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Odor identification ability predicts PET amyloid status and memory decline in older adults

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Abstract

Background: Odor identification deficits occur in Alzheimer's disease (AD), as measured by the 40-item University of Pennsylvania Smell Identification Test (UPSIT).

Objective: To determine if UPSIT scores predict amyloid- β status, determined by ¹¹C-Pittsburgh Compound B PET. We also compared UPSIT scores to amyloid- β status in predicting future memory decline.

Methods: Subjects were recruited into a longitudinal clinical prediction study. We analyzed data from those who had UPSIT, cognitive testing, PIB PET, and at least 12 months' clinical follow-up. Forty-six amnesic mild cognitive impairment patients and 25 cognitively normal controls were included. Amyloid-positivity was defined as composite PIB standardized uptake value ratio >1.5. Logistic regression and Receiver Operating Characteristic Curve analyses tested the predictive utility of impaired olfaction (defined as UPSIT score <35) and amyloid-positivity for memory decline.

Results: High UPSIT scores predicted absence of amyloidosis on PET, with negative predictive value of 100%. Positive predictive value of low UPSIT scores on positive amyloid- β status was only 41%. Both low UPSIT score (OR = 4.301, 95% CI = 1.248, 14.821, $p = 0.021$) and positive PET scan (OR = 20.898, 95% CI = 2.222, 1196.581, $p = 0.008$) predicted memory decline.

Conclusion: Individuals with high UPSIT scores are less likely to have cerebral amyloidosis or experience memory decline. Therefore, UPSIT has potential as a screening tool to determine utility of amyloid- β PET in clinical practice or enrollment in clinical trials. Low UPSIT score is a

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CONFLICT OF INTEREST DISCLOSURES

The other authors have no conflicts of interest to report.

non-specific marker of neurodegeneration that could indicate further workup in patients with memory complaints.

Keywords

Alzheimer Disease; Amyloid; Positron-Emission Tomography; Olfactory Perception

INTRODUCTION

Odor identification deficits occur in Alzheimer's disease (AD) [1]. Olfactory receptor cells project to olfactory bulb neurons, which then project to limbic regions where the earliest pathological changes of AD occur [2]. Neurofibrillary tangles are prominent in the olfactory bulb in early stages of AD [3, 4]. Impaired odor identification is associated with memory decline and progression to dementia [5, 6], and with post-mortem findings of amyloid- β plaque and tau pathology [7].

PET imaging of fibrillar amyloid- β plaques can detect AD pathophysiology in vivo. High amyloid- β plaque burden increases the probability of cognitive decline in healthy elders [8] and mild cognitive impairment (MCI) patients [9, 10]. However, the high cost of PET limits the utility of using amyloid- β radioligands in clinical practice. Low concentration of A β_{42} in CSF has also been shown to increase the risk of cognitive decline in healthy elders [11] and in MCI patients [12], but such measurement requires a lumbar puncture. With the aging population there is increasing need for a pragmatic approach to evaluating dementia risk. In addition, a sizable proportion of patients diagnosed with MCI or AD who enter clinical trials are found to have a negative amyloid- β PET scan, and these individuals tend to have lower rates of cognitive decline. Both these factors are serious confounds in determining the efficacy of an AD modifying drug. A convenient, inexpensive test that predicts amyloid- β status and memory decline would therefore reduce burden and cost in clinical AD trials.

The University of Pennsylvania Smell Identification Test (UPSIT) is inexpensive, non-invasive, and can be performed in an office setting [13]. Low UPSIT scores predict cognitive decline in community-based cohorts [5, 14] and are associated with markers of neurodegeneration in cognitively normal elders [15, 16]. Prior PET studies have shown modest or no correlation between odor identification ability and amyloid- β burden on PET [15, 17, 18]. In this study, we sought to compare the predictive utility of UPSIT and amyloid- β status—determined by PIB PET—in a cohort of older adults.

