Validation of olfactory deficit as a biomarker of Alzheimer disease

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Abstract

Background: We evaluated smell identification as a biomarker for Alzheimer disease (AD) by assessing its utility in differentiating normal aging from an amnesic disorder and determining its predictive value for conversion from amnesic mild cognitive impairment (aMCI) to AD. **Methods:** Cross-sectional study (AD = 262, aMCI = 110, controls = 194) measuring smell identification (University of Pennsylvania Smell Identification Test [UPSIT]) and cognitive status was performed, as well as longitudinal analysis of aMCI participants (n = 96) with at least 1 year follow-up (mean 477.6 ± 223.3 days), to determine conversion by National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria. **Results:** Odor identification and disease status were highly correlated after correcting for age, sex, and APOE ($p < 0.001$). Receiver operating characteristic (ROC)/area under the curve (AUC) was similar for the 40-item UPSIT, the top 10 smells in our study, and the 10-item subset previously proposed. Smeller/nonsmeller based on the 10-item subset with a cutoff of 7 (≤ 7 , nonsmeller; > 7 , smeller) had a sensitivity and specificity of 88% and 71% for identifying AD and 74% sensitivity and 71% specificity for identifying an amnesic disorder. A total of 36.4% of participants with impaired olfaction and 17.3% with intact olfaction converted to AD ($p = 0.03$). The ROC/AUC for prediction of conversion to AD was 0.62. **Conclusions:** Olfactory identification deficit is a useful screening tool for AD-related amnesic disorder, with sensitivity and specificity comparable to other established biomarkers, with benefits such as ease of administration and low cost. Olfactory identification deficit can be utilized to stratify risk of conversion from aMCI to AD and enrich clinical trials of disease-modifying therapy. **Classification of evidence:** This study provides Class III evidence that smell identification (10-item UPSIT subset) accurately identifies patients with amnesic disorders. *Neurol Clin Pract* 2017;7:5–14

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article** at Neurology.org/cp.

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Alzheimer disease (AD) is the most common form of dementia and leads to unrelenting cognitive decline.¹ With increased longevity, the prevalence of AD in the elderly represents a major public health problem.² At the time of clinical diagnosis, neuronal loss is marked, and disease-modifying therapy under development is thought to be most useful early in the disease course.^{3,4} Olfactory deficit has been studied in aging, mild cognitive impairment (MCI), and AD.⁵ Odor identification appears to be the most sensitive method to measure olfactory dysfunction.⁶ Clinical observations suggest that approximately 85% of patients with early-stage AD exhibit olfactory dysfunction.⁷ Prospective cohort studies established that olfactory deficit infers risk for development of cognitive impairment.^{8–10} Olfactory deficit, defined as University of Pennsylvania Smell Identification Test (UPSIT) score ≤ 34 out of 40, in participants with MCI predicted conversion to AD at 2-year follow-up.¹¹ Congruent with the early olfactory loss of AD are pathologic changes in the olfactory bulb and anterior olfactory nucleus, specifically cell loss and the presence of neuritic plaques and neurofibrillary tangles.¹² Although the mechanism by which olfactory deficit is related to AD is unclear, retrograde neurodegenerative process or a shared vulnerability of the cholinergic systems have been proposed.¹³

In this study, we assessed if olfactory deficit can differentiate normal aging from an amnesic disorder (AD and amnesic MCI [aMCI]) and if olfactory deficit can be used for risk stratification for conversion to AD.

METHODS

Study participants

A total of 576 patients participated in this multicenter study. Ten participants were excluded for diagnosis of nonamnesic MCI. The diagnosis of aMCI was based on the Petersen criteria.¹⁴ Probable AD was diagnosed based on National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.¹⁵ Furthermore, clinical diagnoses were confirmed by consensus among the clinical team at each study site. The methodology of the Texas Alzheimer Research and Care Consortium project has been described.¹⁶ Exclusion criteria included a Hachinski score >4 and clinical or imaging evidence of a stroke, as well as patients with active cold or allergies. History of head trauma and smoking in pack-years were captured. The control group consisted of participants without dementia; inclusion criteria were the following: age over 65 years, normal performance on activities of daily living, and Clinical Dementia Rating global score 0 (by surrogate historian). Control participants underwent neuropsychological testing (NPT) and were excluded if any measure had a Z score < -1.5 .

Standard protocol approvals and participant consents

Institutional ethical standards committee on human experimentation at each site approved the study and written informed consent was obtained from each research participant. Due to the vulnerable population, for participants with Mini-Mental State Examination (MMSE) score <18 , after verbal assent from the participant the legally authorized representative consented.

