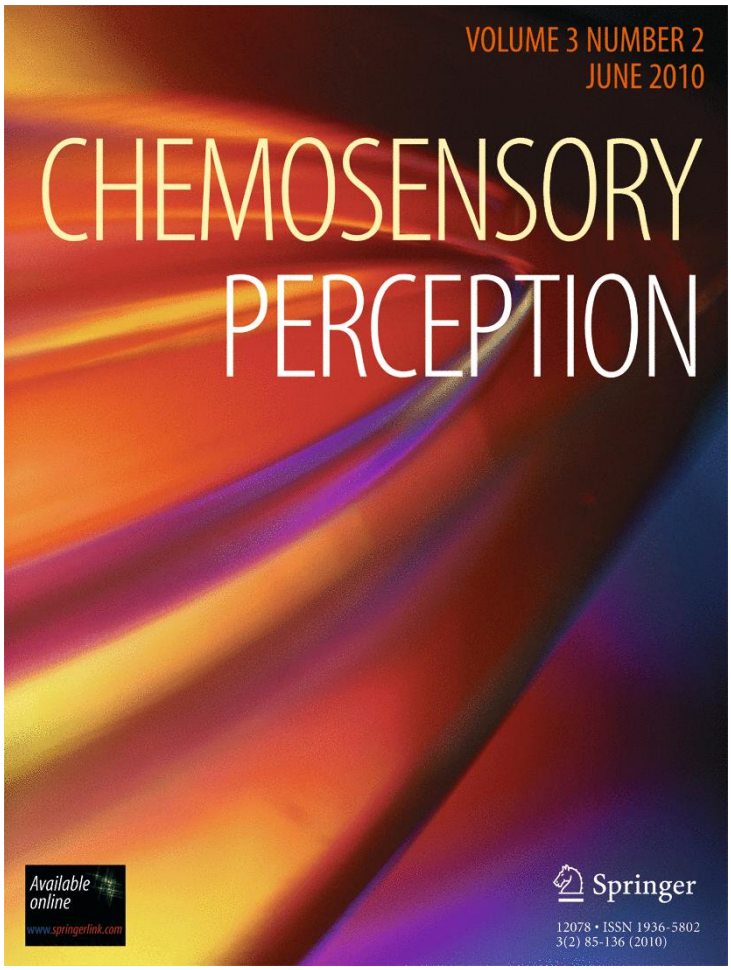
ISSN 1936-5802, Volume 3, Number 2



Chem. Percept. (2010) 3:118–128
DOI 10.1007/s12078-010-9069-x

Can I Smell Gas (or Is It Lilac)? Olfactory Semantic Deficits in Mild Cognitive Impairment and Alzheimer's Disease

Alex Bahar-Fuchs · Simon Moss · Christopher Rowe · Greg Savage

Received: 16 December 2009 / Accepted: 29 March 2010 / Published online: 17 April 2010

Abstract Olfactory decline represents one of the earliest signs of Alzheimer's disease (AD), and deficits in olfactory identification have now been identified in persons with amnestic mild cognitive impairment (aMCI). Whether the olfactory identification deficit in AD reflects underlying degraded semantic knowledge or lower-order olfactory deficits is uncertain. To address this question, we focused on the kinds of errors committed when participants were given a unirhinal olfactory identification task at baseline and after 1 year. The aim was to assess whether more errors were committed when the target smell is either semantically related or unrelated to the distracters. Fourteen AD, 13 aMCI, and 10 control participants were tested using a modified version of the University of Pennsylvania Smell Identification Test. Examination of error types showed that the control group predominantly selected distracters which were related to the target; in contrast, distracters that were unrelated to the target odor were selected as frequently as related odors by the AD and aMCI groups, for both nostrils. This pattern was maintained 1 year later, and previously designated aMCI patients who then met criteria for AD were more inclined to choose the unrelated distracters than were aMCI patients who did not meet AD criteria. Olfactory identification deficits in AD and aMCI plausibly reflect deterioration in ability to access olfactory-mediated semantic knowledge. This pattern of errors may help distinguish the olfactory identification deficits observed in AD from olfactory identification deficits observed in other conditions not associated with semantic loss.

Keywords Error Analysis · Semantic Memory · Olfaction · Mild Cognitive Impairment

Abbreviations

AD	Alzheimer's disease
aMCI	Amnestic mild cognitive impairment
HC	Healthy control
SIT	Smell Identification Test

Introduction

Reports of olfactory identification deficits in Alzheimer's disease (AD) first appeared in the literature over two decades ago (Koss et al. 1988; Serby et al. 1985; Warner et al. 1986) and now represent an established part of the clinical picture in this disorder (Bacon et al. 1998; Luzzi et al. 2007; Murphy et al. 1998; Nordin and Murphy 1996; Serby et al. 1991). Individuals with AD are significantly less capable than matched controls of choosing which of several verbal labels most likely represents an odor (Warner et al. 1986). This finding cannot be ascribed to the lexical nature of the task, as similar findings have been found

A. Bahar-Fuchs · S. Moss · G. Savage
School of Psychology, Psychiatry & Psychological Medicine,
Monash University,
Melbourne, Australia

C. Rowe
Department of Nuclear Medicine, Austin Health,
Heidelberg, Victoria, Australia

G. Savage
Macquarie Centre for Cognitive Science, Macquarie University,
Sydney, Australia

A. Bahar-Fuchs (✉)
Center for PET, Department of Nuclear Medicine, Austin Health,
145 Studley Road,
Heidelberg 3084 Victoria, Australia
e-mail: bfalex@gmail.com

when the alternatives were presented pictorially (Morgan et al. 1995).

