Combining olfaction and cognition measures to screen for mild cognitive impairment

Mary Ann F Kirkpatrick[1]
Wendell Combest[1]
Marian Newton[1]
Yvonne Teske[1]
John Cavendish[2]
Rhonda McGee[2]
Danielle Przychodzin[2]

[1]Shenandoah University, Winchester, VA, USA;
[2]formerly Shenandoah University

Purpose: This exploratory study examined the relationship between performance on the University of Pennsylvania Smell Identification Test (UPSIT) and the Addenbrooke's Cognitive Examination (ACE) to identify a possible association between olfaction and mild cognitive impairment(MCI).

Design and Methods: 54 community-dwelling older (ages 49–91) volunteers were given the UPSIT and ACE.

Results: The ACE identified 7 subjects (13%) who had probable MCI. UPSIT total scores were significantly related to ACE total scores (r = 0.37, p = 0.005). Four specific odorants (mint, lime, chocolate, and cheddar cheese) from the UPSIT identified 4 of the 7 (57.1%) probable MCI subjects. The prevalence rate of MCI in subjects over 65 was 19.4%.

Implications: Selective odorants in UPSIT used with ACE show promise as a non-invasive method of detecting MCI in community dwelling elders. Detection of MCI could facilitate earlier interventions and treatment of dementia.

Keywords: memory, smell, elderly, community-dwelling, tests

Introduction

This exploratory study grew out of a perceived need by the authors (pharmacist, occupational therapist, pharmacologist, and geropsychiatric nurse practitioner) to develop a non-invasive, easy-to-use tool for identifying community dwelling older adults with mild cognitive impairment (MCI). Our practices show that instruments used in health care settings often fail to detect small changes in cognition resulting in delayed diagnosis of mental decline. These delays reduce or eliminate the opportunity to make crucial life decisions such as health, financial, and housing decisions plus postpone early pharmacological treatments to slow declines associated with dementia.

In this paper, we discuss the concept of MCI and olfactory deficits associated with cognition. In the methods section, we describe our study subjects, community dwelling elders who volunteered to take two tests: the Addenbrooke's Cognitive Examination (ACE) and the University of Pennsylvania Smell Identification Test (UPSIT). We also describe data collection and analysis methods, and present and discuss our study results.

Background
MCI

Considerable evidence documents the predictive value of individuals diagnosed with MCI (Knopman et al 2000; Relkin 2000) and the eventual progression to a diagnosis of dementia (Petersen et al 2001a; Bennett et al 2002). Petersen et al (2001a) describe mild cognitive impairment as "mildly impaired individuals who may be in a transitional stage between normal aging and dementia" (p. 1134). MCI criteria are (1) memory complaint, preferably corroborated by an informant; (2) objective memory impairment that is abnormal for age and educational background; (3) normal general cognitive function; (4) intact activities of daily living; (5) absence of [diagnosed] dementia (Petersen et al

Correspondence: Mary Ann F. Kirkpatrick
1460 University Drive, Winchester, VA 22601, USA
Email mkirkpat@su.edu

2001a). There are many concepts used to describe age-associated cognitive decline (Crook et al 1986) but not all lead to dementia (Hanninen 1996). However, studies from clinic-based practices have reported that approximately 44% of individuals diagnosed with MCI convert to dementia over a three-year follow-up period, demonstrating an annual conversion rate of 10% to 15% of individuals per year (Grundman et al 1996). This is consistent with a more recent study showing an annual conversion rate from MCI to dementia of 12% (Petersen et al 2001b). Research (Knopman et al 2000; Bennett et al 2002; Tabert et al 2006) shows the progression of cognitive decline from a recognition of early signs of disease by care givers to the development of defined symptoms of dementia by healthcare providers to be between 3 and 4 years, opening a window for possible early interventions.

Interventions include the monitoring of activities of daily living such as financial management, estate planning, driving ability, medical advance directives, housing, and mobility (Hogan and McKeith 2001; Karlawish and Clark 2003). Interventions may also include medications such as anticholinesterase or nootropic agents that show potential in slowing the progression of selected dementias and possibly enhancing cognition (Zanni and Wick 2002).