Longitudinal subset of participants with aMCI

A total of 129 participants with aMCI were recruited. Ninety-six participants with aMCI were available for follow-up with an approximately 1-year interval for repeat NPT and clinical assessment. Clinical diagnoses were revised after each follow-up visit and repeat NPT based on the Peterson and NINCDS-ADRDA criteria. Conversion was defined as the participant meeting NINCDS-ADRDA criteria for AD at follow-up.

University of Pennsylvania Smell Identification Test

Odor identification was measured by the UPSIT at the time of enrollment, within 3 months of the NPT.¹⁷ The UPSIT is a 40-item scratch-and-sniff smell identification test with forced

Odor identification deficit was independent from APOE status, history of head trauma, and smoking.

selection multiple choice format. The packets were obtained from Sensonics (Haddon Heights, NJ).

Neuropsychological testing

Demographic information including age, sex, race, ethnicity, history of smoking in pack-years, education, and history of head trauma were gathered on each participant. The following neuropsychological tests were administered: global cognitive functioning/status (MMSE and Clinical Dementia Rating),^{18,19} attention (Digit Span and Trail-Making Test Part A),^{20,21} executive function (Trail-Making Test Part B),²¹ memory (Wechsler Memory Scale [WMS3 or R] Logical Memory I story A and WMS3 or R Logical Memory II story A),²² language (Boston Naming Test and FAS Verbal Fluency),^{23,24} premorbid IQ (American National Adult Reading Test),²⁵ visuospatial memory (WMS–Visual Reproduction I and II),²² psychiatric (Geriatric Depression Scale),²⁶ functional assessment (Lawton-Brody Activities of Daily Living, Physical Self-Maintenance Scale, Instrumental Activities of Daily Living).²⁷ Testing was administered by board-certified neuropsychologists and research staff under the supervision of neuropsychologists. The UPSIT and NPT assessments were performed by 2 independent individuals who were naive to the diagnosis.

APOE genotyping

Genomic DNA was extracted from whole blood with the Puregene DNA isolation kit (Qiagen, Venlo, Netherlands). *APOE* genotyping was performed using real-time PCR according to the manufacturer's instructions. The amplifications were done on an ABI 7900HT thermal cycler (Applied Biosystems, Foster City, CA). The custom TaqMan probes (Applied Biosystems) were unique to single nucleotide polymorphisms at nucleotide positions 112 (rs7412) and 158 (rs429358) of the *APOE* gene, respectively. The combination of alleles at the 2 polymorphisms determined the *APOE* genotype.

Statistical analysis

Demographic characteristics, including age, sex, MMSE, years of education, and *APOE* allele frequency, were analyzed using a one-way analysis of variance with a Tukey honestly significant difference post hoc test. Differences in age at onset between patients with MCI and AD were examined using a Student *t* test. Correlation trend test was used to determine the relationship between the total UPSIT score and disease categories. Age, sex, and *APOE* were added as covariates into the model. A receiver operating characteristic (ROC) curve was generated and the area under the curve (AUC) was calculated for the 40-item test. A parameter selection procedure based on logistic regression model was used to identify the top 10 smells. This methodology was based on the analysis performed by Tabert et al.²⁸ ROC curves were generated for our top 10 smells and the 10-item subset proposed by Tabert et al.²⁸ AUC was calculated for the top 10 smells and contrasted to the 40-item test. Smellers (>7) and nonsmellers (≤7) were defined based on the AUC to optimize sensitivity and specificity. Sensitivities and specificities were examined comparing normal controls (NC) to patients with amnesic disorders (aMCI and AD), as well as NC vs AD to assess utility of the full UPSIT and 10-item subsets as screening tools.

Wilcoxon rank-sum test was used to compare the Logical Memory story A1 and A2 between smellers and nonsmellers in each disease category, as the distribution of the data deviated from normality. In the longitudinal section of the study, participants with MCI were reevaluated yearly. Conversion rate between smellers and nonsmellers was compared using the Fisher exact

Supplemental Data

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test for count data. Additionally, sensitivities and specificities were calculated for the full UPSIT and the 10-item subsets to examine utility as a screening tool for conversion from aMCI to AD. A p value of 0.05 was considered significant in this study.

