Published in final edited form as:
J Neurol Sci. 2013 October 15; 333(0): . doi:10.1016/j.jns.2013.06.033.

A Brief Olfactory Test for Alzheimer's Disease

Jennifer J. Stamps, BA[1], **Linda M. Bartoshuk, PhD**[2], and **Kenneth M. Heilman, MD**[3]

[1]Department of Neuroscience, The Clinical and Translational Science Institute, University of Florida, College of Medicine, Gainesville, FL, USA

[2]Department of Community Dentistry and Behavioral Science, University of Florida, College of Dentistry, Gainesville, FL, USA

[3]Department of Neurology, The Center for Neuropsychological Studies, University of Florida, College of Medicine, Gainesville, FL, USA

Abstract

Background—The early diagnosis of Alzheimer's disease (AD) may help reduce disability, enhance quality of life, and aid clinical trials. Portions of olfactory cortex are the initial sites of AD pathology and patients with AD often have more degeneration of their left than right hemisphere. Since the olfactory epithelium projects mainly to the ipsilateral olfactory cortex, patients with AD may demonstrate an asymmetrical (left greater than right) decrement of odor detection sensitivity. This retrospective, case-control study assessed a quick olfactory test that may help diagnose AD.

Methods—Participants with probable AD (N=18), mild cognitive impairment (MCI, N=24), other causes of dementia (OD, N=26) and matched controls (OC, N=26) were tested, with closed eyes, for their ability to detect an odor, one nostril at a time. A container of 14g of peanut butter was opened, held medially at the bottom of a 30 cm ruler, and moved up 1cm at a time during the participants' exhale. Upon odor detection, the distance between the subject's nostril and container was measured.

Results—The mean odor detection distance of AD patients' left nostril (5.1 cm), and not their right (17.4 cm), was significantly less ($F(3,90) = 22.28$, $p < 0.0001$) than the other groups. The mean, standard error, and 95% Confidence Interval of the L R nostril odor detection difference (cm) for AD was −12.4 ±0.5, (−15.0, −9.8); for MCI was −1.9 ±1.2, (−4.2,0.4); for OD was 4.8 ±1.0, (2.6,6.9); and for OC was 0.0 ±1.4 (−2.2,2.1).

Conclusion—This non-invasive and inexpensive left-right nostril odor detection test appears to be a sensitive and specific test for probable AD.

Correspondence to: Jennifer J. Stamps, McKnight Brain Institute, 1149 Newell Drive, Department of Neuroscience, Room L1-100, Gainesville, FL 32611, USA;phone: 352-514-5311; fax: 352-273-5257; jstamps@ufl.edu.

Contributors: JJS conceived and administered the odor detection test, and drafted and submitted the manuscript. LMB analyzed the data and critically reviewed the manuscript. KMH provided clinical assessment and diagnoses, drafted and critically reviewed the manuscript. All authors had full access to all the data and take full responsibility for the integrity of the data and the accuracy of the data analyses.

Competing interests: None

Keywords

Smell disorders; Cranial Nerve I disorders; Alzheimer Disease; Neurologic Examination; Olfaction

INTRODUCTION

The U.S. Census Bureau estimates that the population of people 65 and older will double to 72 million over the next 20 years and studies indicate that the number of people with Alzheimer's disease (AD) doubles for every 5-year interval past age 65 [1]. The NINCDS-ADRDA criteria for diagnosing AD require an extensive evaluation by a clinician [2, 3]. To help confirm the diagnosis of AD several institutions use biomarkers such as f^{11}C- PiB, a radioisotope that marks cerebral amyloid during PET imaging [4], or examination of the cerebral spinal fluid for the ratio of tau to amyloid-β 1–42 levels [5]. All of these tests are expensive and require highly trained personnel or equipment that is available in only a limited number of locations. Except for the lumbar puncture, which is invasive with potential complications, these procedures are neither highly sensitive nor specific for AD [2–7]. Thus, having a sensitive, specific, inexpensive and readily available clinical screening test for AD during the earliest possible phase would be of value.

Many of the eight structures lying on the surface of the basal forebrain and within the mesial temporal lobes that comprise olfactory cortex [8, 9] are the sites of initial pathology in AD [10–12]. Because olfactory dysfunction occurs in preclinical AD [13,14], assessing olfactory sensitivity during the neurologic examination could prove especially helpful for early diagnosis.

Davidson and Murphy designed an odor detection task called the Alcohol Sniff Test that has a low cognitive load and good test-retest reliability [15,16]. The presence of alcohol can be detected by the trigeminal nerve and since our primary interest was testing CN I and its cerebral connections, we changed the stimulus to peanut butter, a pure odorant. To learn if there were asymmetries we tested one nostril at time (unirhinal). This unirhinal peanut butter odor detection test (UPBODT) is a part of the examination of the cranial nerves we use to evaluate patients at the University of Florida Memory and Cognitive Disorders Clinic.