Early detection of MCI is challenging as there is still limited and conflicting information on normal age-related cognitive and sensory changes. For example, the rate of age-associated anosmia, the loss of the sense of smell, has been reported between 5% and 50% in individuals 60–90 years of age but specific causes for the deficits can be difficult to identify. Common diseases and commonly used medications can cause anosmia (Ackerman and Kasbekar 1997).

Olfaction

Studies by several investigators (Doty 1995; Devanand et al 2000) show a relationship between olfaction and dementia. Doty (1995) used the inability to select odorants to identify individuals with dementia using the UPSIT. Recent studies (Devanand et al 2000) identified a characteristic deficit in the olfactory sense associated with dementia. Graves and colleagues (1999) found a smell identification test detected cognitive decline better than a test of global cognition. This decline in the sense of smell occurs very early in the process and also occurs to a lesser degree in normal aging (Larsson et al 1999; Peters et al 2003). In Alzheimer's disease (AD), degeneration occurs in the entorhinal-hippocampal-subicular complex, and the neurons of the olfactory neuroepithelium show numerous neurofibrillary tangles (Talamo et al 1989; Royet et al 2001) which may partially explain olfactory dysfunction. Brain imagining methods such as magnetic resonance imaging (MRI) and positron emission tomography (PET) have detected subtle structural changes early in MCI and during progression to AD (Graves et al 1999; Kantarci et al 2000). Chertkow (2002) described very early structural changes in the entorhinal cortex leading to olfactory deficits which have been detected by these imaging methods before any measurable change in cognition.

Information associating olfactory decline with MCI is limited; however, Devanand et al (2000) report that individuals with MCI have olfactory identification deficits and lack awareness of these deficits. Several chemical substances, disease states, and treatment procedures affect the sense of smell. Examples include α-interferon treatment, cocaine (when insufflated), nifedipine, tobacco products, and antineoplastic agents for cancer treatment. Among conditions associated with anosmia are those affecting the central nervous system, such as stroke, head trauma, brain tumors, and Parkinsonism, diabetes mellitus, aneurysm, artery rupture, allergic rhinitis, (Ackerman and Nishamony 1997) as well as nasal obstruction.

MCI diagnosis

Increasing progress is being made in our understanding of the disease process underlying dementia as well as the design of novel therapeutic agents which may slow or possibly prevent the progression of the disease. Yet studies show a widespread failure to recognize dementias in their early stages. Relkin (2000) reported studies that found primary care physicians failed to recognize dementia in 24%–72% of known cases and that general practitioners recognized MCI in only 3.2% of cases.

Early detection of MCI would allow the maximum use of potential therapeutic intervention before irreversible neuronal damage has occurred. There is a need to develop ways to detect early cognitive deficits long before symptoms of dementia such as objective memory impairment are apparent (Karlawish and Clark 2003). Unfortunately, currently available non-invasive measures such as the Mini-Mental State Exam (MMSE) (Folstein et al 1975) have not been adequate to measure small changes in cognition (Salmon et al 2002; Boeve et al 2003) or to distinguish between MCI and depression (Bensen et al 2005). By correlating and combining the discriminating power of the UPSIT and ACE, we were able to detect signs of MCI.

Methods
Subjects
Investigators recruited volunteers over the age of 45 years from a number of senior housing complexes, senior centers, a local university, and local churches. A prescreening process excluded from the study individuals who smoked, had selective medical conditions or used medication (see Appendix) that might interfere with olfaction. The final sample of 54 subjects was comprised of 37 females and 17 males. The ages of the subjects ranged from 46 to 91 with the median being 67 years of age. The educational level ranged from 7 to 24 years of formal schooling, with the median being 15 years.

Instruments
Cognition
The Addenbrooke's Cognitive Examination was used in this study to distinguish those subjects with MCI from the total sample population. It is a validated instrument which can be used to detect dementia and mild cognitive impairment (Mathuranath et al 2000). In studies completed by Mathuranath et al (2000, p 1619), "age, number of years of education, or gender did not influence the predictive outcome using the ACE".