Recent studies have shown that olfactory deficits are present and can be detected well before patients meet clinical criteria for AD. Patients diagnosed with mild cognitive impairment (MCI) are now a natural target for scientific investigation of preclinical AD, with 12% of cases of so-called amnestic MCI (aMCI) representing the prodromal stage of AD (Petersen et al. 2001; Yaffe et al. 2006). Several studies focusing on this heterogeneous group of patients have uncovered deficits in olfactory abilities, particularly in olfactory identification (Djordjevic et al. 2008; Eibenstein et al. 2005; Wang et al. 2002). Moreover, impaired olfactory identification in aMCI can predict conversion to AD (Albers et al. 2006; Devanand et al. 2000; Nordin and Murphy 1996; Peters et al. 2003) and cognitive decline among healthy community-dwelling volunteers (Wilson et al. 2007), particularly if the olfactory deficit is detected among individuals with at least one ApoE-ε4 allele (Graves et al. 1999).

The process of olfactory identification represents a complex task involving the need to access semantic memory representations (Stevenson and Boakes 2003). Identification represents a late stage in the chain of olfactory information processing and assumes the intact functioning of lower-order sensory and perceptual abilities, such as detection and discrimination. Because impaired semantic processing is prominent in AD (Adlam et al. 2006), some authors maintain the observed olfactory identification abilities might, at least in part, reflect such semantic deterioration (Nagy and Loveland 2001). This association, however, is seldom explored directly, and the issue is not resolved.

Findings from two recent studies that addressed this question more directly have provided conflicting data. Luzzi et al. (2007) compared the performance of patients with four neurodegenerative disorders—AD, semantic dementia (SD), frontotemporal dementia, and corticobasal degeneration—on various tests of olfactory ability: odor discrimination, matching, and spontaneous naming. Although the AD and SD groups did not differ significantly on olfactory naming, the AD group performed significantly worse than the SD group on the olfactory discrimination task. Luzzi et al. concluded that the observed naming deficit in AD is secondary to a deficit at the perceptual level—that is, in olfactory discrimination.

Djordjevic et al. (2008) compared aMCI, AD, and healthy elderly controls on olfactory detection, discrimination, and identification. They found that impaired olfactory identification performance of AD patients could not be ascribed to deficits in olfactory threshold or discrimination. An olfactory discrimination deficit observed in the aMCI group, however, was eliminated once deficits in olfactory threshold were controlled. On this basis, Djordjevic et al. concluded that the deficit in olfactory identification observed in AD cannot fully be ascribed to deficits in lower-level olfactory functions; this finding aligns with the findings of observations of other authors (Morgan et al. 1995).

Olfactory Semantic Error Analysis

The aim of the current study was to assess the extent to which impaired semantic processing underpins the olfactory identification deficits observed in patients with early AD and aMCI. One approach to evaluating the integrity of semantic networks is through an observation of the types of errors that participants commit on forced-choice object identification or naming tasks (Barbarotto et al. 1998; Hodges et al. 1992; Moreaud et al. 2001). Analysis of error types has been suggested by other authors to differentiate diagnoses when global scores do not distinguish categories adequately (Finton et al. 1998; Ska et al. 1990). The type of errors AD patients commit on semantic tasks has been studied using different kinds of task and in different modalities, predominantly in the visual and verbal domains (Finton et al. 1998; Hodges et al. 1995; Hodges et al. 1992; Rogers et al. 2004a; Ska et al. 1990). To date, however, no research has explored the pattern of errors AD or aMCI patients commit on olfactory identification tasks.

Multiple choice tasks are commonly used to study the pattern of errors that participants commit (Barbarotto et al. 1998; Moreaud et al. 2001; Rogers et al. 2004a; Warrington and Crutch 2007). In the case of olfactory identification, multiple choice tasks are usually the preferred approach because of the observation that spontaneous naming of odors is poor even among individuals with intact olfactory functioning (Doty 1995). Instead, participants are typically presented with a target odor and they need to identify which option from a series of verbal labels represents the target.