Considering that the olfactory network from olfactory epithelium to olfactory cortex is primarily ipsilateral [8,9,17,18], and that voxel-based morphometric studies of grey matter volume loss consistently find significantly greater left than right mesial temporal lobe atrophy at the earliest phases of AD [19–21], the purpose of this retrospective, case control study was to learn whether patients with probable AD have an asymmetrical decrease in their ability to detect an odor and whether the UPBODT could be used as a marker to detect AD.

METHODS

Participants

We reviewed the medical records of 133 consecutive new patients evaluated at our clinic from August 31, 2010 when we began including the UPBODT in our neurological exam to March 16, 2012, which was the date of our data review request. Medical history was gathered from both the patient and from a knowledgeable family member or caregiver. A board certified neurologist performed a detailed general examination and neurological examination. Patients were cognitively assessed using the full Florida Mental State Exam (FMSE)[22], which includes the Mini-Mental Status Examination [23], the Hopkins Verbal

Learning Test [24], the Boston Naming Test [25], the Controlled Oral Word Association test [26], the Gerstmann's syndrome score [27], as well as other neuropsychological tests. Gerstmann's syndrome is commonly seen in Alzheimer's patients and so within the FMSE this syndrome is actually scored with a possible 5 points given for the ability to calculate, 3 possible points given for the ability to tell left from right, and 1 possible point given for the ability to properly name the index finger. A brain MRI scan and diagnostic laboratory studies were obtained to evaluate for reversible causes of dementia.

In accordance with the current criteria [2,3], the patients in this study diagnosed with probable Alzheimer's disease had 1) an insidious onset; 2) a clear-cut history of worsening of cognition by report or observation; 3) the initial and most prominent cognitive deficits on history and examination was amnesia (defective episodic memory) and cognitive dysfunction, such as disorders of language (e.g., anomia) and/or visuospatial disorders; and 4) did not have evidence of a stroke, Lewy body dementia, frontotemporal lobar degeneration, or other known neurological diseases that can cause a cognitive decline.

From the 133 new patients seen between the specified dates, we excluded 27 patients who did not complete our evaluation and/or were not diagnosed with a specific disease that induced their cognitive disorder. From the remaining 106, we excluded 35 patients with histories that introduced confounding variables for olfactory dysfunction. This list included comorbid dementia or other neurological disorder, MRI evidence of a cerebral infarction or brain tumor, and any history of severe head injury with a loss of consciousness, hypoxia, seizures, or nasal polyps. Out of concern for their ability to understand the task, three patients with severe AD (MMSE <10) were also excluded. Based on these exclusionary criteria 68 patients were included.

For the purposes of this study we grouped the eligible patients into three groups; 18 diagnosed with probable AD (AD) [2, 3], 24 diagnosed with amnestic mild cognitive impairment (MCI) [27], and 26 patients diagnosed with various other causes of dementia (OD). The number of patients in each group was determined by the number of patients seen during the specified time period and by their diagnoses. Because this was a retrospective study on an existing data set, a power analysis was not done. To be clinically relevant we were looking for a large effect, which according to Keppel would need to reach significance with a number of 17 in each group to achieve a power of 0.80 [29]. The 26 cognitively normal control participants recruited from the community were age and gender matched to the probable AD patients, cognitively assessed with the FMSE, and screened using the same exclusionary criteria. All controls gave written, informed consent, a HIPAA waiver of consent was obtained for all patients, and the University of Florida Institutional Review Board approved the study. We followed the reporting guidelines set forth by the STROBE Statement for case-control, observational studies [30].

Apparatus

14 g of peanut butter, plain ground peanuts, within an air tight, one-ounce container was used as the olfactory stimulus. A 30 cm metric ruler was used to measure the distance from the nostril to the stimulus upon odor detection.

Procedure

The participants were instructed to close their eyes and mouth and to breathe normally through their nose without sniffing or inhaling deeply. They were asked to use their finger to close one nostril. The metric ruler was held up next to their open nostril and the stimulus carefully aligned within the participants' sagittal plane to avoid potential effects from possible hemispatial neglect. They were asked to inform the examiner when they first

detected an odor and if possible, to identify it. After their eyes, mouth, and one nostril were closed, the container of peanut butter was opened at the bottom of the ruler and moved up 1 cm upon each exhale until the person indicated that they detected the odor. The distance between the edge of the nostril and the top of the container was measured and recorded. The procedure was repeated with the other nostril after a 90 sec delay. In addition to providing precision, moving the stimulus up 1 cm/exhale helps provide equality of space and time of the odor plume for each patient.

