

Olfactory identification deficits and MCI in a multi-ethnic elderly community sample

D.P. Devanand^{a,b,*}, Matthias H. Tabert^a, Katrina Cuasay^a, Jennifer J. Manly^{b,c,d},
Nicole Schupf^{b,c,d,e}, Adam M. Brickman^{b,c,d}, Howard Andrews^f, Truman R. Brown^{g,h},
Charles DeCarliⁱ, Richard Mayeux^{a,b,c,d,e}

^a Division of Geriatric Psychiatry, Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, United States

^b Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, United States

^c Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, United States

^d Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, United States

^e Department of Epidemiology, Joseph P. Mailman School of Public Health, Columbia University, New York, NY, United States

^f Department of Biostatistics, Joseph P. Mailman School of Public Health, Columbia University, New York, NY, United States

^g Department of Radiology, College of Physicians and Surgeons, Columbia University, New York, NY, United States

^h Department of Biomedical Engineering, Columbia University, New York, NY, United States

ⁱ Department of Neurology and Imaging of Dementia and Aging (IDeA) Laboratory, Center for Neuroscience, University of California, Sacramento, CA, United States

Received 27 March 2008; received in revised form 20 August 2008; accepted 11 September 2008

Available online 28 October 2008

Abstract

Odor identification deficits occur in Alzheimer's disease (AD) and mild cognitive impairment (MCI), and predict clinical conversion from MCI to AD. In an epidemiologic study conducted in a multi-ethnic community elderly sample (average 80 years old), the University of Pennsylvania Smell Identification Test (UPSIT, range 0–40) was administered to 1092 non-demented subjects. Women (mean 26.6, S.D. 6.6) scored higher than men (mean 24.4, S.D. 7.4, $p < .02$), and ethnic differences were not significant after controlling for age and education. UPSIT scores correlated inversely with age ($r = -0.24$, $p < .0001$) and positively with Selective Reminding Test immediate recall ($r = 0.33$), delayed recall ($r = 0.28$), category fluency ($r = 0.28$) and the 15-item Boston Naming Test ($r = 0.23$), all $ps < .0001$. In a sub-sample in which MRI was done, UPSIT scores showed a significant correlation with hippocampal volume ($n = 571$, $r = 0.16$, $p < .001$) but not entorhinal cortex volume nor total number of white matter hyperintensities. In ANOVA, UPSIT scores differed ($p < .0001$) as a function of MCI classification: no MCI (mean 26.6, S.D. 6.8), non-amnesic MCI (mean 24.4, S.D. 7.2), and amnesic MCI (mean 23.5, S.D. 6.7). The difference between amnesic MCI and no MCI remained significant after controlling for relevant covariates. These findings indicate that the predictive utility of olfactory identification deficits for decline from no MCI to MCI and AD needs to be assessed in longitudinal studies of elderly community samples.

© 2008 Elsevier Inc. All rights reserved.

Keywords: Olfaction; Mild cognitive impairment; Hippocampal volume; Entorhinal cortex volume; Verbal recall; Ethnicity; Epidemiology

1. Introduction

Alzheimer's disease (AD) is the major cause of dementia, with prevalence estimates of approximately 10% in individuals over age 65 and 30% in individuals over age 85 in the U.S. Prospective studies show that elderly subjects who exhibit mild cognitive impairment (MCI), a transitional stage between “normal” and “dementia”, go on to develop

* Corresponding author at: Professor of Clinical Psychiatry and Neurology, New York State Psychiatric Institute, College of Physicians and Surgeons, Columbia University, 1051 Riverside Drive, Unit 126, New York, NY 10032, United States. Tel.: +212 543 5612; fax: +212 543 5088.

E-mail address: ddp3@columbia.edu (D.P. Devanand).

dementia at a rate of 10–15% per year, which is 5–7 times higher than for age-matched individuals without such impairment (Petersen, 2004).

Early in the course of Alzheimer's disease (AD), degeneration occurs in the entorhinal–hippocampal–subicular complex (Price and Morris, 1999; Reyes et al., 1993). The olfactory bulb, particularly the anterior olfactory nucleus, shows numerous neurofibrillary tangles, a pathological feature of AD (Hyman et al., 1991; Kovacs et al., 1999). Odor identification deficits during life may be associated with neurofibrillary tangles in the hippocampus after death (Wilson et al., 2007a). Clinically, AD patients consistently show deficits in odor identification compared to controls (Doty et al., 1991; Serby et al., 1991). These deficits have been shown to be a true decline in odor identification ability that cannot be explained by lexical difficulty in interpreting written words in the multiple choice test format (Morgan et al., 1995). There is predictive utility for these deficits in cognitively impaired outpatients without dementia for the follow-up diagnosis of AD, and predictive accuracy may be comparable to that of widely used neuropsychological tests (Devanand et al., 2000; Murphy, 2002; Tabert et al., 2006).