Early models of semantic memory (Collins and Loftus 1975), as well as more recent accounts (Rogers et al. 2004b), assert that when presented with a target object, participants may erroneously recognize it as a different object if the two objects share many properties. The odor of a lilac might coactivate representations of a rose: lilacs share many properties with roses, with similarity in phenomenological odor character as well as coordinate membership of a semantic category (i.e., flowers). Thus, individuals with intact semantic networks may erroneously select alike options, such as rose, that share properties with a target such as lilac. They are less likely to select distracters that share fewer properties with the target item, such as cherries, which might smell broadly similar to lilacs but correspond to a distinctly different semantic category. In contrast, when semantic knowledge is degraded—such

as in AD—objects and concepts are thought to gradually share an increasing number of features, making the distinction between normally dissimilar items more challenging (Alathari et al. 2004; Garrard et al. 2005; Patterson 2007). Therefore, the presentation of an odor such as strawberry might result in the activation of semantic categories that are normally unrelated to the target, such as natural gas. Hence, the type of errors that aMCI and AD patients commit on olfactory identification tasks might reflect semantic degradation.

Manipulating the degree of similarity between target and distracter items in multiple choice olfactory identification paradigms has been shown to affect the performance of healthy volunteers (Engen 1987). The most commonly used olfactory identification test is the Smell Identification Test (SIT; Doty et al. 1984). The distracters employed in this test "were selected for each odorant so as to maximize their distinctiveness from one another as well as from the target stimulus" (Doty et al. 1984, p. 495). As such, the SIT and later derivations do not permit researchers to explore the type of identification errors participants commit.

In the present study, a manipulation was applied to a subset of SIT items that enabled an investigation of whether increasing semantic similarities between targets and distracters affects identification performance. We were also interested in whether any patterns in the baseline olfactory identification performance of aMCI patients, and in particular the pattern of errors, were related to the likelihood of conversion to AD status 1 year later.

Method

Participants

Fourteen patients diagnosed with AD, 13 patients diagnosed with aMCI and 11 healthy elderly controls (denoted HC) were recruited for the current study. The AD, aMCI, and HC participants had been recruited and assessed as part of their participation in a large-scale longitudinal project on imaging brain beta-amyloid (Aβ) using PiB-PET at Austin Health, Melbourne, Australia. Recruitment procedures, as well as inclusion and exclusion criteria for the PiB study, have been published elsewhere (Rowe et al. 2007). Briefly, all AD patients met the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria for "probable AD" (McKhann et al. 1984). The classification of aMCI was based on (1) a clinical opinion that they were neither demented nor unimpaired, (2) subjective report of decline over time with objective evidence of impairment and (3) no significant functional loss (Winblad et al. 2004). Cognitive impairment was defined as at least one neuropsychological memory test score falling 1.5 SD or more below the relevant normative data, in the context of normal non-memory test scores. Healthy control participants from the large-scale longitudinal Melbourne Healthy Aging Study (Collie et al. 2001; Weaver Cargin et al. 2006) were invited to participate. Screening of data for outliers revealed that one of the control participants was a multivariate outlier, as indicated by an elevated Mahalanobis distance, and this participant was excluded from analyses. Approximately 12 months following the initial assessment, 28 participants (8 HC, 13 aMCI, 7 AD) completed a follow-up assessment.

Exclusion criteria for the olfactory testing procedure included a recent history of viral infections and allergies, acute medical complications, or chronic medical conditions affecting olfactory function, or a history of head injury.

All participants provided their consent for the olfactory testing independently of their consent to participate in the PiB study or the healthy aging study. Where capacity to consent was uncertain, consent was also obtained from the primary carer, usually a spouse. This project was conducted under the approval of the ethics committees at Monash University and Austin Health, Melbourne, in accordance with the Declaration of Helsinki.

Materials

Development of the Semantic Smell Task

The SIT (Doty et al. 1984) is a 40-item, suprathreshold, scratch-and-sniff test. Respondents are instructed to smell an odor and are required to select the option that most likely represents the odor from a set of four written alternatives. Since its development over two decades ago, the SIT has become the test of choice for numerous research protocols, partly because the task is easy to administer, is ecologically valid, and is well tolerated by clinical populations. The test has been translated and normed for use in several languages, and several shorter versions have been developed for briefer procedures (Doty et al. 1996; Duff et al. 2002; Kjelvik et al. 2007).

A subset of 10 items selected from the SIT was used to construct an olfactory assessment procedure that differentiated two types of errors. The 10 items that were selected were: *menthol*, *clove*, *leather*, *strawberry*, *lilac*, *pineapple*, *smoke*, *lemon*, *soap*, and *natural gas.* These odors have been found by Tabert et al. (2005) to be most predictive of conversion from healthy ageing status to aMCI status to AD status when compared with the overall SIT.[1]

[1] The item *pizza* was substituted for Tabert et al.'s *lemon* due to widespread detection difficulties with the latter item in pilot testing.