RESULTS

The study flowchart is depicted in figure 1. Demographic characteristics are presented in table 1. *APOE* frequencies in each disease category were similar to previous reports. Demographic characteristics were comparable between groups. Age was different between control and disease groups; however, age was added to each statistical model to correct for the effect of age on smell sensation. Odor identification deficit was independent from *APOE* status, history of head trauma, and smoking. Disease status and total UPSIT were highly correlated ($p < 0.001$), and this correlation remained after adding age, sex, and number of *APOE4* alleles into the regression model ($p < 0.001$). The top 10 smells identified in the parameter selection procedure based on the logistic regression model to differentiate between groups are depicted in table e-1 at Neurology.org/cp. The ROC AUC for the 40-item UPSIT, the top 10 smells in the current study, and the 10-item subset proposed by Tabert et al. were 0.84, 0.83, and 0.80, respectively (figure 2A). The sensitivities and specificities for each previously reported cutoff are depicted in table 2. The cutoff of 7 for smeller vs nonsmeller (inclusive) resulted in a sensitivity of 74% and a specificity of 71% for predicting an amnesic disorder vs healthy controls. The ROC AUC for the 40-item UPSIT, our top 10 smells, and the 10 items proposed by Tabert et al. were 0.91, 0.90, and 0.87, respectively, in predicting AD vs normal control (figure 2B). The sensitivity and specificity for our 10-item subset were 88% and 71%, respectively, for predicting AD vs NC. The previously reported 10-smell subset¹⁸ was comparable with the top 10 smells identified by

Figure 1 Study flow of participants

Ten participants were excluded due to non-amnesic mild cognitive impairment (MCI) diagnosis. All participants completed the University of Pennsylvania Smell Identification Test (UPSIT) and neuropsychological testing.

Table 1 Demographic data

	Total	NC	MCI	AD
No. of patients	566	194	110	262
Age, y, mean $\pm$ SD	74.17	72.29 $\pm$ 8.41	74.05 $\pm$ 9.03	75.62 $\pm$ 8.29 ^a
Age at onset, y, mean $\pm$ SD	NA	NA	69.07 $\pm$ 9.09	69.05 $\pm$ 8.26
% Female	56.36	69.59 ^{b,c}	48.18 ^a	50 ^a
Years of education, mean $\pm$ SD	15.34	15.96 $\pm$ 2.38 ^{b,c}	14.95 $\pm$ 2.69 ^a	15.03 $\pm$ 2.84 ^a
MMSE score, mean $\pm$ SD	25.90	29.15 $\pm$ 1.29 ^{b,c}	27.63 $\pm$ 2.07 ^{a,c}	22.76 $\pm$ 3.69 ^{a,b}
40-Item UPSIT, mean $\pm$ SD	25.21	32.32 $\pm$ 5.47 ^{b,c}	28.01 $\pm$ 7.97 ^{a,c}	18.76 $\pm$ 7.91 ^{a,b}
10-Item SIT, mean $\pm$ SD	6.25	8.23 $\pm$ 1.59 ^{b,c}	7.09 $\pm$ 2.26 ^{a,c}	4.41 $\pm$ 2.33 ^{a,b}
APOE4 allele frequency	0.28	0.1295 ^{b,c}	0.2431 ^{a,c}	0.4085 ^{a,b}

Abbreviations: AD = Alzheimer disease; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NC = normal control; SIT = Smell Identification Test; UPSIT = University of Pennsylvania Smell Identification Test.

^a $p < 0.01$, Comparison to NC.

^b $p < 0.01$, Comparison to MCI.

^c $p < 0.01$, Comparison to AD.

our group. Four smells overlapped with those reported by Tabert et al.: clove, strawberry, lemon, and soap (table e-1). Comparison with other AD biomarkers is depicted in table e-2.

There was a trend for lower memory scores in nonsmellers when compared to smellers in each diagnostic category ($p < 0.05$, uncorrected) in LMA1 in the NC and AD groups (figure 2, C and D). All other cognitive domains were not found to be correlated ($p > 0.05$).

In the longitudinal portion of the study, 17.3% of smellers and 36.4% of nonsmellers ($p = 0.03$) converted with a mean follow-up of 485.9 days for smellers and 467.8 days for nonsmellers (table 3). ROC AUC for conversion of aMCI to AD within the follow-up period was 0.61, 0.62, and 0.65 based on the 40-item, our 10-item, and the Tabert et al. 10-item UPSIT, respectively. These are compared with other biomarkers to predict conversion from aMCI to AD in table e-3. Of note, the conversion rate within the first 2 years of follow-up was 2.5 times higher in the nonsmeller group (25% compared to 9.62%).

DISCUSSION

We found that the 40-item UPSIT was useful for differentiating cases and controls, as well as for predicting the short-term conversion of participants with aMCI to AD, thus confirming prior work in a large dataset.