Odor identification deficits have been shown to correlate with hippocampal atrophy in small samples (Murphy et al., 2003), and there is fMRI evidence of decreased activation in medial temporal lobe regions in older compared to young adults (Wang et al., 2005). There is lack of information on the associations of olfactory identification deficits with structural and functional brain imaging measures in large samples. Such information may be useful to help clarify if the olfactory identification deficit is because of damage to the primary and secondary olfactory brain regions that are known to process olfactory stimuli, or whether the damage in higher order centers in AD leads to loss of olfactory memory and consequent olfactory identification deficits. Further, there is limited information on the prevalence and cognitive correlates of odor identification deficits in elderly subjects living in the community (Wilson et al., 2007b).

To address these outstanding issues, the University of Pennsylvania Smell Identification Test (UPSIT, range 0–40) was administered to non-demented elderly subjects participating in the Washington Heights-Inwood Columbia Aging Project (WHICAP), which is an ongoing, community-based study of aging and dementia in an urban community. The UPSIT first began to be administered in 2003. A unique aspect of the cohort is the inclusion of Caribbean Hispanics and African American participants, which facilitates the examination of ethnicity as a modifying factor in cognitive aging. The purpose of the current study was to examine the impact of age, sex, ethnicity, and language of administration on UPSIT scores, and to evaluate the associations of UPSIT scores with cognitive test performance and MRI measures of medial temporal lobe atrophy and cerebrovascular disease.

2. Methods

2.1. Study population

Study participants were drawn by random sampling of healthy Medicare beneficiaries aged ≥ 65 years, and resided within a geographically defined area of northern Manhattan, New York (Stern et al., 1992). The cohort represents a combination of continuing members of a cohort originally recruited in 1992 and members of a new cohort recruited between 1999 and 2001; approximately one-quarter of the sample was from the original 1992 cohort and three-quarters from the new cohort (Manly et al., 2005). Recruitment of all participants was initially achieved by contacting a stratified random sample of 50% of all persons age 65 years and older obtained from the Health Care Finance Administration (Center for Medicare Services). As of February 23, 2007, data were available on 1511 participants who were evaluated between 2004 and 2006; for the original 1992 cohort this represented their fifth follow-up assessment and for the new cohort this represented their third follow-up assessment. This assessment was chosen for these analyses because it was only during this last assessment that the UPSIT was administered.

All participants underwent a standardized neuropsychological battery designed to assess cognitive functions that are typically affected in dementia, and included measures of learning and memory, orientation, abstract reasoning, language, and visuospatial ability (Manly et al., 2005). Participants were excluded if they met DSM-III-R criteria (presence of deficits in memory and one other cognitive domain, plus functional impairment) for dementia (DSM-III-R, American Psychiatric Association, 1987). Each participant underwent a standardized neurological examination, which included an abbreviated (10-item) version of the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) (Stern, 1978). We assigned a diagnosis of PD or Parkinson Plus syndrome based on research criteria (de Rijk et al., 1997). Participants were considered to have PD or Parkinson Plus syndrome if they had previously received these diagnoses, or if they had two or more cardinal signs of parkinsonism (UPDRS rating ≥ 2) on the standardized neurological examination.

2.2. Final sample

There were 1,511 participants (mean age = 81.6 ± 6.3 years, 1062 [70.3%] women, mean education = 10.1 ± 4.9 years). Subjects were self-identified as white ($n=345$), Hispanic ($n=393$), African-American ($n=339$) or Other ($n=15$). We excluded 214 participants with dementia (mean UPSIT score = 17.8 ± 6.5), 17 with Parkinson's disease or Parkinson plus syndrome, and 190 without complete UPSIT evaluations. This left 1,092 participants in our final sample (mean age = 80.6 ± 5.7 years, 749 [68.6%] women, mean education = 10.8 ± 4.7 years).

2.3. Olfactory testing

Odor identification testing was performed with the University of Pennsylvania Smell Identification Test (UPSIT, Sensonics Inc., Haddon Heights NJ; Doty, 1995) and was administered by the research rater to the subject. Testing was not performed if participants had active upper respiratory tract infections or allergies. In this test, each of 40 common odorants is embedded in a microcapsule on a separate page. The subject scratches the item, sniffs, and then chooses the best answer from 4 items listed as multiple choice on the same page. Therefore, the score ranges from 0 to 40 (all odors correctly identified). The UPSIT is highly reliable (Doty et al., 1989) and sensitive to a variety of olfactory deficits (Murphy, 2002).

3. MRI protocol

3.1. Acquisition

Scan acquisition was performed on a 1.5T Philips Intera scanner at Columbia University Medical Center and transferred electronically to the University of California at Davis for morphometric analysis in the Imaging of Dementia and Aging Laboratory. Fluid attenuated inverse recovery (FLAIR) weighted images (TR = 11,000 ms, TE = 144.0 ms, 2800 inversion time, FOV 25 cm, 2 nex, 256 × 192 matrix with 3 mm slice thickness) were acquired in the axial orientation and used to assess white matter hyperintensities (WMH). T1-weighted images acquired in the axial plane and re-sectioned coronally were used to quantify hippocampus and entorhinal cortex volumes (TR = 20 ms, TE = 2.1 ms, FOV 240 cm, 256 × 160 matrix with 1.3 mm slice thickness).