To select distracters, a short pilot study was conducted with 12 healthy volunteers (six males, six females; mean age=38.7) who received a list of all 40 items in the SIT and were asked to categorize the names of smells in two different ways. First, raters were asked to assemble together items based on their character—that is, items they thought smelled alike. Second, they were asked to assemble together items based on their semantic membership—such as flowers, food, and so on. These data were then used to derive a set of items that were most often ranked as related to the 10 target items either in character or because they belonged to the same category. The item sets were not orthogonal with respect to semantic and characterological overlap; rather, we attempted to create a hierarchical design. At the highest level of similarity, distracters were highly confusable with the target in terms of semantic membership (e.g., the target *lilac* and the foil *rose* are both flowers) as well as in the way they smell (e.g., they are typically "floral"). At the next level of similarity, the distracter shared some physical similarity with the target item but did not belong to the same semantic category (e.g., the foil might be a fruit such as *cherry*). At the lowest level of similarity, foils did not share semantics or physical similarity with the target item (e.g., *natural gas*).

Neuropsychological Assessment

All participants underwent a neuropsychological evaluation that included the mini-mental state examination (MMSE; Folstein et al. 1975), 30-item Boston Naming Test (BNT; Saxton et al. 2000), Digit Span (DS), and Digit Symbol-Coding (DS-C) subtests from the Wechsler Adult Intelligence Scale—Third edition (Wechsler 1997), California Verbal Learning Test-Second edition (CVLT-II; Delis et al. 2000), Rey Complex Figure Test (RCFT; Meyers and Meyers 1995) and subtests of The Delis–Kaplan Executive Function System verbal fluency (Delis et al. 2000).

A composite episodic memory score was calculated by computing the average of the *z* scores (generated using the HC group as the reference) for RCFT and CVLT-II long-delay trials. A composite semantic memory score was calculated by computing the average of the *z* scores for the category fluency (animals and boys' names total) and the BNT. A composite non-memory cognition score was derived by computing the average of the *z* scores for letter fluency, DS, DS-C, and RCFT copy.

Demographic characteristics of the three participant groups, along with their mean composite scores in the three cognitive domains—episodic memory, semantic memory, and non-memory, are presented in Table 1. Mean age, educational attainment, and gender ratio did not vary significantly across the groups. As expected, the AD group exhibited lower scores on the MMSE compared with the aMCI group, which in turn demonstrated lower scores than the HC group. Performances of the aMCI group were worse than the HC group and no different from the AD group on both the composite episodic memory score and the composite semantic memory score. The aMCI group's performances were not different from the HC group's and significantly better than the AD group's on the composite non-memory score.

Procedures

Unirhinal olfactory testing has been the preferred methodology in several recent protocols with other clinical populations (Good et al. 2002; Szeszko et al. 2004). In early AD, subtle asymmetries in the neuropathological burden may manifest in functional asymmetries on olfactory tasks and may have implications for differential

Table 1 Selected participant characteristics and composite scores

	HC (n=10)	aMCI (n=13)	AD (n=14)
Age	73(5.3) a	74.5 (7.1) a	74.14 (10.2) a
Education	13 (2.3) a	14.8 (5.9) a	13.8 (4.5) a
% Male	30 a	53.8 a	50 a
MMSE	29.5 (0.8) a	25.6 (2.4) b	23.3 (3.3) c
Composite episodic memory[a]	−0.07 (0.94) a	−3.65 (1.50) b	−4.38 (1.08) b
Composite semantic memory[b]	−0.08 (0.95) a	−2.85 (2.81) b	−3.35 (2.53) b
Non-memory composite[c]	−0.02 (0.76) a	−1.29 (1.22) a	−2.96 (1.98) b

Data are presented as means (standard deviations) unless otherwise indicated. Figures in the same row that do not share the same letter are different at $p<0.01$.

AD Alzheimer's disease, *aMCI* amnestic mild cognitive impairment, *HC* healthy controls, *MMSE* mini-mental state examination

[a] Calculated as the average of the *z* score for CVLT-II Long Delay Free Recall and RCFT 30-min delayed recall

[b] Calculated as the average of the *z* scores for BNT and category fluency

[c] Calculated as the average of the *z* scores for RCFT copy, DS, DS-C, and letter fluency

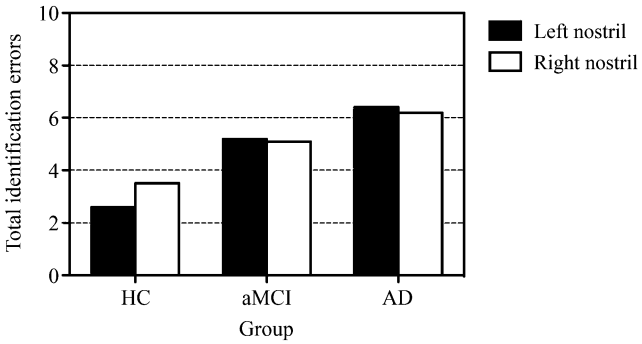


Fig. 1 Mean overall error rate in identification on the left and right nostril in each group

diagnosis. We have reported elsewhere the contribution of unirhinal olfactory testing to the differentiation of people with aMCI from AD patients (Bahar-Fuchs et al. 2007). Accordingly, the 10 items were presented to each patient unirhinally in a randomized order. The first nostril of presentation was counterbalanced between participants. Foam plugs were used to occlude one nostril, and participants were asked to block their open nostril briefly to confirm that air was not entering through the occluded nostril. The 10 test items were administered one at a time, and for each item the participant was asked to read the four alternatives aloud (e.g., *clove*, *cinnamon*, *gingerbread,* and *petrol*).