METHODS

Subject selection

Adults 55–90 years of age were recruited for longitudinal observational study of AD biomarkers. Amnesic MCI patients were recruited from a Memory Disorders Center, and control subjects, group-matched for age and sex, were recruited by local advertising. Tests to identify amnesic MCI were Free and Cued Selective Reminding Test immediate and delayed recall, Wechsler Memory Scale–III Visual Reproduction I and II immediate and delayed recall, and Wechsler Memory Scale–Revised Logical Memory I and II immediate

and delayed recall. Subjects were designated MCI if they had memory complaints, Mini Mental State Exam (MMSE) score between 23 and 30, and scores more than 1.5 SD below standardized norms on at least 1 of the above three tests of episodic verbal memory. All MCI subjects met established clinical and cognitive criteria [19]. Cognitively intact controls had MMSE score equal to or greater than 28 and scores within 1 SD of standardized norms on all three tests of memory. Exclusion criteria were stroke or radiographic evidence of cortical or large subcortical infarct, impairment due to medical conditions or medications, specific neurological diagnoses (e.g., Parkinson's disease, epilepsy), alcohol or drug abuse or dependence, current major depressive disorder, or history of psychosis. Subjects were asked to return for follow-up clinical evaluation at 12, 24, 36, 48, and 60 months post-baseline.

From this cohort, we selected subjects who had completed UPSIT, brain MRI, and PIB PET at baseline. In addition, at least 12 months' follow-up for repeat cognitive testing was required. To maximize the sample size, we included both controls and subjects who met criteria for amnesic MCI at baseline.

Results of cognitive tests from the control subjects at the baseline visit were used to normalize test data for all individual subjects. Thus, z-scores were created for each subject for each test at each testing interval. Composite z-scores were then created from scores on Free and Cued Selective Reminding Test, Visual Reproduction, and Logical Memory for each subject at each testing interval [20]. Memory decline was determined using clinical data from the last follow-up visit and was defined as a decrease from baseline of 1 SD over 4 years, 0.5 SD over 2 years, or 0.25 SD over 1 year's follow-up [5].

The study was approved by the New York State Psychiatric Institute/Columbia University Institutional Review Board and all subjects signed informed consent.

Olfactory testing

At baseline, the 40-item UPSIT was used to measure odor identification. The UPSIT has common odorants embedded in microcapsules for the subject to scratch and sniff. The subject chooses from 4 multiple choices to identify the item that corresponds to the odor. Total scores range from 0 (no odors identified) to 40 (all odors identified). To be included in analysis, subjects had to complete at least 38 of 40 items. If only 38 or 39 items were completed, missing items were scored as 0.25 to reflect the 25% probability of a correct answer. To avoid confounding effects from smoking and congenital anosmia, we excluded current smokers and those with UPSIT score <14. UPSIT scores were defined as "low" or "high" using a cutoff of <35, as this score is at the threshold for microsmia based on normative UPSIT data [21]. This cutoff corresponds to the 90% quantile for a separate cohort of 757 elders who had baseline UPSIT testing (Supplementary Table 1). Because this UPSIT threshold is relatively high, we also used a cutoff of <32 in a secondary analysis.

Imaging methods

PIB PET scans were performed at CUMC Kreitchman PET Center (n=45) on an ECAT EXACT HR+ (Siemens, Knoxville, TN) or Weill Cornell Medicine Citigroup Biomedical Imaging Center (n=32) on a Siemens Biograph mCT. Immediately following 30-second intravenous PIB injection, dynamic images were acquired in 3D mode at 3 × 20 sec, 3 × 1

min, 3×2 min, 2×5 min, and 7×10 min. Low-dose CT scan was performed for attenuation correction. A 3D SPGR T1 Sequence was performed on a GE Signa 3 Tesla MRI scanner. PET scans were performed within one year of UPSIT (mean interval = 93.9 ± 93.1 days), with the exception of one subject who had PET scan performed 16.5 months after UPSIT.

PET analysis was performed using PMOD 3.6. MR images were segmented using the PNEURO tool and the Hammers-N30R83-1MM atlas was used to define regions-of-interest (ROIs). ROIs were inspected and manually corrected if necessary. PET images 50–70 min post-injection were averaged, co-registered to the corresponding MR image, and individual subject ROIs were then applied. Mean uptake over 50–70 min from a composite gray matter ROI from frontal, parietal, and lateral temporal cortex (excluding sensorimotor cortex) was divided by mean uptake in cerebellar gray matter to create a global standardized uptake value ratio (SUVR). PIB SUVR > 1.5 was used to define amyloid- β positivity [22, 23].