The ACE consists of 22 scored items with an emphasis on measuring episodic memory, executive function, and language ability. The ACE also incorporates the MMSE in its entirety. The ACE evaluates 6 discrete cognitive domains: orientation, attention, memory, verbal fluency, language, and visual-spatial ability. Scores for each domain are calculated and combined for an ACE total score. Past studies have shown the ACE to be 82% sensitive and 96% specific in detecting early dementias. Developers of the ACE used Chronbach's alpha coefficient of internal consistency to measure reliability. "The Chronbach's alpha for the ACE was 0.78." (Mathuranath et al 2000, p 1616).

The ACE total score ranges from 0 to 100. To identify subjects with MCI, researchers used an ACE calculation called the VL/OM to eliminate subjects who might have dementia. The VL/OM, calculated by summing the scores on the verbal fluency and language sections on the ACE and dividing by the sum of the orientation and delayed recall sections, identified and eliminated subjects with probable Alzheimer's disease and frontotemporal dementias.

To identify MCI, Mathuranath et al (2000, p 1618) recommend using a "cut off score of 83…for research studies…which require high specificity, or when screening populations with low base rate dementia". Test developers (Mathuranath et al 2000) selected 83 from the ACE total score of 100 by estimating the probability of accurately diagnosing dementia in their criterion group.

In addition, the diagnostic criteria for MCI require normal general cognitive function. Following the ACE recommendations, researchers eliminated subjects scoring below one standard deviation on the ACE total score mean (less than 84). Finally, to meet the criteria of objective memory impairment, subjects whose score on delayed-recall items on the ACE was one standard deviation below the predicted score for their age and/or educational level were selected for inclusion in the selected MCI group.

Olfaction
The University of Pennsylvania Smell Identification Test (UPSIT) is a 40-item "scratch-and-sniff" odor identification panel which has been used to identify individuals with dementia. The UPSIT consists of 4 booklets, each containing 10 odorants. Odorants are released by scratching the strips in which they are embedded with a pencil tip. Subjects are asked to select the odorant from a list of 4 choices. A forced-choice format is used in which subjects are asked to mark 1 of the 4 alternatives, even if they report not being able to perceive an odorant. This procedure reduces the dependence on working memory and language (Peters et al 2003). The normal range of scores (number of correct responses out of a possible 40) on the UPSIT for males is 34–40 and 35–40 for females. The test-retest and split-half reliability have consistently been found to be over 0.90 (Doty et al 1984; Doty 2000).

Data collection
Prior to data collection to improve inter-rater reliability, researchers tested procedures by video taping administration of the ACE to 5 community volunteers. Video tapes were compared and protocols written for research testing. Five members of the research team collected data from June–October 2002 at senior housing complexes, senior centers, churches, and in a university building. To maximize consistency, 3 investigators administered the ACE to all participants and two investigators administered the UPSIT exclusively. The order of administration of these two instruments was randomly assigned. Responses to the ACE were entered on a score sheet by the interviewer. Subjects recorded their own responses to the 40 items on the UPSIT.

Data analysis

Data analysis included calculations of descriptive statistics for all variables and split-half reliability coefficients for each instrument. In addition, the data were analyzed to identify individuals who met the diagnostic criteria for mild cognitive impairment. This step eliminated 7 subjects who scored in the dementia range on the ACE. To ensure our MCI sample did not include persons with dementia, we also eliminated 6 subjects with ACE total scores below 84, one standard deviation below the mean. A new ACE variable was created by combining the scores on the two delayed recall items with a possible range of 0–10. Using the ACE criterion, subjects whose score on this variable was one standard deviation below the predicted score for their age and/or educational level were classified as the MCI subgroup. A step-wise binary regression model was constructed using the dichotomous MCI-normal classification as the dependent variable and scores on the UPSIT as independent variables. The purpose of this analysis was to establish a "best predictor" model whereby the highest percentage of cases could be correctly classified with respect to being in the MCI or normal groups. Kappa statistics were calculated to determine if group membership was due to chance.

The final stage in the analysis was to examine the extent to which the UPSIT could accurately predict group membership (MCI vs normal). In this stage, we ran two stepwise regressions. In the first, the total UPSIT score was used as covariate (independent variable), and in the second, 35 of the individual odors on the UPSIT were entered as covariates using the stepwise method.

