, diminished olfactory neurogenesis, and deficits in fine olfactory discrimination. *J Neurosci* 2004;**24**: 8354–65
7 Attems J, Walker L, Jellinger KA. Olfaction and aging: a mini-review. *Gerontology* 2015;**61**:485–90
8 Frasnelli J, Lundström JN, Schöpf V, Negoias S, Hummel T, Lepore F. Dual processing streams in chemosensory perception. *Front Hum Neurosci* 2012;**6**:288
9 Wilson RS, Arnold SE, Schneider JA, Tang Y, Bennett DA. The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. *J Neurol Neurosurg Psychiatry* 2007;**78**:30–5
10 Green AJ, Cervantez M, Graves LV, Morgan CD, Murphy C. Age and apolipoprotein E ε4 effects on neural correlates of odor memory. *Behav Neurosci* 2013;**127**:339–49
11 Olofsson JK, Nordin S, Wiens S, Hedner M, Nilsson L-G, Larsson M. Odor identification impairment in carriers of ApoE-ε4 is independent of clinical dementia. *Neurobiol Aging* 2010;**31**:567–77
12 Getchell ML, Shah DS, Buch SK, Davis DG, Getchell TV. 3-Nitrotyrosine immunoreactivity in olfactory receptor neurons of patients with Alzheimer's disease: implications for impaired odor sensitivity. *Neurobiol Aging* 2003;**24**:663–73
13 Nordin S, Murphy C. Impaired sensory and cognitive olfactory function in questionable Alzheimer's disease. *Neuropsychology* 1996;**10**:113–19
14 Bacon AW, Bondi MW, Salmon DP, Murphy C. Very early changes in olfactory functioning due to Alzheimer's disease and the role of apolipoprotein E in olfaction. *Ann N Y Acad Sci* 1998;**855**:723–31
15 Murphy C, Gilmore M, Seery C, Salmon D, Lasker B. Olfactory thresholds are associated with degree of dementia in Alzheimer's disease. *Neurobiol Aging* 1990;**11**:465–9
16 Stamps JJ, Bartoshuk LM, Heilman KM. A brief olfactory test for Alzheimer's disease. *J Neurol Sci* 2013;**333**:19–24
17 Landis BN, Burkhard PR. Phantosmias and Parkinson disease. *Arch Neurol* 2008;**65**:1237–9
18 Hirsch AR. Parkinsonism: the hyposmia and phantosmia connection. *Arch Neurol* 2009;**66**:538–9
19 Landis BN, Reden J, Haehner A. Idiopathic phantosmia: outcome and clinical significance. *ORL J Otorhinolaryngol Relat Spec* 2010;**72**:252–5
20 Moller P, Wulff C, Koster EP. Do age differences in odour memory depend on differences in verbal memory? *Neuroreport* 2004;**15**:915–17
21 Moller P, Mojet J, Koster EP. Incidental and intentional flavor memory in young and older subjects. *Chem Senses* 2007;**32**: 557–67
22 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
23 Sohrabi HR, Bates KA, Weinborn MG, Johnston ANB, Bahramian A, Taddei K, *et al*. Olfactory discrimination predicts cognitive decline among community-dwelling older adults. *Transl Psychiatry* 2012;**2**:e118
24 Naudin M, Mondon K, El-Hage W, Desmidt T, Jaafari N, Belzung C *et al*. Long-term odor recognition memory in unipolar major depression and Alzheimer's disease. *Psychiatry Res* 2014;**220**:861–6
25 Pentzek M, Grass-Kapanke B, Ihl R. Odor identification in Alzheimer's disease and depression. *Aging Clin Exp Res* 2007;**19**:255–8
26 Growdon ME, Schultz AP, Dagley AS, Amariglio RE, Hedden T, Rentz DM *et al*. Odor identification and Alzheimer disease biomarkers in clinically normal elderly. *Neurology* 2015;**84**: 2153–60
27 Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004:**256**:183–94
28 Vyhnalek M, Magerova H, Andel R, Nikolai T, Kadlecova A, Laczo J *et al*. Olfactory identification in amnestic and non-amnestic mild cognitive impairment and its neuropsychological correlates. *J Neurol Sci* 2015;**349**:179–84
29 Devanand DP, Lee S, Manly J, Andrews H, Schupf N, Doty RL *et al*. Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. *Neurology* 2015;**84**:182–9
30 Devanand DP, Michaels-Marston KS, Liu X, Pelton GH, Padilla M, Marder K *et al*. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am J Psychiatry* 2000;**157**:1399–405
31 Makowska I, Kloszewska I, Grabowska A, Szatkowska I, Rymarczyk K. Olfactory deficits in normal aging and

https://doi.org/10.1017/S0022215117000858 Published online by Cambridge University Press