APOE genotyping

A subset of subjects ($n = 39$ or 85% of MCI patients and $n = 23$ or 92% of controls) had *APOE* genotyping performed. DNA was amplified by PCR and genotypes were assessed by sizes of DNA fragments. *APOE* genotypes were determined blinded to participant status. Presence of one or two $\epsilon 4$ alleles defined positive carrier status.

Statistical analysis

Analyses were performed with SAS 9.4 software and R version 3.3.1 after verifying that data did not include any outliers. Group differences between memory decliners and non-decliners were assessed using two-sample t-tests for continuous variables and χ^2 tests for categorical variables. Simple and multiple logistic-regression models were used to assess predictive abilities of amyloid- β status and UPSIT on memory decline over follow-up, correcting for age, gender, and education. Exact logistic regression was used when some of the cells formed by the outcome and categorical predictor variable have no observation. To compare predictive abilities between amyloid- β status and UPSIT, we compared the areas under the ROC curve [24]. $P < 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical measures

Data from 71 subjects (46 MCI and 25 cognitively normal at baseline) were included in our analysis (Table 1). All subjects were required to have at least one follow-up visit after the baseline visit. Supplemental Table 2 shows the number of final subject visits for each 12-month follow-up interval. Cognitive data from the baseline and final visits were used to define memory decline. The time interval between first and last clinical (final) visit was 2.4 ± 1.1 years, ranging from 12–60 months.

Sixty-two% of participants ($n = 44$) showed memory decline between the baseline and last follow-up visit. Decline was more frequent among MCI patients than controls (83% vs. 24%, $p < 0.0001$). Baseline UPSIT score was not significantly different between MCI and

controls, although there was a trend towards lower UPSIT scores in MCI patients (29.0 ± 6.4 vs. 31.9 ± 5.8 , $p = 0.0564$). Baseline PIB binding (composite SUVR) was greater in MCI patients than controls (1.47 ± 0.44 vs. 1.18 ± 0.16 , $p < 0.0001$). We found no association between *APOE-ε4* carrier status and UPSIT status (i.e., UPSIT < 35 or UPSIT ≥ 35) (OR = 1.75; 95% CI = 0.56, 5.44; $p = 0.3352$); however, the association was strong between *APOE-ε4* carrier status and amyloid-positive status (OR = 8.50; 95% CI = 2.30, 31.47; $p = 0.0006$). The proportion of *APOE-ε4* carriers was non-significantly higher in MCI than controls (44% vs. 30%, $\chi^2 = 0.57$, $p = 0.4488$).

Odor identification ability predicts amyloid-negativity

UPSIT showed high sensitivity (100%) to amyloid-positive status in that no subject with UPSIT ≥ 35 had a positive PET scan. Therefore, the negative predictive value of high UPSIT was also 100%, both when MCI and controls were combined and when considered separately (Table 2). However, specificity of UPSIT to amyloid-positive status was lower (53%), with positive predictive value of low UPSIT of only 41%. Overall concordance between UPSIT and amyloid- β status was 59% (Table 2). Correlation analysis between UPSIT and PIB SUVRs showed that UPSIT score was inversely correlated with PIB binding ($r = -0.5486$, $p < 0.0001$, Fig 1). However, this correlation appeared to be driven mainly by subjects with high UPSIT score and low PIB binding.

Both odor identification deficits and amyloid-positivity predict memory decline

In a combined group of MCI patients and cognitively normal controls ($n = 71$), low UPSIT and positive amyloid- β status both predicted memory decline, even after correcting for age, education, and gender (Table 3). When including only MCI patients ($n = 46$), similar results were found for low UPSIT score and positive amyloid- β status. However, UPSIT was not a significant predictor of decline when including only controls ($n = 26$). Positive amyloid- β status was not significantly associated with memory decline when controls were considered separately without controlling for covariates. However, when correcting for age, education, and gender, the model did not converge, resulting in undefined OR values. Correcting for *APOE-ε4* carrier status did not change these results. When baseline memory z-score was included as a covariate, neither UPSIT score nor PIB predicted memory decline.