To avoid bias, the person testing odor detection was never the same person who performed the cognitive testing, the physical neurological exam, or gathered any patient history, and was unaware of the diagnosis at the time of the testing. Additionally, the diagnosis of our patients was usually not confirmed until weeks after our initial clinical testing when these patients' lab and imaging results had been received.

Participants were allowed to choose the order their nostrils were tested as many patients with AD have left/right confusion and using these terms in the instructions would raise the cognitive load [27]. The nostril chosen first was not related to handedness ($t = 0.124$, $df = 92$, $p = 0.904$) nor did it differ from a random order generated by Excel ($t = -1.377$, $df = 206$, $p = 0.17$). Also, results for detection and recognition distance were similar and only the detection results will be discussed here. See the supplementary data for odor recognition distance and odor identification results.

Statistical analyses

T-tests were used to test whether handedness was related to the first nostril chosen and whether the nostril chosen by the patients differed from that assigned by random order. We performed an analysis of variance (ANOVA) with Fisher's PLSD post-hoc tests on age, gender, and years of education between our participant groups. We also conducted an ANOVA on the difference score of the left minus right nostril odor detection distance of each group. We ran a 2-way interaction multivariate analysis of variance (MANOVA) with the between subject factor being diagnostic group and within subject factor of detection distance of the left and right nostril. A Fisher's PLSD test was used for post-hoc analyses. We used the chi-square test to detect any significance between groups of the frequency distribution of participants' left minus right nostril odor detection difference. We calculated the sensitivity and specificity with a binary classification test using the left minus right nostril odor detection difference as the dichotomizing variable. 2-tailed Pearson's r tests were employed to examine correlations between odor detection distances of each nostril and cognitive tests scores. To test for order effects we used a Fisher's exact test. These analyses were performed with SPSS 21.0 (IBM, Armonk, NY) and StatView 5.01 (SAS Institute, Cary, NC) statistical software.

RESULTS

Demographics

The demographic descriptions and the cognitive testing scores for each group are described in Table 1. AD is more commonly diagnosed in women than men, possibly related to women having longer life expectancy [31]. We had significantly more women than men in our AD, OD, and matched control (OC) groups ($F(2,66) = 2.64$, $p = 0.035$) so that only the gender ratio of the AD group and the MCI group were significantly different from each other ($p = 0.007$). There were no significant age differences between groups. There were no significant differences among the three patient groups in the average years of education. However, the control group had significantly more years of education than the patient groups. We ran a multiple regression analysis to insure that the variable years of education,

was not significantly contributing to our variable of interest, an asymmetry of odor detection (left minus right nostril odor detection distance). Only diagnosis made a significant contribution to left minus right odor detection difference ($t = 4.861$, $p < 0.001$). Years of education did not ($t = 0.266$, $p = 0.791$).

Odor detection asymmetry in Alzheimer's

For participants with probable AD, the mean odor detection distance between the left nostril and the edge of the peanut butter container (5.1 cm) was significantly less than that of the other groups ($F(3,90) = 22.28$, $p < 0.0001$). In contrast, the mean detection distance of the right nostril of the probable AD patients (17.4 cm) was not different from the other groups (Table1).

An ANOVA confirmed that the mean difference of left minus right nostril odor detection distance was significantly different between groups ($F(3,90) = 28.33$, $p < 0.0001$) and that the AD group demonstrated significantly more asymmetry of odor detection between nostrils than all other groups due to a left nostril impairment ($p < 0.0001$) (Figure1). The mean, standard error of the mean, and 95% Confidence Intervals of the L R nostril odor detection difference (cm) for AD were −12.4 ±0.5, (−15.0, −9.8); for MCI were −1.9 ±1.2, (−4.2,0.4); for OD were 4.8 ±1.0, (2.6,6.9); and for OC were 0.0 ±1.4 (−2.2,2.1) (Figure 1). The frequency distribution of the L R nostril odor detection difference of the AD group was also significantly different from the OD group ($\chi^2(N=44) = 39.96$, $p < 0.0001$), the OC group ($\chi^2(N=44) = 29.91$, $p < 0.0001$), and even the MCI group ($\chi^2(N=42) = 18.68$, $p < 0.0001$) (Figure 2). No overlap existed between the AD group and the other groups.

Compared to patients with other causes of dementia this nostril asymmetry of odor detection unveiled by the UPBODT was 100% sensitive and 100% specific for probable AD. Compared to matched controls, it was 100% sensitive and 92% specific for probable AD (2 SE cutoff, using L R nostril odor detection difference to dichotomize). In fact, this level of sensitivity and specificity held true when the L R nostril detection difference was ≥ −5 cm.