Alzheimer's disease in the Polish elderly population. *Arch Clin Neuropsychol* 2011;**26**:270–9
32 Devanand DP, Liu X, Tabert MH, Pradhaban G, Cuasay K, Bell K *et al*. Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. *Biol Psychiatry* 2008;**64**:871–9
33 Steinbach S, Hundt W, Vaitl A, Heinrich P, Förster S, Bürger K *et al*. Taste in mild cognitive impairment and Alzheimer's disease. *J Neurol* 2010;**257**:238–46
34 Kjelvik G, Saltvedt I, White LR, Stenumgård P, Sletvold O, Engedal K *et al*. The brain structural and cognitive basis of odor identification deficits in mild cognitive impairment and Alzheimer's disease. *BMC Neurol* 2014;**14**:168
35 Vyhnalek M, Magerova H, Andel R, Nikolai T, Kadlecova A, Laczo J *et al*. Olfactory identification in amnestic and non-amnestic mild cognitive impairment and its neuropsychological correlates. *J Neurol Sci* 2015;**349**:179–84
36 Li Y, Wang Y, Wu G, Shi F, Zhou L, Lin W *et al*. Discriminant analysis of longitudinal cortical thickness changes in Alzheimer's disease using dynamic and network features. *Neurobiol Aging* 2012;**33**:427
37 Solomon GS, Petrie WM, Hart JR, Brackin HB. Olfactory dysfunction discriminates Alzheimer's dementia from major depression. *J Neuropsychiatry Clin Neurosci* 1998;**10**:64–7
38 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**:1455–62
39 Doty RL, Marcus A, William Lee W. Development of the 12-Item Cross-Cultural Smell Identification Test (CC-SIT). *Laryngoscope* 1996;**106**:353–6
40 Delahaye L, Le Gac MS, Martins-Carvalho C, Vazel L, Potard G, Marianowski R. Gap between odor perception threshold and identification threshold: calculation based on a graph of the Biolfa(®) olfactory test. *Eur Ann Otorhinolaryngol Head Neck Dis* 2010;**127**:130–6
41 Cenedese V, Mezzavilla M, Morgan A, Marino R, Ettorre CP, Margaglione M *et al*. Assessment of the olfactory function in Italian patients with type 3 von Willebrand disease caused by a homozygous 253 Kb deletion involving VWF and TMEM16B/ANO2. *PLoS One* 2015;**10**:e0116483
42 Strauss GP, Keller WR, Koenig JI, Gold JM, Ossenfort KL, Buchanan RW. Plasma oxytocin levels predict olfactory identification and negative symptoms in individuals with schizophrenia. *Schizophr Res* 2015;**162**:57–61
43 Lin A, Brewer WJ, Yung AR, Nelson B, Pantelis C, Wood SJ. Olfactory identification deficits at identification as ultra-high risk for psychosis are associated with poor functional outcome. *Schizophr Res* 2015;**161**:156–62
44 Prashanth R, Roy SD, Mandal PK, Ghosh S. Parkinson's disease detection using olfactory loss and REM sleep disorder features. *Conf Proc IEEE Eng Med Biol Soc* 2014;**2014**:5764–7
45 Sharer JD, Leon-Sarmiento FE, Morley JF, Weintraub D, Doty RL. Olfactory dysfunction in Parkinson's disease: positive effect of cigarette smoking. *Mov Disord* 2015;**30**:859–62
46 Gaig C, Vilas D, Infante J, Sierra M, García-Gorostiaga I, Buongiorno M *et al*. Nonmotor symptoms in LRRK2 G2019S associated Parkinson's disease. *PLoS One* 2014;**9**:e108982
47 Whiting AC, Marmura MJ, Hegarty SE, Keith SW. Olfactory acuity in chronic migraine: a cross-sectional study. *Headache* 2015;**55**(1):71–5
48 Velayudhan L, Pritchard M, Powell JF, Proitsi P, Lovestone S. Smell identification function as a severity and progression marker in Alzheimer's disease. *Int Psychogeriatr* 2013;**25**:1157–66
49 Tonacci A, Borghini A, Mercuri A, Pioggia G, Andreassi MG. Brain-derived neurotrophic factor (Val66 Met) polymorphism and olfactory ability in young adults. *J Biomed Sci* 2013;**20**:57
50 Fusetti M, Fioretti AB, Silvagni F, Simaskou M, Sucapane P, Necozione S *et al*. Smell and preclinical Alzheimer disease: study of 29 patients with amnesic mild cognitive impairment. *J Otolaryngol Head Neck Surg* 2010;**39**:175–81
51 Förster S, Vaitl A, Teipel SJ, Yakushev I, Mustafa M, la Fougère C *et al*. Functional representation of olfactory impairment in early Alzheimer's disease. *J Alzheimers Dis* 2010;**22**:581–91
52 Seligman SC, Kamath V, Giovannetti T, Arnold SE, Moberg PJ. Olfaction and apathy in Alzheimer's disease, mild cognitive impairment, and healthy older adults. *Aging Ment Health* 2013;**17**:564–70