Because the UPSIT cutoff of 35 is relatively high, we also used a cutoff of 32 in the predictive analysis. This UPSIT cutoff did not significantly predict memory decline in MCI patients, controls, or both groups combined. However, in the combined group the predictive ability of UPSIT < 32 was near trend level, with OR = 2.639 (95% CI = 0.803, 8.676, $p = 0.110$). A less conservative PIB SUVR cutoff of 1.2 predicted memory decline about as well at the cutoff of 1.5 (OR 4.135, 95% CI 1.161, 14.727, $p = 0.029$).

We sought to determine if combining UPSIT with amyloid- β status in the model improved prediction of memory decline. However, only PIB > 1.5 remained a significant predictor when combined with UPSIT < 35 (OR = 14.402, 95% CI = 1.419, 146.212, $p = 0.024$). In the ROC analysis, there was a trend towards greater AUC when the model included both UPSIT and PIB than when the model included UPSIT alone (0.8763 vs. 0.8312, $p = 0.0721$). No difference was observed among AUCs for PIB vs. UPSIT or PIB vs. UPSIT + PIB ($p > 0.18$,

Supplementary Figure 1). No difference in AUCs among any of the models was observed when MCI patients and controls were considered separately.

DISCUSSION

To our knowledge, this is the first study to directly compare odor identification to amyloid- β positivity in predicting memory decline in a longitudinal study. We found that UPSIT score ≥ 35 was 100% predictive of a negative PIB scan. However, concordance between UPSIT < 35 and positive amyloid- β status was only 59%. Therefore, odor identification deficits do not appear to be completely driven by amyloid- β burden. Both low UPSIT and PIB-positivity predicted decline in older adults, with similar OR and area under the ROC curve. Combining both UPSIT and amyloid- β status did not significantly improve prediction of decline, possibly due to high collinearity as UPSIT score negatively correlated with PIB SUVRs. Taken together, these results suggest that cerebral amyloidosis is uncommon in elders with intact odor identification ability. Further, while impaired odor identification is a risk for memory decline, such decline may not necessarily be mediated by AD pathophysiology.

Amyloid- β PET provides biomarker evidence of amyloid- β deposition. However, the expense and limited accessibility of PET imaging restricts widespread clinical use. In addition, amyloid- β status is not definitive in determining risk of AD or future cognitive decline. Results from community-based studies have shown that up to 30% of cognitively normal elders are amyloid-positive on PET [25,26]. The prevalence of incidental positivity increases with age and is particularly high in *APOE- ϵ 4* carriers [26]. The positive predictive value of the amyloid- β radioligand florbetapir for conversion of MCI to AD over 3 years was only 35% in a recent study [27], while the negative predictive value was 90%. Similar predictive value for florbetapir was found in a larger study with mean 1.6 years' follow-up [28].

Odor identification has potential as a low-cost, non-invasive method of evaluating olfactory cortex function as a predictor of neurodegeneration. Reduced odor identification is associated with memory impairment, smaller volumes of hippocampal and entorhinal cortex, amyloid-positivity on PIB PET [15], and AD pathology at autopsy [7]. A recent study showed that the combination of small entorhinal cortex volume and amyloid-positivity on PET was associated with worse odor identification [15], suggesting that UPSIT could provide complementary information of amyloid- β status. Odor identification deficits predict memory decline and conversion to dementia [5, 6]. Therefore, the UPSIT has potential as a surrogate biomarker of limbic function. That no subjects with UPSIT ≥ 35 were amyloid-positive suggests that olfactory testing may be a useful screening tool prior to PET imaging. Amyloid- β status is likely to be negative in patients with intact odor identification. Moreover, because UPSIT predicted future memory decline in both our combined sample and in MCI patients alone, odor identification testing may be a useful screening test to enrich clinical trials. Subjects with low UPSIT scores would be expected to be at higher risk for progression in the absence of a disease-modifying therapy. As memory complaints are often associated with conditions such as depression [29] or sleep apnea [30], UPSIT might

also be a useful tool in distinguishing degenerative and non-degenerative causes of cognitive impairment.