3.2. Quantification of WMH volume, hippocampus volume, and entorhinal cortex volume

Four morphological variables were derived for the current analyses: WMH volume, total relative brain volume (ratio of absolute brain volume to intracranial volume), hippocampus volume, and entorhinal cortex volume. User operated image analysis was performed on a Sun Microsystems Ultra 5 workstation using the Quantum 6.2 package. Subject identifying information was not available to the operator.

Total brain and WMH volumes were derived on FLAIR-weighted images following a two-step process, as previously described (Brickman et al., 2008; DeCarli et al., 1995). Once brain matter was isolated, a single Gaussian distribution was fitted to image data and a segmentation threshold for WMH was set *a priori* at 3.5 S.D.s in pixel intensity above the mean of the fitted distribution of brain matter. Erosion of two exterior image pixels was applied to the brain matter image before modeling to remove partial volume effects and ventricular ependyma on WMH determination. White matter hyperintensity volume was calculated as the sum of voxels greater to or

equal to 3.5 S.D. above the mean intensity value of the image and multiplied by voxel dimensions and slice thickness.

3.2.1. Hippocampus

Boundaries for the hippocampus were manually traced from the coronal 3D-T1 weighted images after reorientation along the axis of the left hippocampus. The methods used, including identification of landmarks and boundaries, are described elsewhere (Brickman et al., 2008). Intra-rater reliability determined for both right and left hippocampus using this method was high with intraclass correlation coefficients of 0.98 for right hippocampus and 0.96 for left hippocampus.

3.2.2. Entorhinal cortex

Measurement of entorhinal cortex area was performed following a protocol developed and described by Killiany et al. (2002). In brief, the entorhinal cortex area was outlined on three consecutive coronal images centered at the level of the mammillary bodies. Inter-rater reliabilities for this process averaged 0.90.

White matter hyperintensity volumes (log-transformed as they were not normally distributed), hippocampus and entorhinal cortex volumes were each adjusted by intracranial volume.

3.3. Statistical analyses

Distribution and differences across groups in demographic data and dichotomous variables were determined with Chi-square analysis, *t*-test and general linear models. Effects of ethnicity, sex, and their interaction on UPSIT scores were examined with analysis of variance (ANOVA). We considered possible covariates: age in years, gender, race (white, African-American, Hispanic, other), years of education, Blessed score (measure of general cognitive function, Blessed et al., 1968), cigarette smoker (ever vs. never), and current cigarette smoker (yes vs. no). These analyses identified three variables (sex, age and education) that were associated with UPSIT (total score used in all analyses). In relevant ANCOVA on language of administration and MCI group classification, we covaried for sex, age and education. Since odor identification incorporates verbal memory and naming abilities, in other analyses we covaried for Selective Reminding Test (SRT) immediate recall as the measure of verbal memory, and the 15-item Boston Naming Test as the measure of language. Spearman correlations between UPSIT scores and cognitive and MRI measures were evaluated. Analyses were conducted in SPSS Version 15.0.

4. Results

The UPSIT score was higher in women ($n = 749$, mean 26.6, S.D. 6.6) than men ($n = 343$, mean 24.4, S.D. 7.4, $t = 4.8, p < .001$). The UPSIT score showed a significant positive correlation with years of education ($r = 0.18, p < .001$)

Table 1
Demographic and clinical variables classified by MCI group subtype.

Variable	Total sample (N = 1092)	No MCI (N = 802)	Non-amnesic MCI (N = 120)	Amnesic MCI (N = 170)	p
Ethnicity					<0.001
White	33%	34%	37%	23%	
Hispanic	32%	36%	17%	45%	
African-American	35%	30%	46%	32%	
Age	80.5 (5.8)	80.2 (5.7)	80.7 (5.9)	82.0 (6.2)	0.007
Sex % female	70%	69%	75%	78%	0.074
Short Blessed					
SRT imm recall	36.9 (10.3)	39.1 (9.6)	34.9 (6.4)	23.8 (6.5)	<0.001
SRT delayed recall	5.0 (2.6)	5.4 (2.5)	4.7 (1.9)	2.2 (1.7)	<0.001
Category Fluency CFL	30.3 (13.6)	32.1 (13.5)	20.5 (10.7)	26.7 (11.8)	<0.001
Boston Naming 15-item	13.6 (2.6)	13.8 (2.7)	12.5 (2.2)	13.2 (2.5)	<0.01
Apolipoprotein E e4%	22.3%	25.3%	18.3%	25.5%	ns
UPSIT	26.2 (6.9)	26.7 (6.8)	24.8 (6.8)	24.0 (6.5)	<0.001

and a significant inverse correlation with age at evaluation ($r = -0.24$, $p < .001$). The inter-quartile range for age was 76–85 years, and the inter-quartile range for the UPSIT score was 19–29.