In this study, all of the probable AD patients had a left nostril detection distance at least 5 cm less than their right nostril detection distance (Figure 2)(Table 2). However, in 14 out of the 18 probable AD patients the difference was ≥ −10 cm. The remaining four with a smaller L R nostril detection difference were also moderate to moderate-severe in their disease course. With MMSE scores of 10 and 11, these patients just missed the MMSE exclusionary cut-off score. In addition, the smaller difference was not a consequence of their left nostril being less impaired, but of their right nostril being more impaired than the other AD patients. For a diagnosis of early to moderate AD, a more definitive critical difference of left minus right nostril detection distance may be ≥ −10 cm.

Uni-rhinal odor detection and cognitive performance

Since the olfactory cortex is anatomically proximal to the areas important for episodic memory [8–12], we posited that odor detection might be more highly correlated with episodic memory than with other cognitive measures. We found significant positive correlations between the left nostril odor detection distance and tests that rely on left hemisphere functions like language and calculation (Table 1). The right nostril odor detection distance did not correlate with any of the cognitive measures we analyzed.

Dichotomous odor detection sensitivity in the MCI group

Ten MCI patients had the AD-like nostril asymmetry of odor detection and 14 did not (Figure 2). Even so, the mean L R nostril odor detection difference of the MCI group was significantly different from the AD group and the OD group ($p < 0.0001$) but not from the

OC group (Figure1). The frequency distribution of the MCI patients' L - R nostril odor detection difference was also significantly different from the AD group and the OD group (χ^2 (N=50) = 6.14, p = 0.013), but not from the OC group (χ^2(N=50) = 1.75, p = 0.186) (Figure 2).

Uni-rhinal odor detection in the other dementia group

The OD participants' performance on the UPBODT could also be divided into two major groups; 15 were symmetric across nostrils and 11 were asymmetric with the left nostril being better than the right, a pattern opposite of the participants with AD (Table 2). Overall, the left nostril was significantly better than the right nostril at odor detection in the OD group (p = 0.007) and was significantly better than the AD and the MCI groups' (p < 0.001) left nostril. However, it was not significantly different from the OC group's left nostril detection distance (Table 1). The mean L R nostril odor detection difference of the OD group was significantly different from that of the AD and MCI groups (p < 0.0001), as well as that of the OC group (p = 0.003) due to the OD patients that displayed an asymmetry with a right nostril odor detection impairment. (Figure 1). Significant difference was detected in the frequency distribution of the L R nostril odor detection differnce of the OD group compared to the AD group, the MCI group, and even to the OC group (χ^2 (N=52) = 4.15, p = 0.042)(Figure 2).

No order effects

To learn if nostril-testing sequence influenced performance, either because of foreknowledge and familiarity of the odor stimulus such that the second nostril is superior, or conversely that the second nostril tested is inferior because of adaptation effects, we compared the performance of the first versus the second nostril tested and found no significant difference (χ^2 (N = 94) = 0.04, p = 0.841).

DISCUSSION

A left nostril impairment of odor detection was present in all the patients with probable AD. This pattern of odor detection was not present in the older control group in which detection distances were symmetric across the nostrils and was absent in the patients with other dementias whose detection distances were either symmetric or asymmetric with a right nostril impairment. While the sensitivity and specificity of this peanut butter odor detection test appear promising for accurately diagnosing AD, at this point, time has not allowed us to determine if the outcomes of this simple test correlate with these participants' neuropathology or laboratory markers such as spinal fluid assays for amyloid-$\beta_{1–42}$ /tau. In order to properly determine sensitivity and specificity, these future studies need to be performed.

We found that ten of our 24 participants with MCI had the same nostril odor asymmetry as our participants with probable AD. A longitudinal study needs to be performed to determine the ability of this test to predict those patients with MCI that will later convert to AD. All of the participants in our three patient groups were already demented at the time of odor detection testing. Following cognitively normal older participants to see how far out this simple test may predict those who will later develop AD would also be informative. Both studies could prove extremely valuable for clinical trials investigating methods to prevent AD.

Besides helping to detect early Alzheimer's, this simple diagnostic tool may also help track the course of the disease. The asymmetry was greatest at the earlier phases of the disease

course. As the disease progressed, the right nostril became more impaired at odor detection thereby resulting in a decrease of asymmetry.

Systematic studies of olfactory function for diagnostic purposes found AD to be positively associated with olfactory dysfunction. Unfortunately, because of confounding variables of olfactory dysfunction and the fact that olfactory dysfunction occurs with many neurological disorders associated with dementia [32–39], the predictive value of olfactory testing for AD was deemed limited [38–40]. The odor detection test used in most studies has been a threshold task that requires more time than a clinic visit allows and informs of the lowest concentration the odor can be detected, not the farthest distance. No study has combined a unirhinal method with a stimulus that can solely be detected by the olfactory nerve, and none have measured the distance of odor detection. Previous findings that in AD, odor identification correlated more with neuropsychological tests and was effected earlier than olfactory detection thresholds tested bi-rhinally [13,32,38,39,41], are consistent with our finding that odor detection in the right nostril of early to moderate AD patients is not different from cognitively normal controls. Also, we looked at several of the neuropsychological tests that are often associated with AD and found them to be correlated with the odor detection distance of the left nostril and not the right.