Immediately after the patch containing the smell was scratched with a pencil to release the odorant, participants were instructed to position the card close to their open nostril and inhale before the odor faded. They were then asked to decide on the label that most likely matched the odor. For each participant, the same procedure was repeated 1 week later with the second nostril.

Data Analysis

Mixed-design ANOVA was used to investigate the effects of group and nostril, and their interaction, on overall error rate in olfactory performance. Three types of errors were differentiated: errors similar in smell and semantic category to the target, errors similar in smell but not category and errors unrelated to the target. After the specific error types were converted to proportions, mixed-design ANOVAs with error type and nostril as within-subjects variables and group as the between-subjects factor were conducted to assess whether types of errors differentiated the groups. Pearson correlations were calculated to measure the association between olfactory measures and other neuropsychological test scores. To minimize the risk of inflated type I error when performing multiple analysis of the same dependant variable, planned contrasts were performed were applicable, and statistical significance was only reported when $p<01$.

Results

Olfactory Identification Error Scores for the Left and Right Nostrils

The mean number of errors on olfactory identification as a function of nostril and group appear in Fig. 1. Identification errors varied across groups, $F(2,34)=16.6$, $p<001$, $\eta^2=0.49$. Planned group contrasts revealed that the control group ($M=2.9$, SD=1.5) committed fewer errors than the aMCI group ($M=5.1$, SD=1.6, $p<01$, $\eta^2=40$), who in turn committed fewer errors than the AD group ($M=6.3$, SD=1.8, $p=04$, $\eta^2=14$). Nostril side did not affect identification nor interact with the differences across groups, both Fs<1.

Examination of Types of Error

The relative incidences of the different error types, expressed as a proportion of the total number of errors, appear in Fig. 2 as a function of nostril side and participant group. A mixed-design ANOVA was conducted, with nostril side and error type as the within-subjects variables and diagnostic group as the between-groups factor. Across nostrils and groups, a difference was found in the likelihood of committing different error types, $F(2,68)=6.47$, $p<001$, $\eta^2=16$.

In addition, the interaction between error type and group also reached significance, $F(4,68)=3.60$, $\eta^2=17$. Analyses

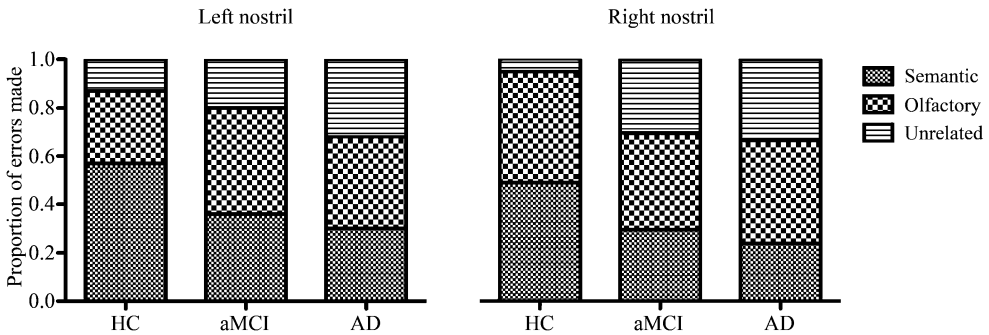


Fig. 2 The distribution of error types among the three participant groups for left and right nostrils

Table 2 Pearson correlations between total errors in olfactory identification on the left and right nostrils and neuropsychological measures

	Total errors: left nostril	Total errors: right nostril
MMSE	−0.34*	−0.49**
Composite episodic memory score	−0.61** (−0.52**)	−0.48** (−0.23)
Composite semantic memory score	−0.27 (−0.01)	−0.34* (−0.03)
Composite non-memory score	−0.28 (−0.09)	−0.38* (−0.13)

Data in parentheses represent the relevant Pearson correlation after controlling for MMSE score

*$p<0.05$, **$p<0.01$

at the group level revealed that the HC group committed few unrelated errors relative to the other types, $F(1,9)=23.9$, $p<01$, $\eta^2=72$, and no difference was observed between the two related types of errors, $F(1,9)=1.2$, ns, or an interaction of type of error with nostril, $F<1$. In contrast, there was no difference between the likelihood of committing any particular type of error among the aMCI group, $F(2,24)=1.4$, ns, or the AD group, $F(2,26)=1.8$, ns. In addition, the types of errors committed did not differ between the left and right nostrils among the AD group, $F<1$; although a tendency to commit fewer unrelated errors in the left relative to the right nostril was observed in the aMCI group (see Fig. 2), the interaction was not significant, $F<1$.