Subjects administered the English version UPSIT scored marginally higher ($n = 711$, mean 26.3, S.D. 7.0) than subjects administered the Spanish version ($n = 373$, mean 25.3, S.D. 6.7; $t = 2.4$, $p < .02$). In ANCOVA on the UPSIT score with language of administration as the between subject factor and age and education as covariates, language of administration was no longer significant ($F = 0.56$, $p = 0.46$). In ANOVA on the UPSIT score, there was no significant effect of ethnicity across the four groups of subjects self-identified as white ($n = 345$, mean 26.5, S.D. 7.1), Hispanic ($n = 393$, mean 25.5, S.D. 6.8), African-American ($n = 339$, mean 25.9, S.D. 6.8) and Other ($n = 15$ mean 24.5, S.D. 7.1), $F = 1.5$, $p = 0.23$. The UPSIT score was not significantly associated with history of smoking or current smoking, history of hypertension, diabetes, or current depression (CES-D 10 item score). The UPSIT score was not significantly associated with the presence of the apolipoprotein E e4 allele (present in 24.4% of sample).

The UPSIT score showed a significant negative correlation with the Short Blessed score in which cognitive errors lead to higher scores ($r = -0.25$, $p < .0001$). As described in Table 2, the UPSIT score correlated positively with neuropsychological measures of memory (SRT immediate recall $r = 0.33$, $p < .0001$; SRT delayed recall $r = 0.28$, $p < .0001$), naming (15-item Boston Naming Test $r = 0.23$, $p < .0001$), and category fluency (CFL naming mean, $r = 0.31$, $p < .0001$; Animal Naming, $r = 0.28$, $p < .0001$).

Using the Petersen classification, there were 170 amnesic MCI, 120 non-amnesic MCI, and 802 subjects without MCI (Table 1). Amnesic MCI patients were older, and 45% of amnesic MCI subjects were Hispanic while 17% of non-amnesic MCI subjects were Hispanic. Amnesic MCI patients scored lower on SRT immediate and delayed recall, and non-amnesic MCI patients scored lower on category fluency and naming (Table 1). Apolipoprotein E e4 allele status was not associated with MCI group status.

In ANOVA, the UPSIT score differed across the three-group MCI classification ($F = 15.3$, $p < .0001$). The UPSIT score was higher in subjects without MCI (mean 26.6, S.D. 6.8) compared to non-amnesic MCI (mean 24.4, S.D. 7.2) or amnesic MCI subjects (mean 23.5, S.D. 6.7), all $ps < .001$ (Fig. 1). Using this three-group MCI classification, in ANOVA on UPSIT score with ethnicity and MCI group as between subject factors, there was a significant MCI group effect ($F = 13.88$, $p < .001$), but no effect of ethnicity and no MCI group by ethnicity interaction. Women scored higher than men in all MCI groups, and there was no sex by MCI group interaction ($F = 0.60$, $p = 0.55$). In ANCOVA on the UPSIT score with MCI group and sex as between subject factors, and age, Short Blessed score, and education as covariates, MCI group remained significant ($F = 8.7$, $p < .001$). In pair-wise comparisons of UPSIT scores from the same model, the amnesic MCI group had lower UPSIT scores than the no MCI group ($F = 15.3$, $p < .001$), and the other pair-wise comparisons were not significant. The UPSIT score was not significantly associated with the total volume of white matter hyperintensities identified on MRI scan of brain. The

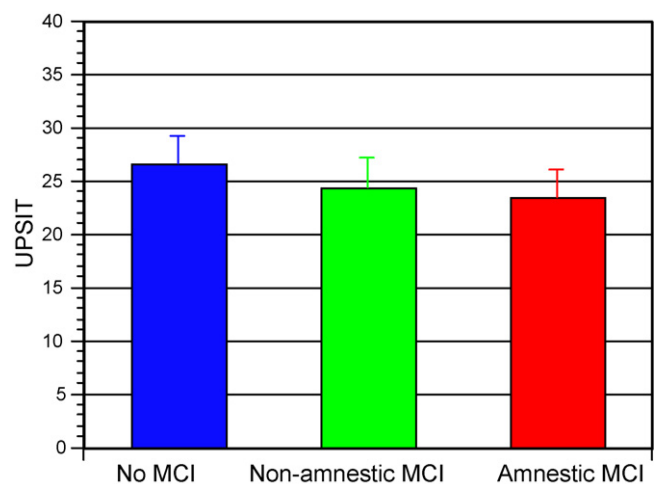


Fig. 1. Comparison of UPSIT scores (range 0–40) by mild cognitive impairment (MCI) classification.

Table 2

Baseline correlations between 40-item UPSIT scores and demographic, clinical and imaging variables in non-demented subjects.