A study by Bahar-Fuchs and coworkers [42] compared unirhinal tests of odor identification and odor memory between AD patients, MCI patients, and healthy controls. They reported that while healthy controls performed the best and AD patients performed the worst on odor identification, the disparity did not depend on nostril side. While not reported by these investigators, within their data was evidence that olfactory memory was significantly worse in the left nostril than the right nostril in both the AD and MCI groups, but was not different between nostrils in the healthy controls [42]. They did not test odor detection.

One caveat to the UPBODT as a diagnostic tool is that it cannot be reliably used in patients with comorbid dementias or that have a history of any other common cause of olfactory loss besides aging. The olfactory test used in this study was designed to overcome the impracticalities that normally inhibit olfactory testing during a typical clinic visit. In the future, investigators using more formal, closed-circuit devices such as an olfactometer, may want to determine the relationship between odor detection in AD and MCI and the degree of atrophy in the olfactory and entorhinal cortices. Another caveat to this and the voxel based morphometric studies of atrophy may be that left hemisphere deficits are more easily detected by patients and their loved ones than right hemisphere deficits. This detection asymmetry may induce AD patients with left hemispheric dysfunction to seek medical attention sooner than those with right hemispheric dysfunction.

Primary olfactory cortex is one of the first sites of pathology in AD [10–12]. In contrast, the primary visual and auditory cortices are usually spared in people with AD. Except for the olfactory cortex, it is primarily the hippocampus, portions of the default network, and sensory association cortices that deteriorate in patients with AD. Thus the only sensory test that may be sensitive and specific for AD are tests of olfaction and this quick, non-invasive, left-right nostril peanut butter odor detection test may be an ideal instrument for the early detection of AD. Future studies will be needed to replicate our major findings as well as assess this test's ability to predict AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported, but in no way influenced, by the NIH/NCRR Clinical and Translational Science Award to the University of Florida UL1 RR029890 and by the State of Florida Memory Disorders Program.

We are grateful to the patients, staff, fellows, and volunteers at the Memory and Cognitive Disorders Clinic at the University of Florida. We thank our Director, Leilani Doty, for her advice and assistance.

References

1. Alzheimer's Disease Education & Referral (ADEAR) Center, A service of the National Institute on Aging, National Institute of Health, US Department of Health and Human Services. Alzheimer's Disease Fact Sheet. 2012 Sep 26. [updated, 2012 Nov 26; cited, 2013 March 27]. Available from: http://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet
2. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services task force on Alzheimer's disease. Neurology. 1984; 34:939–44. [PubMed: 6610841]
3. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, 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 work groups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May; 7(3):263–9. [PubMed: 21514250]
4. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergström M, Savitcheva I, Huang GF, Estrada S, Ausén B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Langström B. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004 Mar; 55(3):306–19. [PubMed: 14991808]
5. Blennow K. Cerebrospinal fluid biomarkers for Alzheimer's disease. NeuroRx. 2004 Apr; 1(2):213–25. [PubMed: 15717022]
6. Rowe CC, Villemagne VL. Brain amyloid imaging. J Nucl Med. 2011 Nov; 52(11):1733–40. [PubMed: 21917849]
7. Irwin DJ, McMillan CT, Toledo JB, Arnold SE, Shaw LM, Wang LS, Van Deerlin V, Lee VM, Trojanowski JQ, Grossman M. Comparison of cerebrospinal fluid levels of Tau and Aβ 1–42 in Alzheimer disease and frontotemporal degeneration using 2 analytical platforms. Arch Neurol. 2012 Aug; 69(8):1018–25. [PubMed: 22490326]
8. Allison AC. The secondary olfactory areas in the human brain. J Anat. 1954 Oct; 88(4):481–8. [PubMed: 13211468]
9. Carmichael ST, Clugnet MC, Price JL. Central olfactory connections in the macaque monkey. J Comp Neurol. 1994 Aug; 346(3):403–34. [PubMed: 7527806]
10. Ferreyra-Moyano H, Barragan E. The olfactory system and Alzheimer's disease. Int J Neurosci. 1989 Dec; 49(3–4):157–97. [PubMed: 2700477]
11. Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging. 1991 Jul-Aug;12(4):295–312. [PubMed: 1961359]
12. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging. 1995 May-Jun;16(3):271–8. discussion 278–84. [PubMed: 7566337]
13. Graves AB, Bowen JD, Rajaram L, McCormick WC, McCurry SM, Schellenberg GD, Larson EB. Impaired olfaction as a marker for cognitive decline: interaction with apolipoprotein E epsilon4 status. Neurology. 1999 Oct; 53(7):1480–7. [PubMed: 10534255]
14. Tabert MH, Liu X, Doty RL, Serby M, Zamora D, Pelton GH, Marder K, Albers MW, Stern Y, Devanand DP. A 10-item smell identification scale related to risk for Alzheimer's disease. Ann Neurol. 2005 Jul; 58(1):155–60. [PubMed: 15984022]