The Relationship Between Olfactory Functioning and Neuropsychological Performance

Table 2 reports the extent to which overall error rate on olfactory identification for the left and right nostrils correlated with global cognition as measured by the MMSE and cognitive domains as measured by the three composite scores—episodic memory, semantic memory, and non-memory. The table also shows in parentheses correlations between olfactory identification and these composite scores, after controlling for MMSE scores to account for global deterioration. Olfactory identification was significantly associated with MMSE scores, and this relationship was stronger on the right nostril. In addition, olfactory error scores showed the strongest relationship with episodic memory; moderate relationships were observed between error scores on the right nostril and the composite semantic memory and non-memory scores. When MMSE scores were statistically controlled, however, only the association between left-nostril error score and the composite episodic memory score remained significantly different from zero.

Olfactory Identification at the 1-Year Review

Approximately 12 months following the baseline examination (mean review lag=12.78 months, range=6–18 months), eight HC, 13 aMCI, and seven AD participants completed a review investigation. All the aMCI patients tested at baseline returned for retesting, and six of the 13 met NINCDS–ADRDA criteria for AD on review; group membership at review was held consistent with baseline assignation in the following treatment of data. A majority of participants who were not retested during this review (seven out of 10) were AD patients. AD patients who were tested again demonstrated higher MMSE scores at baseline ($M=25.8$, SD=2.3) than AD patients who were not tested again ($M=21.1$, SD=2.3), $t(11)=3.6$, $p<01$.

The number of olfactory identification errors during this review is shown in Fig. 3. A repeated-measures analysis with nostril side as the within-subjects variable and diagnostic group at baseline as the between-groups variable revealed that the groups varied on their olfactory identification ability. Planned contrasts indicated that the HC group ($M=3.3$, SD=1.2) committed significantly fewer errors than the AD group ($M=6.2$, SD=2.7), $F(1,14)=17.2$, $p<01$, $\eta^2=55$, and the difference between the HC and the aMCI group ($M=4.6$, SD=2.1) approached significance $F(1,19)=3.3$, $p=07$, $\eta^2=14$. Similarly, the aMCI group committed fewer errors than the AD group, and this difference approached significance $F(1,19)=3.8$, $p=06$, $\eta^2=16$. Across groups, there was no consistent nostril difference, $F(1,27)=2.2$, ns, or interaction between nostril and group, $F<1$.

The probabilities of the three groups committing the various types of error at the 1-year review are presented in Fig. 4. A repeated-measures ANOVA with nostril and type of error as within-subjects variables and group as the between-subjects variable revealed there were differences in the extent to which participants selected different types of errors, $F(2,48)=9.4$, $p<001$, $\eta^2=28$. Examination of simple contrasts revealed that all groups tended to select unrelated

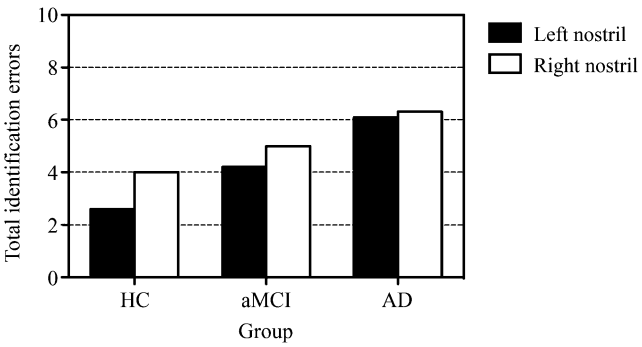


Fig. 3 Total errors in identification on the left and right nostrils in each group at the 1-year review

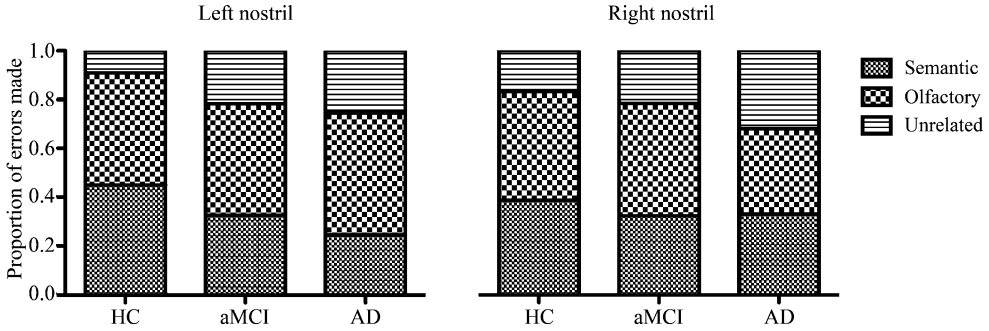


Fig. 4 The distribution of error types among the three participant groups on the left and right nostrils at the 1-year review

distracters less often than other distracter types, $F(1,24)=23.3$, $p<001$, $\eta^2=49$.