Results

ACE

ACE scores for all subjects ranged from 49 to 100, with a mean of 90.6, a median of 94, and a standard deviation of 3.4. Age had a significant negative correlation with the total score ($r = -0.53$, $p = 0.001$); education had a significant positive correlation with this score ($r = 0.43$, $p = 0.002$). Males scored significantly higher than females with means being 93.7 and 89.1 respectively ($t = 2.19$, $df = 48$, $p = 0.03$).

The VL/OM calculation identified two subjects with probable Alzheimer's disease and five subjects with probable frontotemporal dementia. These 7 subjects were eliminated from our analysis.

UPSIT

UPSIT scores for all subjects ranged from 24 to 38 with a mean of 32.8, a median of 33.5, and a standard deviation of 2. Scores were significantly related to the ACE total score ($r = 0.37$, $p = 0.005$). There was a negative correlation with age ($r = -0.35$, $p = 0.01$), and a positive correlation with education ($r = 0.35$, $p = 0.01$). Gender was not significantly related to the total score on the UPSIT.

Table 1 presents the demographic breakdown of the final groups and their scores on the ACE and UPSIT. The MCI group included 2 males and 5 females; the normal group included 13 males and 21 females. Correlations between the demographic variables and the total scores on the ACE and UPSIT are shown in Table 2.

Motor oil, gasoline, leather, root beer, and peanut were excluded from the analysis because all of the subjects correctly identified them. The results of this stage suggest that four specific odors (mint, chocolate, lime, and cheddar cheese) of the 40 odorants of the UPSIT best predict the presence of MCI (see Table 3) in older individuals. A Kappa statistic was calculated to assess the extent to which the prediction model predicted MCI-Normal group membership taking chance agreements in group membership. The Kappa statistic was 0.61, $p < 0.0001$, indicating that the model generated a better than 61% improvement in prediction over chance.

Discussion

The primary findings of this exploratory study are that community-dwelling older individuals with probable MCI lack the ability to identify a small group of odorants (mint,

Table 1 Age, education, ACE, and UPSIT Scores for MCI[a] and normal[b] groups

Age		Education		ACE		UPSIT	
MCI	Normal	MCI	Normal	MCI	Normal	MCI	Normal
70.71	64.03	15.00	16.12	91.14	95.21	33.14	33.50
(8.16)	(11.44)	(3.11)	(3.54)	(2.48)	(2.97)	(2.19)	(3.05)

Note: Mean values are reported with standard deviations. [a]n = 7 [b]n = 34.
Abbreviations: ACE, Addenbrooke's Cognitive Examination; MCI, mild cognitive impairment; UPSIT, University of Pennsylvania Smell Identification Test.

Table 2 Intercorrelations between age, education, and scores on the ACE, UPSIT, and MMSE for all subjects

Variable	Age	Education	MMSE[a]	ACE	UPSIT
Age	—	−0.23	−0.18	−0.34[*]	−0.44[**]
Educat		—	0.47[**]	0.62[**]	0.23
MMSE[a]			—	0.67[**]	0.26
ACE				—	0.29

Note: n = 41 [a]The MMSE is embedded in ACE. [*]p < 0.05, two-tailed. [**]p < 0.01, two-tailed.
Abbreviations: ACE, Addenbrooke's Cognitive Examination; MMSE, Mini Mental State Examination; UPSIT, University of Pennsylvania Smell Identification Test.

lime, chocolate, and cheddar cheese); whereas all subjects, regardless of cognitive status, can correctly identify a different group of odorants (motor oil, gasoline, leather, root beer and peanut). This finding suggests that a small selective group of odorants can be used as a quick, easy, non-invasive tool to identify individuals with MCI. The advantages of early diagnosis include earlier treatment to prevent or delay neuronal damage associated with dementias such as Alzheimer's and allowing individuals with MCI time to seek available services and make future living decisions.