15. Davidson TM, Murphy C. Rapid clinical evaluation of anosmia-the alcohol sniff test. Arch Otolaryngol Head Neck Surg. 1997 Jun; 123(6):591–4. [PubMed: 9193218]
16. Davidson TM, Freed C, Healy MP, Murphy C. Rapid clinical evaluation of anosmia in children: the alcohol sniff test. Ann N Y Acad Sci. 1998 Nov.855:787–92. [PubMed: 9929685]
17. Shipley M, Ennis M. Functional organization of the olfactory system. J Neurobiol. 1999 May; 30(1):123–76. [PubMed: 8727988]
18. Mori K, Nagao H, Yoshihara Y. The olfactory bulb: coding and processing of odor molecule information. Science. 1999 Oct; 286(5440):711–5. [PubMed: 10531048]
19. Whitwell JL, Przybelski SA, Weigand SD, Knopman DS, Boeve BF, Petersen RC, Jack CR Jr. 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. Brain. 2007 Jul; 130(Pt 7):1777–86. [PubMed: 17533169]
20. Ferreira LK, Diniz BS, Forlenza OV, Busatto GF, Zanetti MV. Neurostructural predictors of Alzheimer's disease: A meta-analysis of VBM studies. Neurobiol Aging. 2011 Oct; 32(10):1733–41. [PubMed: 20005012]
21. Rami L, Solé-Padullés C, Fortea J, Bosch B, Lladó A, Antonell A, Olives J, Castellví M, Bartres-Faz D, Sánchez-Valle R, Molinuevo JL. Applying new research diagnostic criteria: MRI findings and neuropsychological correlations of prodromal AD. Int J Geriatr Psychiatry. 2012 Feb; 27(2): 127–34. [PubMed: 21384432]
22. Doty L, Bowers D, Heilman KM. Florida Mental Status Exam for progressive dementia screening. Gerontologist. 1990; 30(Special issue):20A.
23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov; 12(3):189–98. [PubMed: 1202204]
24. Brandt J. The Hopkins Verbal Learning Test: development of a new memory test with six equivalent forms. Clin Neuropsychol. 1991; 5(2):125–42.
25. Kaplan, EF.; Goodglass, H.; Weintraub, S. The Boston Naming Test. 2. Philadelphia (PA): Lea and Febinger; 1983.
26. Benton AL. Development of a multilingual aphasia battery: progress and problems. J Neurol Sci. 1969; 9:39–48. [PubMed: 5820858]
27. Benton AL. Gerstmann's syndrome. Arch Neurol. 1992; 49:445–7. [PubMed: 1580804]
28. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999 Mar; 56(3):303–8. [PubMed: 10190820]
29. Keppel, G.; Wickens, TD. Design and Analysis: a researcher's handbook. 4. Upper Saddle River (NJ): Pearson Prentice Hall; 2004.
30. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M. STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med. 2007 Oct 16; 147(8):W163–94. [PubMed: 17938389]
31. Hebert LE, Scherr PA, McCann JJ, Beckett LA, Evans DA. Is the risk of developing Alzheimer's disease greater for women than for men? Am J Epidemiol. 2001 Jan; 153(2):132–6. [PubMed: 11159157]
32. Knupfer L, Spiegel R. Differences in olfactory test performance between normal aged, Alzheimer and vascular type dementia individuals. Int J Geriatr Psychiatry. 1986; 1:3–14.
33. Moberg PJ, Pearlson GD, Speedie LJ, Lipsey JR, Strauss ME, Folstein. Olfactory recognition: differetial impairments in early and late Huntington's and Alzheimer's diseases. J Clin Exp Neuropsychol. 1987 Dec; 9(6):650–64. [PubMed: 2961789]
34. Razani J, Murphy C, Davidson TM, Grant I, McCutchan A. Odor sensitivity is impaired in HIV-positive cognitively impaired patients. Physiol Behav. 1996 Apr-May;59(4–5):877–81. [PubMed: 8778881]
35. Bailie JM, Gilbert PE, Murphy C. Odor identification deficits in Lewy body variant of Alzheimer's disease. J Int Neuropsychol Soc. 2003; 9:164–5.