Analyses at the group level revealed that the HC group committed fewer unrelated errors relative to the other types, $F(1,7)=30.5$, $p<01$, $\eta^2=81$; there was no difference between the two related types of errors or an interaction between type of error and nostril, both Fs<1.

Similarly, the aMCI group committed few unrelated errors relative to the other types, $F(1,12)=8.6$, $p<01$, $\eta^2=45$, and there was no difference between the two related types of errors, $F(1,12)=1.6$, ns, or an interaction between type of error and nostril $F<1$. Finally, among the AD group, no difference was observed in the likelihood to commit any particular type of error, $F(2,12)=1.6$, ns, and no interaction was observed with the tested nostril, $F<1$.

Olfactory Performance of aMCI Participants Who Met and Those Who Did Meet Criteria for AD at the 1-Year Review

Table 3 displays baseline characteristics of aMCI patients who met AD criteria at the 1-year review, designated *converters*, and of the aMCI patients who did not meet these criteria at the review, designated *non-converters*. Converters were older than non-converters, $F(1,11)=7.89$, $p=01$, and had lower baseline episodic memory composite scores, $F(1,11)=14.1$, $p<01$. No differences were observed on other cognitive or demographic measures.

Figure 5 shows olfactory error scores, at baseline and at 1-year review, of aMCI patients who remained stable and aMCI patients who met AD criteria at the follow-up assessment. There were no significant changes in total number of identification errors for either subgroup over time nor any differences in overall olfactory identification ability for the left or right nostrils or in the likelihood of selecting different types of distracters between converters and non-converters, all Fs<1. At the review assessment, converters did not commit more errors overall on olfactory identification ($M=5.0$, SD=2.0) compared with non-converters ($M=5.0$, SD=1.5), $F<1$. However, converters did select unrelated distracters at chance levels (0.33) on both the left and right nostrils ($M=0.31$, SD=0.19 and $M=0.31$, SD=0.20, respectively), whereas non-converters showed significantly lower than chance levels of selecting an unrelated distracter on their left nostril ($M=0.14$, SD=0.14, $d=1.8$, $p<01$). Although this probability did not deviate from chance levels on the right nostril, the effect size was moderate ($M=0.20$, SD=0.24, $d=0.54$).

At baseline, a significant difference was found between the mean error rate across nostrils of AD patients ($M=6.2$, SD=1.1) and that of converters ($M=4.7$, SD=1.0), $t(11)=2.4$, $p=03$. However, at the 1-year review, there was no significant difference in the mean olfactory error score between converters ($M=5.0$, SD=2.0) and AD patients on review ($M=6.2$, SD=1.7), $t(9)=0.9$, ns.

Discussion

Consistent with results demonstrated in numerous studies using a birhinal procedure, AD patients in this study demonstrated significant deficits in olfactory identification

Table 3 Baseline characteristics and composite scores of aMCI converters and non-converters

	Converters ($n=6$)	Non-converters ($n=7$)
Age	79.3 (5.0) a	70.4 (6.1) b
Education	14.3 (5.8) a	15.3 (6.5) a
% Male	50 a	57.1 a
MMSE	24.8 (3.1) a	26.4 (1.6) a
Composite episodic memory[a]	−4.6 (0.9) a	−2.4 (1.0) b
Composite semantic memory[b]	−2.4 (2.1) a	−3.3 (3.6) a
Non-memory composite[c]	−1.7 (1.3) a	−0.7 (0.9) a

Figures in the same row that do not share the same letter are different at $p<0.01$

AD Alzheimer's disease, *aMCI* amnestic mild cognitive impairment, *HC* healthy controls, *MMSE* mini-mental state examination

[a] Calculated as the average of the z score for CVLT-II Long Delay Free Recall and RCFT 30-min delayed recall

[b] Calculated as the average of the z scores for BNT and category fluency

[c] Calculated as the average of the z scores for RCFT copy, DS, DS-C, and letter fluency

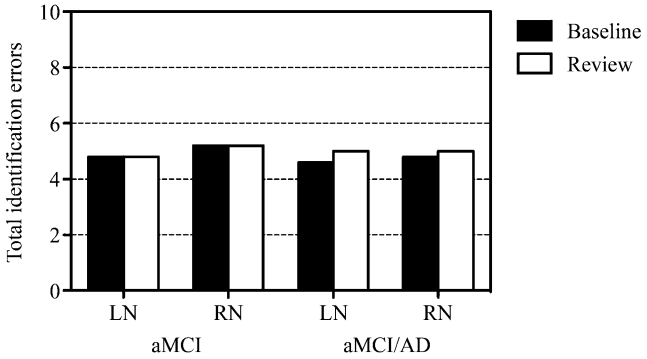


Fig. 5 Olfactory error scores across nostrils at baseline and at the 1-year follow-up among aMCI participants who remained stable and aMCI participants who converted

when compared with healthy elderly people. Patients with aMCI also displayed impaired olfactory identification on both nostrils when compared to the control group. The results of the study also indicated, albeit tentatively, that the AD and aMCI groups were as likely to select an unrelated distracter when committing an error as they were to select a related distracter. When committing errors, participants in the control group, on both nostrils, were very unlikely to select the unrelated distracter, and the errors committed were more predictable in their nature. aMCI participants who met criteria for AD at the time of review showed an increased tendency to select an unrelated distracter when committing errors compared with aMCI participants who did not meet criteria for AD.