Variable	UPSIT score, <i>r</i>	<i>p</i>
Age (<i>n</i> = 1092)	−0.244	<.0001
Education (<i>n</i> = 1089)	0.175	<.0001
SRT total (immediate) recall (<i>n</i> = 1073)	0.325	<.0001
SRT delayed recall (<i>n</i> = 1073)	0.276	<.0001
Boston naming (15-item) (<i>n</i> = 1076)	0.228	<.0001
Category fluency mean CFL (<i>n</i> = 1075)	0.308	<.0001
Category fluency number of animals (<i>n</i> = 1075)	0.276	<.0001
Short Blessed total (<i>n</i> = 1072)	−0.251	<.0001
Mean hippocampal volume (right and left)/intracranial volume (<i>n</i> = 571)	0.157	<.0001
Mean entorhinal cortex volume (right and left)/intracranial volume (<i>n</i> = 486)	0.031	0.489

r = Spearman correlation coefficient.

UPSIT score showed a significant correlation with hippocampal volume (*n* = 571, *r* = 0.16, *p* < .001) but not with entorhinal cortex volume (*n* = 486, *r* = 0.03; Table 2). In ANCOVA on the UPSIT score with MCI group as the between subject factor, the between group effect remained significant when age, education, Short Blessed score, and hippocampal volume were included as covariates.

5. Discussion

The relatively low UPSIT scores in this elderly sample are likely to be related to subjects having an average age of 80 years. There are well-established age-related reductions in odor identification, discrimination, and threshold detection, and peak olfactory performance occurs in the third through fifth decades of life with marked declines after the seventh decade (Doty et al., 1984). In our sample, lower UPSIT score showed moderate associations with lower education, as expected. The lack of differences in performance on the English and Spanish versions of the test after covarying for age and education supported the use of these two test versions and justified combining their data for analyses. Prior work with the 40-item UPSIT and shorter versions of this test have been validated cross-culturally in several countries (Ahmad et al., 2007; Doty et al., 1996), and the comparability of the Spanish and English versions in our study extends this validation. Women scored higher than men, consistent with reports that women outperform men on tests of odor identification in all age groups, particularly after the 5th decade (Doty et al., 1985; Westervelt et al., 2007). There is fMRI evidence of greater odorant-induced activation in women than men (Yousem et al., 1999).

The sensitivity and specificity of olfactory identification deficits in distinguishing AD patients from healthy controls (Doty et al., 1987; Doty et al., 1989; Serby et al., 1991), and for predicting conversion to AD in cognitively impaired, non-demented subjects, are comparable to those obtained from several commonly used neuropsychological tests of memory

(Devanand et al., 2000; Murphy, 2002; Tabert et al., 2005). In another study of cognitively intact elderly individuals, impaired baseline odor identification was related to a greater decline in several indices of verbal memory over 4 years, but not other types of cognitive deficits (Swan and Carmelli, 2002). Recent findings from a large sample of community-dwelling subjects suggests that odor identification deficits in subjects predicts conversion from “normal” to MCI, particularly decline in measures of verbal memory, during follow-up (Wilson et al., 2007a). In our study, the relatively strong associations observed between UPSIT scores and measures of verbal memory are consistent with this finding. Further, there was an increase in odor identification deficits from the no MCI to non-amnesic MCI to amnesic MCI groups, though only the amnesic MCI versus no MCI comparison was statistically significant. The lack of a significant difference between the amnesic MCI and non-amnesic MCI groups suggests that odor identification deficits may also be present in non-amnesic MCI that is a heterogeneous group with a variety of underlying brain pathologies. The findings also suggest that odor identification testing in the general community population is unlikely to be diagnostic because of considerable overlap in UPSIT scores across groups. In contrast, UPSIT scores in amnesic MCI patients who participate in research studies in specialty settings do show strong discrimination with less overlap between groups, and this may be related to self-selection bias and the use of rigorous exclusion criteria for specific neurological and psychiatric comorbid conditions in such studies (Tabert et al., 2005). The findings in this study indirectly support the notion that non-amnesic MCI patients may have underlying brain pathology different from AD, e.g., cerebrovascular disease, and that amnesic MCI patients are more likely to be diagnosed with AD over time.

There were no significant associations between the UPSIT score and the presence of the apolipoprotein E ε4 allele. While some cross-sectional studies in clinical samples have shown an association between odor identification deficits and the apolipoprotein E ε4 allele (Handley et al., 2006; Murphy et al., 1998), other longitudinal work suggests that the association between odor identification deficits and decline in verbal memory is independent of apolipoprotein E genotype (Swan and Carmelli, 2002). However, there are epidemiological data showing that the prediction of cognitive decline by odor identification deficits may be enhanced in subjects who carry the apolipoprotein E ε4 allele (Graves et al., 1999). Overall, the associations between odor identification deficits and apolipoprotein E genotype are not consistent or strong, and the pathophysiological basis for such an association remains unclear.