53 Alt JA, Mace JC, Buniel MCF, Soler ZM, Smith TL. Predictors of olfactory dysfunction in rhinosinusitis using the brief smell identification test. *Laryngoscope* 2014;**124**:E259–66
54 Kim BG, Oh J-H, Choi HN, Park SY. Simple assessment of olfaction in patients with chronic rhinosinusitis. *Acta Otolaryngol* 2015;**135**:258–63
55 Soler ZM, Hyer JM, Ramakrishnan V, Smith TL, Mace J, Rudmik L *et al*. Identification of chronic rhinosinusitis phenotypes using cluster analysis. *Int Forum Allergy Rhinol* 2015;**5**:399–407
56 Jones DE, Rowland M, Bracewell RM. Olfactory examination in Korsakoff's syndrome: implications for early diagnosis. *ISRN Otolaryngology* 2011;**2011**:1–4
57 Silva AM, Santos E, Moreira I, Bettencourt A, Coutinho E, Gonçalves A *et al*. Olfactory dysfunction in multiple sclerosis: association with secondary progression. *Mult Scler* 2012;**18**:616–21
58 Bersani G, Quartini A, Ratti F, Pagliuca G, Gallo A. Olfactory identification deficits and associated response inhibition in obsessive-compulsive disorder: on the scent of the orbito-fronto-striatal model. *Psychiatry Res* 2013;**210**:208–14
59 Demirhan A, Erdem K, Akkaya A, Tekelioglu UY, Bilgi M, Isik C *et al*. Evaluation of the olfactory memory after spinal anaesthesia: a pilot study. *Eur Rev Med Pharmacol Sci* 2013;**17**:2428–32
60 Ådén E, Carlsson M, Poortvliet E, Stenlund H, Linder J, Edström M *et al*. Dietary intake and olfactory function in patients with newly diagnosed Parkinson's disease: a case–control study. *Nutr Neurosci* 2011;**14**:25–31
61 Cramer CK, Friedman JH, Amick MM. Olfaction and apathy in Parkinson's disease. *Parkinsonism Relat Disord* 2010;**16**:124–6
62 Johansen KK, Warø BJ, Aasly JO. Olfactory dysfunction in sporadic Parkinson's disease and LRRK2 carriers. *Acta Neurol Scand* 2014;**129**:300–6
63 Rodríguez-Violante M, Lees AJ, Cervantes-Arriaga A, Corona T, Silveira-Moriyama L. Use of smell test identification in Parkinson's disease in Mexico: a matched case–control study. *Mov Disord* 2011;**26**:173–6
64 Jiang R-S, Kuo L-T, Wu S-H, Su M-C, Liang K-L. Validation of the applicability of the traditional Chinese version of the University of Pennsylvania Smell Identification Test in patients with chronic rhinosinusitis. *Allergy Rhinol (Providence)* 2014;**5**:28–35
65 Sorokowska A, Hummel T. Polish version of the Sniffin' Sticks Test – adaptation and normalization [in Polish]. *Otolaryngol Pol* 2014;**68**:308–14
66 Fjaeldstad A, Kjaergaard T, Van Hartevelt TJ, Moeller A, Kringelbach ML, Ovesen T. Olfactory screening: validation of Sniffin' Sticks in Denmark. *Clin Otolaryngol* 2015;**40**:545–50
67 Lecanu JB, Faulcon P, Werner A, Bonfils P. Normative data of the Biolfa(®) olfactory test [in French]. *Ann Otolaryngol Chir Cervicofac* 2002;**119**:164–9
68 Driver-Dunckley E, Adler CH, Hentz JG, Dugger BN, Shill HA, Caviness JN *et al*. Olfactory dysfunction in incidental Lewy body disease and Parkinson's disease. *Parkinsonism Relat Disord* 2014;**20**:1260–2
69 Velayudhan L, Gasper A, Pritchard M, Baillon S, Messer C, Proitsi P. Pattern of smell identification impairment in Alzheimer's disease. *J Alzheimers Dis* 2015;**30**:381–7
70 Mahlknecht P, Pechlaner R, Boesveldt S, Volc D, Pinter B, Reiter E *et al*. Optimizing odor identification testing as quick and accurate diagnostic tool for Parkinson's disease: odor identification in PD. *Mov Disord* 2016;**31**:1408–13
71 Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept Psychophys* 1989;**45**:381–4
72 Hugh SC, Siu J, Hummel T, Forte V, Campisi P, Papsin BC *et al*. Olfactory testing in children using objective tools: comparison of Sniffin' Sticks and University of Pennsylvania Smell Identification Test (UPSIT). *J Otolaryngol Head Neck Surg* 2015;**44**:10
73 Doty RL. Office procedures for quantitative assessment of olfactory function. *Am J Rhinol* 2007;**21**:460–73
74 Joussain P, Bessy M, Faure F, Bellil D, Landis BN, Hugentobler M *et al*. Application of the European Test of Olfactory Capabilities in patients with olfactory impairment. *Eur Arch Otorhinolaryngol* 2016;**273**:381–90
75 Gu D, Li P. Comparison of application of several psychophysical olfactory test methods in clinic [in Chinese]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2014;**28**:715–17