The ACE demonstrated its usefulness as an instrument. ACE total score identified 7 subjects of 54 (13%) community-dwelling individuals, between 49 and 91 years of age, with probable MCI. This is an important finding since nearly half of individuals with MCI tend to develop dementia within three years (Grundman et al 1996). The prevalence of MCI in our subjects over sixty-five was 19.4%, which is well within the range of most previously reported prevalence rates (Grundman et al 1996). ACE total score was

able to distinguish among normal subjects, 2 subjects (3.7%) with probable Alzheimer's disease, and 5 subjects (9.3%) with probable frontotemporal dementia. Alzheimer's and frontotemporal dementias represented 13% of our total sample of community-dwelling elders which approaches the prevalence rates of 14.5 to 26.2% for lifetime risk of Alzheimer's reported by Chertkow (2002).

The results of this study demonstrate the need to adjust scores on cognitive assessments such as the ACE for age and education before applying them to screening criteria. The ACE total score showed a positive correlation with years of education and a significant negative correlation with age. Gender was not significantly related to the full scale score on the UPSIT which is not consistent with findings by Peters et al (2003); males, however, scored significantly higher than females on the ACE.

The UPSIT total scores showed a significantly negative correlation with age. Using age-adjusted total scores did not improve the predictive ability of the UPSIT.

This exploratory study had several limitations. The small sample of individuals (n = 7) with MCI was drawn from a regional population of convenience, rather than by random selection. Investigators were unable to ascertain if fatigue was a factor in subject performance. Administration of the complete UPSIT and complete ACE required concentration and took approximately 1 hour, a long time for subjects unaccustomed to such activities. Another limitation was the diversity of testing environments. Distractions in the various community-based environments may have effected how subjects responded to the ACE and UPSIT.

In conclusion, by administering the UPSIT, four specific odorants (mint, lime, chocolate, and cheddar cheese) were found to be predictive of MCI, as defined by ACE total score in community-dwelling older individuals. These selective 4 odorants proved to be better predictors of MCI than UPSIT total scores.

Studies by Peters et al (2003) and Tabert et al (2006) highlight the importance of evaluating dysfunction in olfaction and specific areas of cognition to identify individuals prior to

Table 3 Predictive ability of UPSIT total score versus selective odorants

	UPSIT total score[a]	Selective odorants[b,c]
		MCI group
Predicted	0	4
Actual	7	7
Sensitivity	0.0%	57.1%
		Normal group
Predicted	34	33
Actual	34	34
Specificity	100%	97.1%

Note: Predicted and actual values are numbers of subjects.
[a]The Nagelkerke R^2 estimator for this model was 0.0.
[b]Four odors (mint, chocolate, cheddar cheese, and lime) were entered in the model.
[c]The Nagelkerke R^2 estimator for this model was 0.50.
Abbreviations: MCI, mild cognitive impairment; UPSIT, University of Pennsylvania Smell Identification Test.

Alzheimer's disease. Future studies would require larger, more diverse populations from community settings to substantiate our exploratory study results. One research direction would be to identify a subset of items in the ACE and UPSIT with the greatest predictive value to increase the sensitivity and specificity to develop a useful, less time consuming, test for clinicians.

References

Ackerman B, Nishamony K. 1997. Disturbances of taste and smell induced by drugs. *Pharmacotherapy*, 17:482–96.

Bennett DA, Wilson RS, Schneider JA, et al. 2002. Natural history of mild cognitive impairment in older individuals. *Neurology*, 59:198–205.

Benson A, Slavin MJ, Tran T-T, et al. 2005. Screening for early alzheimer's disease: is there still a role for mini-mental state examination? *Prim Care Companion J Clin Psychiatry*, 7:62–9.

Boeve B, McCormick J, Smith G, et al. 2003. Mild cognitive impairment in the oldest old. *Neurology*, 60:477–80.

Chertkow H. 2002. Mild cognitive impairment. *Curr Opin Neurol*, 15:401–7.

Crook T, Bartus RT, Ferris SH, et al. 1986. Age-associated memory impairment: proposed diagnostic criteria and measures of clinical change – report of a national institute of mental health work group. *Dev Neuropsychol*, 2:261–76.

Devanand DP, Michaels-Marston KS, Liu X, et al. 2000. Olfactory deficits in patients with Mild Cognitive Impairment predict Alzheimer's disease at follow-up. *Am J Psychiatry*,157:1399–405.