36. Hulshoff Pol HE, Hijman R, Tulleken CA, Heeren TJ, Schneider N, van Ree JM. Odor discrimination in patients with frontal lobe damage and Korsakoff's syndrome. Neuropsychologia. 2002; 40(7):888–91. [PubMed: 11900740]

37. Luzzi S, Snowden JS, Neary D, Coccia M, Provinciali L, Ralph MAL. Distinct patterns of olfactory impairment in Alzheimer's disease, semantic dementia, frontotemporal dementia, and corticobasal degeneration. Neuropsychologia. 2007 Apr; 45(8):1823–31. [PubMed: 17270222]

38. Rahayel S, Frasnelli J, Joubert S. The effect of Alzheimer's disease and Parkinson's disease on olfaction: A meta-analysis. Behav Brain Res. 2012 Mar.231:60–74. [PubMed: 22414849]

39. Mesholam RI, Moberg PJ, Mahr RN, Doty RL. Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. Arch Neurol. 1998 Jan; 55(1):84–90. [PubMed: 9443714]

40. 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 Jul; 122(7): 1455–62. [PubMed: 22552846]

41. Koss E, Weiffenbach JM, Haxby JV, Friedland RP. Olfactory detection and identification performance are dissociated in early Alzheimer's disease. Neurology. 1988 Aug; 38(8):1228–32. [PubMed: 3399073]

42. Bahar-Fuchs A, Moss S, Rowe C, Savage G. Olfactory performance in AD, aMCI, and healthy ageing: a unirhinal approach. Chem Senses. 2010 Nov; 35(9):855–862. [PubMed: 20870956]

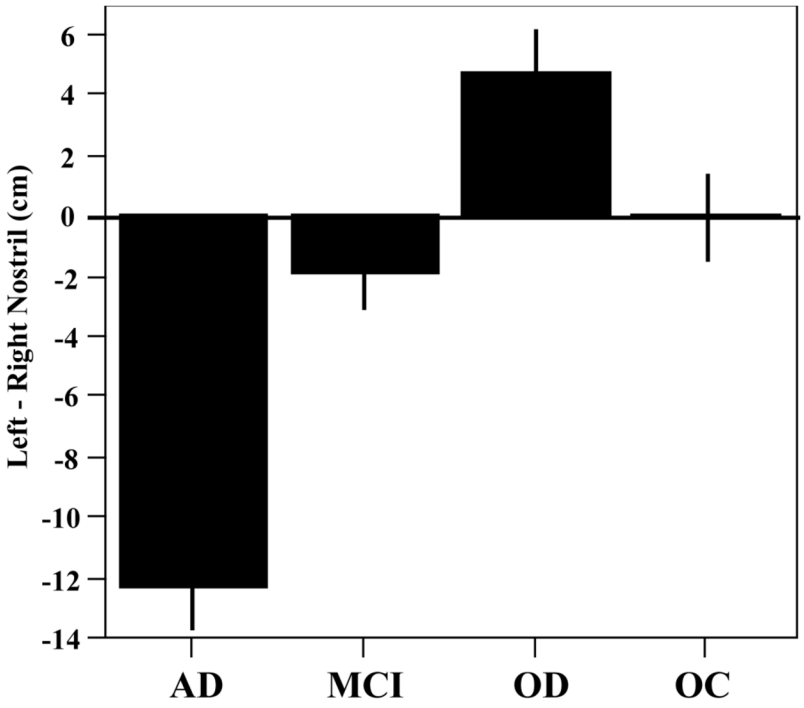

Figure 1. The mean L R nostril odor detection difference (cm) for each group

AD is Alzheimer's disease, MCI is mild cognitive impairment, OD is other dementias, and OC is older controls. ANOVA confirmed a significant difference between groups ($F(3,90) = 28.33$, $p < 0.0001$) and the L R nostril detection difference of the AD patients was significantly larger than all other groups ($p < 0.0001$).