While high UPSIT predicted absence of amyloidosis on PET, low UPSIT did not discriminate amyloid-positive and amyloid-negative subjects. This should not be surprising as olfactory impairment has been reported in Parkinson's disease, dementia with Lewy bodies, Huntington's disease, and frontotemporal dementia [31]. Therefore, low UPSIT may reflect neurodegeneration of the olfactory bulb and its cortical targets irrespective of underlying pathology. However, this underscores the potential utility of UPSIT for clinicians deciding whether to order an amyloid- β PET scan. Whereas a high UPSIT score signifies that a positive amyloid- β scan is unlikely, a low UPSIT score suggests that amyloid- β determination would be helpful to distinguish odor identification deficits associated with AD pathophysiology from those caused by other neurodegenerative disorders.

Our study has several limitations, including a modest sample size that prevents broad generalizations of the results. To increase our sample size we included both MCI patients and controls in the primary analysis. In addition, because MCI patients were recruited from a memory clinic and controls were recruited from the community via advertisement, there was an inherent selection bias. However, high UPSIT did predict amyloid-negativity and low UPSIT predicted memory decline when MCI patients were considered separately. Although our regression model showed significant predictive decline for UPSIT but not PIB among MCI patients, because of the smaller sample size it is possible that this comparison was underpowered and therefore we cannot conclude that UPSIT is superior to PIB in MCI. Similarly, because of the smaller number of cognitive controls and the lower incidence of memory decline in this group, we cannot conclude that UPSIT or amyloid- β status can be used to predict decline in elders without memory symptoms. Larger studies are required to better determine the ability of UPSIT to predict decline in elders who do not yet have memory symptoms.

To avoid confounding effects from smoking, we excluded smokers from the study regardless of their UPSIT score. While congenital anosmia is rare, we did want to exclude subjects with complete or near-complete anosmia and we chose a cutoff of UPSIT score < 14 for this reason. We excluded 3 subjects who had UPSIT < 14 . Two of these had MCI at baseline and showed cognitive decline at follow up while the third was cognitively normal at baseline and did not decline. The OR and area under the curve for the ROC analysis did not significantly change for UPSIT after including these 3 subjects.

Interestingly, we found that neither UPSIT score nor PIB SUVR predicted decline after correcting for baseline memory z-score. Prior studies have shown that both positive amyloid- β PET scan [32] and low UPSIT scores [33] are associated with lower memory scores on cognitive testing. Therefore, one might expect collinearity between UPSIT and baseline memory score and between PIB SUVR and baseline memory score. From our results, we can still conclude that UPSIT score predicts memory decline about as well as PIB PET does; however, with our modest sample size we could not determine if either variable predicted decline independent of baseline memory impairment. Nevertheless, prior studies have shown that both UPSIT score [5] and amyloid PET [8] predict cognitive decline in older adults

without baseline cognitive impairment, suggesting that the predictive ability of either variable is not dependent on the presence of baseline low memory score.

The results of our study may have been affected by the choice of cutoff for UPSIT. We chose <35 to define low UPSIT because scores of 35 and 36 define lower limits of normosmia for males and females, respectively [21]. Our cutoff is higher than those used in some other studies [5, 14] and higher than the mean UPSIT scores for both MCI patients and controls. However, our subjects were younger, less impaired, and more highly-educated than those in community-based cohorts [5, 14]. Because UPSIT scores decrease with age [34], a lower cutoff is expected in older cohorts. Using a lower UPSIT cutoff of 32 showed a trend toward predicting memory decline; however, this result was not statistically significant. Cutoffs for PIB are also expected to have influenced our results. We chose SUVR cutoff 1.5 for PIB to define amyloid-positivity because this is a commonly used threshold [22, 23]. However, reports have suggested that this cutoff may be too conservative [35]. However, a more liberal SUVR cutoff of 1.2 did not improve the ability of PIB PET to predict memory decline in our sample. Tau PET imaging promises to provide complementary information to amyloid PET; however, tau scans are presently available only in a research setting. The data in our study was collected prior to the availability of ¹⁸F-AV-1451 for PET imaging.

Another limitation of this study is that the time period between UPSIT and PIB PET was variable among subjects, with one subject having PET scan 16.5 months after UPSIT testing. However, this subject was amyloid-negative, with PIB SUVR of 1.13. Therefore, we can be certain that the subject was also amyloid-negative at the time of UPSIT administration.