Animal studies suggest that the piriform cortex may be the primary way-station for the olfactory system, receiving input from the olfactory bulb (and other cortical areas) with output to the hippocampus, entorhinal cortex, thalamus and hypothalamus (Zald and Pardo, 2000). Based on an olfactory recognition memory task in rats, theta cells in the

CA1 and CA3 regions of the hippocampus have been shown to participate in odor recognition memory processing and play a specific role in shaping the cognitive firing properties of the hippocampal principal cells (Wiebe and Staubli, 2001). These findings support the role of the hippocampus as an important center in the pathway to process olfactory information, including recall and identification of odors. In our sample, UPSIT scores showed moderately significant associations with hippocampal volume.

In AD, there is a concentration of neuropathological lesions in layer II stellate projection neurons in the entorhinal cortex that form the primary projection to the hippocampus (Gomez-Isla et al., 1996). Braak and Braak (1998) suggested that lesions in the entorhinal and transentorhinal areas effectively disconnect the hippocampus from the isocortex, thereby disrupting the flow of olfactory information essential to higher-order olfactory tasks including odor identification and odor memory (Murphy et al., 2003). However, in our sample, there was no association between UPSIT scores and entorhinal cortex volume. One possible explanation is that a gross measure of atrophy as assessed by entorhinal cortex volume does not capture the subtle changes that occur with initial neurofibrillary tangle infiltration in that brain region. Also, olfactory projections reach only the anterior-most region of the entorhinal cortex, and the Killiany method used to assess entorhinal cortex volume typically does not include this region.

The UPSIT score was not associated with the total volume of MRI white matter hyperintensities. The literature on odor identification and either vascular cognitive impairment or vascular dementia is inconsistent (Duff et al., 2002; Gray et al., 2001), and there has been a lack of information on regionality of cerebrovascular brain lesion and association with UPSIT scores. Presumably, vascular lesions in the primary and olfactory pathways may be more likely to be associated with odor identification deficits.

The odor identification task relies on both olfactory sensory/perceptual functioning and semantic memory. Impaired odor identification performance cannot be explained solely by cognitive impairment, and the moderately strong correlations between the UPSIT and SRT measures in this study explained approximately 11% of the variance. The olfactory identification paradigm of the UPSIT involves simultaneously testing olfactory detection ability and olfactory memory. The subject's ability to integrate these two components and respond accurately to identify test items in the UPSIT appears to be compromised early in AD.

The specific brain regions responsible for olfactory recognition and identification remain unclear. Odor identification deficits are associated with pathological findings of Lewy bodies and AD (Wilson et al., 2007b). In a human autopsy study, impaired odor identification was shown to be related to increased density of tangles in the entorhinal cortex and the CA1/subiculum region of hippocampus, marginally related to tangles in temporal cortex, and unrelated to tangles in other

neocortical areas (Wilson et al., 2007b). While the correlations, or lack thereof, observed in our study are intriguing, it is clear that longitudinal work is needed to clarify the relationships between odor identification deficits and regional brain pathology.

The strength of the WHICAP cohort is that it includes participants who are under-represented in most studies that examine brain aging. This study is among the first to compare odor identification performance in an elderly community study with the distribution of ethnicity being almost equal among Caucasians, African Americans, and Caribbean Hispanics. After controlling for age and education, the three ethnic groups did not differ in UPSIT scores, and therefore the use of the 40-item UPSIT is appropriate in this population. The restricted age range of the sample may have affected the correlations between age and UPSIT scores. WHICAP participants are older, come from diverse educational and socioeconomic backgrounds, and vary widely in their health status. Therefore, the findings are more likely to reflect the general older population in the U.S.A. where ethnic diversity is increasing. Furthermore, WHICAP participants are evaluated with comprehensive neuropsychological, medical, and behavioral assessments and followed longitudinally. Future work will examine the association between odor identification deficits and cognitive and functional measures, and we will be able to evaluate their value in predicting cognitive decline.

Only odor identification was evaluated. Odor discrimination and odor threshold were not assessed in order to reduce excessive subject burden in this community study in which a large number of procedures are conducted (Manly et al., 2005). One limitation was that although the three main ethnic groups represented in the WHICAP imaging sample were similar in terms of age, they varied systematically and substantially on other factors. For example, Hispanic participants had markedly fewer years of formal education than African American and Caucasian participants, which impacted on UPSIT scores. Therefore, including age and education as covariates in the analyses was necessary, and these demographic factors need to be taken into account in the administration and interpretation of the UPSIT or any other odor identification test in elderly subjects. Many correlations were done without adjustment for multiple comparisons, though most correlations were significant enough to survive correction. A final limitation is the cross-sectional nature of the findings, but this sample is being followed longitudinally to evaluate the predictive utility of odor identification deficits and its associations with change in disease severity within subjects over time.

Acknowledgements

This work was supported by National Institutes of Health grants AG007232 and AG029949 and AG17761. The authors report no conflicts of interest related to this research.