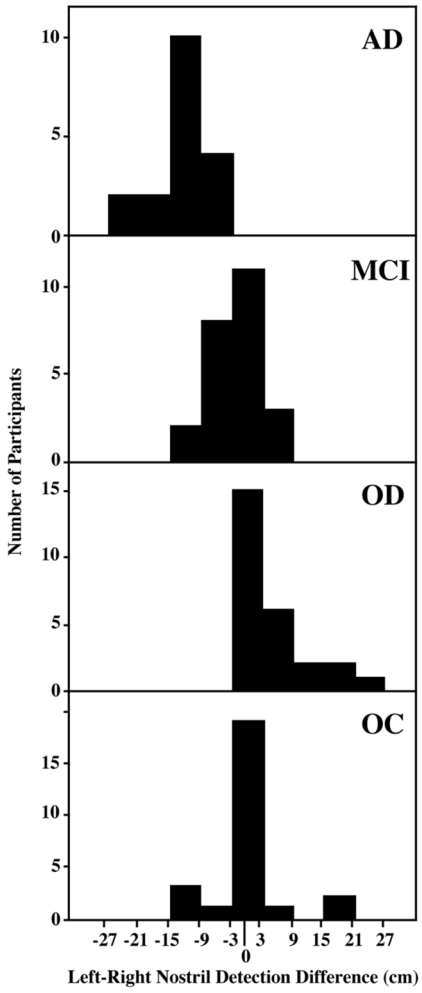

Figure 2. Frequency distribution of the difference score of the L R nostril detection distance (cm) for each group

The frequency distribution of the AD group is significantly different from all other groups, Fisher's test of the χ^2, $p < 0.0001$.

Table 1

Characteristics of the participants & Correlations between odor detection distances and cognitive test scores.

	AD N = 18	MCI N = 24	OD N = 26	OC N = 26	Corr. With R nostril	Corr. With L nostril
L nostril (cm)	5.1 ± 4.9	15.0 ± 10.7	20.2 ± 8.5	18.0 ± 9.1		
R nostril (cm)	17.4 ± 6.6	17.0 ± 10.2	15.5 ± 9.7	17.9 ± 8.7		
Age	75.5 ± 9.7	74.5 ± 10.5	70.7 ± 7.8	69.1 ± 9.6		
Sex	15 F/3 M	10 F/14 M	16 F/10 M	17 F/11 M		
Education (yrs)	15.3 ± 6.3	15.4 ± 2.9	15.7 ± 3.1	17.9 ± 3.0		
MMSE	19.2 ± 4.8	26.2 ± 2.6	25.3 ± 5.1	29.2 ± 0.8	.140	.338**
Gerstmann's	4.4 ± 2.3	7.1 ± 1.7	6.8 ± 2.7	8.5 ± 1.1	.128	.303**
BNT	36.8 ± 14.7	52.4 ± 6.7	48.3 ± 13.4	59.3 ± 1.5	.095	.294**
HVLT learning	11.3 ± 5.5	18.1 ± 5.4	17.9 ± 7.3	28.7 ± 4.8	.106	.286**
HVLT delay	0.6 ± 1.4	3.7 ± 3.7	5.1 ± 3.8	10.3 ± 1.9	.018	.240*
HVLT recognize	4.7 ± 2.5	7.24 ± 3.4	8.46 ± 2.8	11.2 ± 1.1	.042	.281**
Category fluency	8.5 ± 4.2	12.9 ± 4.1	12.2 ± 4.5	23.0 ± 4.4	.123	.241*
Word fluency	24.6 ± 12.1	34.3 ± 10.9	23.7 ± 13.6	46.4 ± 13.5	.131	.095

Deomographic, odor detection distances (cm), and test score data are mean ± SD. Corr = 2-tailed Pearson's Correlations, r.

* significance at $p < 0.03$,

** significance at $p < 0.01$

AD = Alzheimer's disease, MCI = mild cognitive impairment, OD = other dementias, OC = matched controls, MMSE = Mini Mental State exam (high score = 30), a Gerstmann's syndrome "score", a subscore within the FMSE (high score = 9, did not include agraphia), BNT = Boston Naming Test (high score = 60), HVLT = Hopkin's Verbal Learning Test (high score = 36 for learning, 12 for delay, 12 for recognition) category-semantic fluency, and the letter-word fluency test from the Controlled Oral Word Association. For all tests, a higher score indicates better

Table 2

Odor detection symmetry across nostrils of each group.

	Symmetric	Asymmetric Left worse	Asymmetric Right worse
AD	**0**	**18**	**0**
MCI	**11**	**10**	**3**
OD	**15** (3 corticobasal degeneration, 3 Parkinson-dementia complex disease, 2 frontotemporal lobar degeneration, 2 vascular dementia, 1 depressive pseudo-dementia, 1 Hashimoto's encephalopathy, 1 hemachromatosis, 1 posterior cortical atrophy, 1 Fahr's disease)	**0**	**11** (5 corticobasal degeneration, 2 iatrogenic on anti-cholinergic medications, 1 depressive pseudo-dementia, 1 Hashimoto's encephalopathy, 1 Lewy-body dementia, 1 semantic dementia)
OC	**21**	**2**	**3**

To be considered symmetric, the difference between the R and L nostril odor detection distance was ≤ 3 cm. To be considered asymmetric, the difference between a person's R and L nostril odor detection distance was ≥ 4 cm.