Doty RL. 2000. Odor Threshold Test™ Administration Manual. Haddon Heights, NJ: Sensonics.

Doty RL, Bromley SM, Stern MB. 1995. Olfactory testing as an aid in the diagnosis of parkinson's disease: development of optimal discrimination criteria. *Neurodegeneration*, 4:93–7.

Doty RL, Shaman P, Dann M. 1984. Development of the university of Pennsylvania smell identification test: a standardized microen-capsulated test of olfactory function. *Physiol Behav*, 32:489–502.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-mental state" a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*, 12:189–98.

Graves AB, Bowen JD, Rajaram L, et al. 1999. Impaired olfaction as a marker for cognitive decline: interaction with apolipoprotein e [small element of] 4 status. *Neurology*, 53:1480–7.

Grundman M, Petersen RC, Morris JC, et al. 1996. ADSC cooperative study: rate of dementia of the Alzheimer type (dat) in subjects with mild cognitive impairment [abstract]. *Neurology*, 46:Abstract No. A403.

Hanninen T. 1996. Age-associated memory impairment: a neuro-psychological and epidemiological study. Doctoral dissertation. Department of Neurology and Medicine, Department of Psychology, University of Kuopio, Finland [online]. Retrieved September 16, 2002. URL: www.ukufi/neuro/39the.htm.

Hogan DB, McKeith IG. 2001. Of mci and dementia: improving diagnosis and treatment. *Neurology*, 56:1131–2.

Kantarci K, Jack CR, Xu YC, et al. 2000. Regional metabolic patterns in mild cognitive impairment and alzheimer's disease: a 1h mrs study. *Neurology*, 55:219–17.

Karlawish JHT, Clark CM. 2003. Diagnostic evaluation of elderly patients with mild memory problems. *Ann Intern Med*, 138:411–19.

Knopman D, Donohue JA, Gutterman EM. 2000. Patterns of care in the early stages of Alzheimer's disease: impediments to timely diagnosis. *Journal of the American Gerontological Society*, 48:300–4.

Larsson M, Semb H, Winblad B, et al. 1991. Odor identification in normal aging and early alzheimer's disease: effects of retrieval support. *Neuropsychology*, 13:47–53.

Mathuranath PS, Nesto PJ, Berrios GE, et al. 2000. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology*, 55:1613–20.

Peters JM, Hummel T, Kratzsch T, et al. 2003. Olfactory function in mild cognitive impairment and alzheimer's disease: an investigation using psychophysical and electrophysiological techniques. *Am J Psychiatry*,160:1995–2002.

Petersen RC, Stevens JC, Gangul M, et al. 2001a. Practice parameter: early detection of dementia: mild cognitive impairment, an evidence-based review. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 56:1133–42.

Petersen RC, Doody R, Kurz A, et al. 2001b. Current concepts in mild cognitive impairment. *Arch Neurol*, 58:1985–92.

Relkin N. 2000. Screening and early diagnosis of dementia. *Am J Manag Care*, 6:S1111–24.

Royet JP, Croisile B, Williamson-Vasta R, et al. 2001. Rating of different olfactory judgements in alzheimer's disease. *Chem Senses*, 26:409–17.

Salmon DP, Thomas RG, Pay MM, et al. 2002. Alzheimer's disease can be accurately diagnosed in very mildly impaired individuals. *Neurology*, 59, 1022–1028.

Tabert MH, Manly JJ, Zinhua L, et al. 2006. Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. *Arch Gen Psychiatry*, 63:916–24.

Talamo BR, Rudel RA, Kosik KS, et al. 1989. Pathological changes in olfactory neurons in patients with alzheimer's disease. *Nature*, 337:736–9.

Zanni GR, Wick JY. 2002. Rethinking Alzheimer's disease. *Consult Pharm*, 17:626–40.

Appendix

Medications and medical conditions included in exclusion criteria.

Medications
- Topical nasal vasoconstrictors (Afrin®)
- Cocaine
- Nifedipine (Adalate®, Procardia®)
- Cancer medications

Medical conditions
- Nasal infections (colds, flu, stuffy nose)
- History of smoking
- History of stroke
- Diabetes mellitus
- Brain tumor
- History of head trauma
- Parkinsonism