References

- Ahmad, A.T., Jbara, M.A., Hiyasat, D., Bateiha, A., Ajlouni, K.M., 2007. The standard clinical smell testing protocol of the National Center for Diabetes, Endocrinology and Genetics in Amman, Jordan: JOR test. *Am. J. Otolaryngol.* 28, 388–391.
- American Psychiatric Association, 1987. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. American Psychiatric Association, Washington, D.C.
- Blessed, G., Tomlinson, B.E., Roth, M., 1968. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br. J. Psychiatry* 114, 797–811.
- Braak, H., Braak, E., 1998. Evolution of neuronal changes in the course of Alzheimer's disease. *J. Neural Transm. Suppl.* 53, 127–140.
- Brickman, A.M., Schupf, N., Manly, J.J., Luchsinger, J.A., Andrews, H., Tang, M.X., Reitz, C., Small, S.A., Mayeux, R., DeCarli, C., Brown, T.R., 2008. Brain morphology in elderly African Americans, Caribbean Hispanics, and Caucasians from Northern Manhattan. *Arch. Neurol.* 65, 1053–1061.
- de Rijk, M.C., Rocca, W.A., Anderson, D.W., Melcon, M.O., Breteler, M.M., Maraganore, D.M., 1997. A population perspective on diagnostic criteria for Parkinson's disease. *Neurology* 48, 1277–1281.
- DeCarli, C., Murphy, D.G., Tran, M., Grady, C.L., Haxby, J.V., Gillette, J.A., Salerno, J.A., Gonzales-Aviles, A., Horwitz, B., Rapoport, S.I., 1995. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. *Neurology* 45, 2077–2084.
- Devanand, D.P., Michaels-Marston, K.S., Liu, X., Pelton, G.H., Padilla, M., Marder, K., Bell, K., Stern, Y., Mayeux, R., 2000. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am. J. Psychiatry* 157, 1399–1405.
- Doty, R.L., 1995. *The Smell Identification Test Administration Manual*. Sensonics, Haddon Heights, New Jersey.
- Doty, R.L., Shaman, P., Applebaum, S.L., Giberson, R., Sikorski, L., Rosenberg, L., 1984. Smell identification ability: changes with age. *Science* 226 (4681), 1441–1443.
- Doty, R.L., Applebaum, S., Zusho, H., Settle, R.G., 1985. Sex differences in odor identification ability: a cross-cultural analysis. *Neuropsychologia* 23, 667–672.
- Doty, R.L., Reyes, P.F., Gregor, T., 1987. Presence of both odor identification and detection deficits in Alzheimer's disease. *Brain Res. Bull.* 18 (5), 597–600.
- Doty, R.L., Frye, R.E., Agrawal, U., 1989. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept. Psychophys.* 45, 381–384.
- Doty, R.L., Perl, D.P., Steele, J.C., Chen, K.M., Pierce Jr., J.D., Reyes, P., Kurland, L.T., 1991. Olfactory dysfunction in three neurodegenerative diseases. *Geriatrics* 46 (Suppl 1), 47–51.
- Doty, R.L., Marcus, A., Lee, W.W., 1996. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). *Laryngoscope* 106, 353–356.
- Duff, K., McCaffrey, R.J., Solomon, G.S., 2002. The Pocket Smell Test: successfully discriminating probable Alzheimer's dementia from vascular dementia and major depression. *J. Neuropsychiatry Clin. Neurosci.* 14 (2), 197–201.
- Gomez-Isla, T., Price, J.L., McKeel Jr., D.W., Morris, J.C., Growdon, J.H., Hyman, B.T., 1996. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. *J. Neurosci.* 16 (14), 4491–4500.
- Graves, A.B., Bowen, J.D., Rajaram, L., McCormick, W.C., McCurry, S.M., Schellenberg, G.D., Larson, E.B., 1999. Impaired olfaction as a marker for cognitive decline: interaction with apolipoprotein E epsilon4 status. *Neurology* 53 (7), 1480–1487.
- Gray, A.J., Staples, V., Murren, K., Dhariwal, A., Bentham, P., 2001. Olfactory identification is impaired in clinic-based patients with vascular dementia and senile dementia of Alzheimer type. *Int. J. Geriatr. Psychiatry* 16 (5), 513–517.
- Handley, O.J., Morrison, C.M., Miles, C., Bayer, A.J., 2006. ApoE gene and familial risk of Alzheimer's disease as predictors of odour identification in older adults. *Neurobiol. Aging* 27, 1425–1430.
- Hyman, B.T., Arriagada, P.V., Van Hoesen, G.W., 1991. Pathologic changes in the olfactory system in aging and Alzheimer's disease. *Ann. N. Y. Acad. Sci.* 640, 14–19.
- Killiany, R.J., Hyman, B.T., Gomez-Isla, T., Moss, M.B., Kikinis, R., Jolesz, F., Tanzi, R., Jones, K., Albert, M.S., 2002. MRI measures of entorhinal cortex vs hippocampus in preclinical AD. *Neurology* 58, 1188–1196.