In conclusion, a high UPSIT score was predictive of a negative PIB scan, suggesting that amyloid- β PET may have lower utility in patients with intact odor identification. However, a low UPSIT score is non-specific for underlying AD pathophysiology, and therefore amyloid-determination may be warranted in patients with memory complaints who also show evidence of impaired odor identification. Low UPSIT predicts memory decline about as well as positive amyloid- β status in a cohort of MCI patients and older controls, and therefore may be a useful clinical tool for early detection of neurodegenerative disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1. UPSIT score negatively correlates with PIB binding on PET imaging ($r = -0.5486$, $p < 0.0001$).

Best-fit line and 95% CI are shown. UPSIT = University of Pennsylvania Smell Identification Test, PIB = ^{11}C -Pittsburgh Compound B.

Table 1.

Demographic information for participants

Variable	All subjects (n = 71)	MCI (n = 46)	Controls (n = 25)	<i>p</i> ^a
Age, mean (SD), y	68.5 (7.5)	68.8 (7.4)	67.9 (7.7)	0.6323
Education, mean (SD), y	16.6 (3.0)	16.2 (3.2)	17.3 (2.4)	0.0983
No. female (%)	41/71 (58%)	26/46 (57%)	15/25 (60%)	0.9746
MMSE score, mean (SD)	27.4 (2.3)	26.5 (2.3)	29.2 (0.8)	<0.0001
No. with memory decline (%)	44/71 (62%)	38/46 (83%)	6/25 (24%)	<0.0001
UPSIT score, mean (SD)	30.0 (6.3)	29.0 (6.4)	31.9 (5.8)	0.0564
PIB SUVR, mean (SD)	1.36 (0.39)	1.47 (0.44)	1.18 (0.16)	<0.001
No. <i>APOE</i> ε4 carrier (%) ^b	24/62 (39%)	17/39 (44%)	7/23 (30%)	0.4488

^a *p* = *p* value based on unpaired *t* test or χ^2 test between MCI patients and controls.

^b Nine subjects (7 MCI and 2 controls) did not have *APOE* testing performed.

Abbreviations: MCI = mild cognitive impairment, MMSE = Mini Mental State Exam, UPSIT = University of Pennsylvania Smell Identification Test, PIB = ¹¹C-Pittsburgh Compound B, SUVR = Standardized Uptake Value Ratio.

Table 2.Concordance between UPSIT score and amyloid- β status

All subjects (n = 71)		
UPSIT score	Aβ (+)	Aβ (–)
< 35	20	29
35	0	22
MCI patients only (n = 46)		
UPSIT score	Aβ (+)	Aβ (–)
< 35	18	17
35	0	11
Controls subjects only (n = 25)		
UPSIT score	Aβ (+)	Aβ (–)
< 35	2	12
35	0	11

Abbreviations: UPSIT = University of Pennsylvania Smell Identification Test.

Amyloid- β (+) defined with ^{11}C -Pittsburgh Compound B PET, with composite standardized uptake value ratio > 1.5.

Table 3.

Comparison of UPSIT score < 35 vs. PIB PET in predicting memory decline.

All subjects (n = 71)			
	OR	95% CI	P
UPSIT	4.301	1.25, 14.82	0.021
PIB > 1.5	20.90	2.22, 196.58	0.008
MCI subjects only (n = 46)			
	OR	95% CI	P
UPSIT	8.07	1.16, 56.28	0.035
PIB > 1.5 *	2.88	N/A	0.029
Control subjects only (n = 25)			
	OR	95% CI	P
UPSIT	0.31	0.006, 14.87	0.552
PIB > 1.5 **	Model did not converge		

Abbreviations: UPSIT = University of Pennsylvania Smell Identification Test, PIB = ¹¹C-Pittsburgh Compound B

In all models, age, education and gender were controlled.

* indicates a median unbiased estimate and a one-sided p-value by exact logistic regression. Therefore, 95% CI is not reported.

** The model did not converge. There were only 2 control subjects with PIB >1.5, one of whom showed memory decline. Without covariates, the OR of PIB >1.5 was OR = 3.60, 95% CI: 0.19–68.34, p = 0.394.