The ROC AUC for the 40-item UPSIT was comparable to the top 10 items for both identifying an amnesic disorder and AD; this is important as the length of time for administering the test is decreased by 75% to approximately 5 minutes. The sensitivities and specificities for each previously reported cutoff is comparable as well and replicates previous reports.²⁸ The ROC AUC for the detection of AD vs controls is only slightly inferior to other, more invasive biomarkers.^{29–36} The sensitivity and specificity of the 10-item short form is optimal at the cutoff of 7, similar to the alternative 10 reported by Tabert et al.²⁸ The Tabert et al.²⁸ top 10 resulted in similar AUC and has 4-item overlap with our set. Thus, the Tabert et al. top 10 provides an alternative test with similar performance, establishing the basis for retesting.

We extend the results of prior studies by showing that in the smeller and the nonsmeller groups, differences were detected in logical memory, suggesting that odor identification deficit is associated with the amnesic phenotype, thus the classic AD presentation. In previous work,³⁷

Figure 2 Receiver operating characteristic (ROC) curves and performance of the 3 groups

(A, B) ROC curves for 3 smell test algorithms (top 10 smells in the current study, 10-item subset proposed by Tabert et al., and the 40-item University of Pennsylvania Smell Identification Test [UPSIT]). (A) Amnesic disorder vs normal control (NC); (B) Alzheimer disease (AD) vs NC. (C, D) Performance of the 3 groups (MCI = mild cognitive impairment) on (A) immediate (LMA1) and (B) delayed (LMA2) recall of the logical memory test. Smell status within each group is depicted by color (smeller, beige; nonsmeller, red). In each disease category, smellers performed better than the nonsmellers. *Statistically significant differences ($p < 0.05$).

we showed a relationship between age at onset of AD and copy number variations in the family of olfactory receptors. Both observations suggest that the olfactory system could be involved in the early pathophysiologic process.

The simplicity of the test and the low cost involved, supplemented by the availability of an alternate form, may make it a useful screening tool. Identified at-risk participants could be referred for more costly and invasive assessments and false-positives could be eliminated at that step. False-negatives might be captured with longitudinal observation or decline of smell sensation over time, and need to be studied to answer this question.

The ultimate measure of a biomarker is its predictive value, and the most studied area in AD is the conversion from MCI to AD.^{29–36} The 10-item smell test performs similarly to the more invasive and expensive biomarkers: it is somewhat inferior to structural MRI (ROC AUC of

Table 2 Sensitivity and specificity values: Comparison among the proposed 10-item smell test, 10-item smell test proposed by Tabert et al., and the 40-item University of Pennsylvania Smell Identification Test (UPSIT)

10-Item SIT								
Smell test cutoff scores	Amnestic disorder vs normal control				Alzheimer disease vs normal control			
	Current study		Tabert et al.		Current study		Tabert et al.	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
>9	96.49	22.68	92.70	27.84	98.46	22.68	96.92	27.84
>8	86.76	53.61	81.62	56.70	94.23	53.61	89.23	56.70
>7	73.78	70.62	68.28	79.90	87.69	70.62	80.77	79.90
>6	66.22	87.11	55.95	90.21	80.38	87.11	68.85	90.21
40-Item UPSIT								
Smell test cutoff scores	Amnestic disorder vs normal control		Alzheimer disease vs normal control					
	Sensitivity, %		Specificity, %		Sensitivity, %		Specificity, %	
>33	88.64		55.91		95.63		55.91	
>32	85.32		61.29		94.84		61.29	
>31	81.72		67.20		93.25		67.20	
>30	78.67		73.12		90.08		73.12	
>29	72.30		76.34		86.51		76.34	

Abbreviation: SIT = Smell Identification Test.

0.69–0.73) and similar to CSF biomarkers (ROC AUC of 0.63–0.67).³⁴ Conversion rate was 2.5 times higher in the nonsmeller group compared to smellers at 2 years. Considering the low cost and ease of administration, the smell test may serve as a tool to enrich MCI populations in clinical trials addressing disease-modifying therapy. The more than doubling of conversion events in nonsmellers within 2 years of follow-up could reduce the sample size of disease-modifying therapy trials in half. Studies suggest that 90% of AD is associated with olfactory deficit; thus clinical trials using this strategy would be applicable to the majority of patients. Furthermore, as olfactory deficit is independent of *APOE* status, its utility for risk stratification is promising.