- Kovacs, T., Cairns, N.J., Lantos, P.L., 1999. Beta-amyloid deposition and neurofibrillary tangle formation in the olfactory bulb in ageing and Alzheimer's disease. *Neuropathol. Appl. Neurobiol.* 25 (6), 481–491.
- Manly, J.J., Bell-McGinty, S., Tang, M.X., Schupf, N., Stern, Y., Mayeux, R., 2005. Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. *Arch. Neurol.* 62, 1739–1746.
- Morgan, C.D., Nordin, S., Murphy, C., 1995. Odor identification as an early marker for Alzheimer's disease: impact of lexical functioning and detection sensitivity. *J. Clin. Exp. Neuropsychol.* 17 (5), 793–803.
- Murphy, C., 2002. Olfactory functional testing: sensitivity and specificity for Alzheimer's disease. *Drug Dev. Res.* 56, 123–131.
- Murphy, C., Bacon, A.W., Bondi, M.W., Salmon, D.P., 1998 Nov 30. Apolipoprotein E status is associated with odor identification deficits in nondemented older persons. *Ann. N. Y. Acad. Sci.* 855, 744–750.
- Murphy, C., Jernigan, T.L., Fennema-Notestine, C., 2003. Left hippocampal volume loss in Alzheimer's disease is reflected in performance on odor identification: a structural MRI study. *J. Int. Neuropsychol. Soc.* 9 (3), 459–471.
- Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. *J. Intern. Med.* 256, 183–194.
- Price, J.L., Morris, J.C., 1999. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann. Neurol.* 45, 358–368.
- Reyes, P.F., Deems, D.A., Suarez, M.G., 1993. Olfactory-related changes in Alzheimer's disease: a quantitative neuropathologic study. *Brain Res. Bull.* 32 (1), 1–5.
- Serby, M., Larson, P., Kalkstein, D., 1991. The nature and course of olfactory deficits in Alzheimer's disease. *Am. J. Psychiatry* 148 (3), 357–360.
- Stern, M.B., 1978. The clinical characteristics of Parkinson's disease and parkinsonian syndromes: diagnosis and assessment. In: Stern, M.B., Hurtig, H.I. (Eds.), *The Comprehensive Management of Parkinson's Disease*. PMA Publishing Corporation, New York, pp. 34–39.
- Stern, Y., Andrews, H., Pittman, J., Sano, M., Tatemichi, T., Lantigua, R., Mayeux, R., 1992. Diagnosis of dementia in a heterogeneous population: development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. *Arch. Neurol.* 49, 453–460.
- Swan, G.E., Carmelli, D., 2002. Impaired olfaction predicts cognitive decline in nondemented older adults. *Neuroepidemiology* 21, 58–67.
- Tabert, M., Liu, X., Doty, R.L., Serby, M., Zamora, D., Pelton, G.H., Marder, K., Albers, M.W., Stern, Y., Devanand, D.P., 2005. A 10-item smell identification scale related to risk for Alzheimer's disease. *Ann. Neurol.* 58, 155–160.
- Tabert, M.H., Manly, J.J., Liu, X., Pelton, G.H., Rosenblum, S., Jacobs, M., Zamora, D., Goodkind, M., Bell, K., Stern, Y., Devanand, D.P., 2006. Neuropsychological prediction of conversion to Alzheimer's disease in patients with mild cognitive impairment. *Arch. Gen. Psychiatry* 63, 916–924.
- Wang, J., Eslinger, P.J., Smith, M.B., Yang, Q.X., 2005. Functional magnetic resonance imaging study of human olfaction and normal aging. *J. Gerontol. A. Biol. Sci. Med. Sci.* 60, 510–514.
- Westervelt, H.J., Carvalho, J., Duff, K., 2007. Presentation of Alzheimer's disease in patients with and without olfactory deficits. *Arch. Clin. Neuropsychol.* 22 (1), 117–122.
- Wiebe, S.P., Staubli, U.V., 2001. Recognition memory correlates of hippocampal theta cells. *J. Neurosci.* 21 (11), 3955–3967.
- Wilson, R.S., Arnold, S.E., Schneider, J.A., Tang, Y., Bennett, D.A., 2007a. The relationship between cerebral Alzheimer's disease pathology and

- odour identification in old age. *J. Neurol. Neurosurg. Psychiatry* 78, 30–35.
- Wilson, R.S., Schneider, J.A., Arnold, S.E., Tang, Y., Boyle, P.A., Bennett, D.A., 2007b. Olfactory identification and incidence of mild cognitive impairment in older age. *Arch. Gen. Psychiatry* 64 (7), 802–808.
- Yousem, D.M., Maldjian, J.A., Siddiqi, F., Hummel, T., Alsop, D.C., Geckle, R.J., Bilker, W.B., Doty, R.L., 1999. Gender effects on odor-stimulated functional magnetic resonance imaging. *Brain Res.* 818 (2), 480–487.
- Zald, D.H., Pardo, J.V., 2000. Functional neuroimaging of the olfactory system in humans. *Int. J. Psychophysiol.* 36 (2), 165–181.