76 Secundo L, Snitz K, Weissler K, Pinchover L, Shoenfeld Y, Loewenthal R *et al*. Individual olfactory perception reveals meaningful nonolfactory genetic information. *Proc Natl Acad Sci U S A* 2015;**112**:8750–5
77 Pelchat ML, Bykowski C, Duke FF, Reed DR. Excretion and perception of a characteristic odor in urine after asparagus ingestion: a psychophysical and genetic study. *Chem Senses* 2011;**36**: 9–17
78 Štenc Bradvica I, Bradvica M, Matić S, Reisz-Majić P. Visual dysfunction in patients with Parkinson's disease and essential tremor. *Neurol Sci* 2015;**36**:257–62
79 Näätänen R, Kujala T, Escera C, Baldeweg T, Kreegipuu K, Carlson S *et al*. The mismatch negativity (MMN) – a unique window to disturbed central auditory processing in ageing and different clinical conditions. *Clin Neurophysiol* 2012;**123**: 424–58
80 Buck L, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* 1991;**65**: 175–87
81 Niimura Y. Olfactory receptor multigene family in vertebrates: from the viewpoint of evolutionary genomics. *Current Genomics* 2012;**13**:103–14
82 De March CA, Ryu S, Sicard G, Moon C, Golebiowski J. Structure–odour relationships reviewed in the postgenomic era: olfactory receptors and odourants. *Flavour Fragr J* 2015; **30**:342–61

Address for correspondence:
Dr A Gros, Centre Mémoire de Ressources et de Recherche, Institut Claude Pompidou, 10 rue Molière 06100, Nice, France

Fax: +33 61437170
E-mail: gros.a2@chu-nice.fr

Dr A Gros takes responsibility for the integrity of the content of the paper
Competing interests: None declared

https://doi.org/10.1017/S0022215117000858 Published online by Cambridge University Press