Strengths of the study are the large sample size, multicenter design, and longitudinal clinical follow-up with detailed neuropsychological evaluation. Weaknesses include the age difference

Table 3 Mild cognitive impairment (MCI) conversion to Alzheimer disease in smellers vs nonsmellers based on the 10-item subset, cutoff of 7, smeller (inclusive)

	Total	Smellers	Nonsmellers
No. of MCI	96	52	44
No. of converters	25	9	16
Mean follow-up, d	477.58	485.90	467.75
% Converters	26.04	17.31	36.36

Considering the low cost and ease of administration, the smell test may serve as a tool to enrich MCI populations in clinical trials addressing disease-modifying therapy.

between the disease categories; however, it is biologically logical and we corrected for age in the statistical models. Additionally, it is possible that medical conditions or prescription drug use can affect olfactory function. While this could potentially add increased noise to the data, the sampling is continuous, with a large sample size and robust results. Longitudinal studies exploring the time relationship between the trajectory of decline in olfactory identification and the development of an amnestic disorder are needed to further characterize the relationship and evaluate its utility. Interestingly, UPSIT top smells tend to vary between studies, indicating that specific smells may be more sensitive in certain cultural contexts. The proposed 10 smells were studied in an English-speaking North American cohort, and extending these findings to other populations requires caution.

Overall, AD is a major public health issue affecting over 6 million people. Due to its insidious onset, superimposed on normal aging, diagnosis is often delayed. Other AD biomarkers are not as practical as screening tools due to cost, complexity, or invasiveness. Early identification of amnestic disorders, along with proper disease management and the promise of disease-modifying therapy, could greatly lessen the burden on the health care system. Thus, an inexpensive, short test, with an alternate form that can be administered during a yearly well visit in the primary care physician's office with relative ease, such as the 10-item subset of the UPSIT, would be invaluable.

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Received February 4, 2016. Accepted in final form June 20, 2016.

AUTHOR CONTRIBUTIONS

M.R. Woodward: acquisition of data, analysis and interpretation, writing of manuscript. C.V. Amrutkar: acquisition of data, analysis and interpretation, writing of manuscript. H. Shah: acquisition of data. R.H.B. Benedict: analysis and interpretation. S. Rajakrishnan: acquisition of data. R. Doody: study concept and design, critical revision of the manuscript for important intellectual content. L. Yan: analysis and interpretation. K. Szigeti: study concept and design, acquisition of data, analysis and interpretation, writing of manuscript, study supervision.

STUDY FUNDING

Partially supported by NIH/NIA K23 AG036852 (K.S.), NIH/NIMH R25 MH071544/MH (M.R.W.), and the University of California, San Diego, Stein Institute for Research on Aging.

DISCLOSURES

M.R. Woodward has received research support from NIH/NIMH. C.V. Amrutkar and H. Shah report no disclosures. R.H.B. Benedict serves on scientific advisory boards and as a consultant for Biogen Idec, Genzyme, Novartis, and Genentech; serves on the editorial boards of *Multiple Sclerosis* and *Journal of the International Neuropsychological Society*; receives publishing royalties for *Brief Visuospatial Memory Test* (Psychological Assessment Resources, 1997); serves on the speakers' bureau of EMD Serono; receives research support from Accorda, Genzyme, Novartis, Mallinckrodt, Biogen, and National Multiple Sclerosis Society; and has provided expert testimony in medico-legal cases. S. Rajakrishnan reports no disclosures. R. Doody has served on Medical and Scientific Advisory Boards for AC Immune, Avanir, AZ Therapies, Biogen, Genentech, Hoffman LaRoche, Octapharma, Suven, vTv, and ACT-AD; has received funding to attend out of town advisory board and consulting meetings; serves on the editorial boards of *Alzheimer's Disease and Associated Disorders*, *Dementia and Geriatric Cognitive Disorders*, and *BioMed Central: Alzheimer's Research and Therapy*; has served as a consultant for AgeneBio, Axovant, Cerespir, Corium, Lundbeck, Shanghai Green Valley, Suven, Takeda, and Transition; serves on the NIA AD Center P30 review committee; receives research support from Accera, Biogen, Genentech, Merck, NIA/Lilly, and Takeda for clinical trials on which she is PI; receives research support from NIH Alzheimer's Disease Cooperative Study Clinical trials, NIH ADNI, and Texas Alzheimer's Research and Care Consortium; and holds stock options in AZ Therapies and QR Pharma. L. Yan reports no disclosures. K. Szigeti serves as Associate Editor for *Journal of Alzheimer's Disease* and on the editorial board of *BBA Clinical*; serves as Director, Alzheimer's Disease and Memory Disorders Center, University at Buffalo (20% effort); and receives/has received research support from NIH/NIA, Alzheimer Association, Community Foundation of Greater Buffalo Edward A. and Stephanie E. Fial Fund, and Western New York Stem Cell Grant. Full disclosure form information provided by the author is available with the **full text of this article at Neurology.org/cp**.

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