Types of Errors Committed by the Groups

This research is the first study of early detection of AD that distinguishes types of errors in olfactory identification. Not only were AD patients impaired in their olfactory identification overall, but the pattern of errors displayed by this group was different from that observed among the control group. When committing errors, healthy elderly volunteers almost invariably tended to select a distracter that shared some attribute with the target (e.g., *cherry* instead of *strawberry*). In contrast, AD patients were as likely to select an unrelated distracter when identifying smells (e.g., choosing *motor oil* instead of *strawberry*) as they were to select a related distracter. This tendency might represent a preclinical feature of preclinical AD, as the same pattern was observed in the aMCI group.

Presumably, healthy elderly participants could readily utilize their semantic networks to differentiate the target odors from unrelated distracters. In contrast, the tendency to confuse the targets and the unrelated distracters in the AD and aMCI groups may reflect a degradation of these semantic associations between odors. One potential explanation for these findings is that, when only an olfactory cue is available, activation disperses more extensively across the semantic network in AD patients compared to healthy controls; semantic categories that are only remotely related to each other are thus more likely to be activated and identification becomes confused.

Several contemporary theories suggest that patients with semantic decline gradually lose knowledge of the features that distinguish members of a semantic category and instead rely on prototypical presentation of objects to correctly identify or recognize a classification (Alathari et al. 2004; Rogers et al. 2004b). During the early stages of semantic loss, the ability of individuals to discriminate members of the same or similar semantic categories becomes impaired, whereas appreciation of the superordinate semantic category is preserved (Rogers et al. 2004b). Most research concerned with the nature of semantic breakdown focuses on the visual, auditory, and verbal modalities (e.g., Adlam et al. 2006; Garrard et al. 2005; Joubert et al. 2008). The current study extends the existing body of knowledge by proposing that the distinctions between broad semantic categories might be degraded when the input modality is olfactory. This proposition was demonstrated by the observation that, when performing on a multiple-choice olfactory identification task, AD patients show a tendency to select an unrelated distracter as often as they tend to select a related distracter. Persons with aMCI are generally found to perform relatively well on traditional visually mediated tests of semantic knowledge such as the Boston Naming Test. The observation that the aMCI group showed a tendency to select unrelated distracters as frequently as related distracters may indicate that the rate of progression in semantic breakdown is faster for stimuli presented through olfaction than for stimuli presented either verbally or pictorially. Indeed, we found no association between olfactory identification and a composite semantic memory task after controlling for the severity of cognitive impairment. Conceivably, early in the course of AD, the degradation of the semantic network is limited to the olfactory modality.

Of particular relevance here is one longitudinal study that conducted a qualitative analysis of error types committed by patients with moderate AD on a confrontation naming task (Barbarotto et al. 1998). As disease severity increased, semantically unrelated errors became more prominent than semantically related errors. These authors proposed a semantic gradient to the declining course of cognition in AD. During the milder stages, patients may commit more semantic errors, reflecting partial preservation of their semantic abilities. During the more severe stages, when semantic abilities are especially limited, unrelated errors become the dominant type of error. Other authors have found support for the proposal that a tendency to make unrelated errors in AD reflects deficits in semantic

knowledge (Moreaud et al. 2001). Most AD patients in our study were classified as mild. These findings, therefore, extend the proposed mechanism suggested by Barbarotto et al., implying that a tendency to select unrelated errors is present in olfaction even in the early stages of AD. Furthermore, consistent with this premise, by the time aMCI patients met criteria for AD at the review assessment, they showed an increased tendency to select unrelated distracters in the olfactory identification task.

Our findings conflict with the conclusions of Luzzi et al. (2007) that olfactory discrimination deficits underpin those observed in olfactory identification. Although these authors found differences between the scores obtained by the AD group and scores obtained by the SD and HC groups on olfactory discrimination, the authors did not provide evidence to indicate that olfactory identification does not differ between AD patients and the other participant groups after discrimination scores are controlled. Assessing the ability of individuals to discriminate between different odorants commonly involves the presentation of two odors consecutively, followed by asking the participant to determine whether the odors are the same or different. In the typical olfactory identification paradigm, however, participants are presented with one odorant only and a list of options from which to choose the target. Therefore, in considering the different response alternatives, respondents need to utilize their knowledge of different qualities of an odor before reaching their decision. Therefore, deficits in olfactory discrimination might not necessarily culminate in errors on multiple-choice olfactory identification. Indeed, evidence indicates that even when healthy elderly persons perform relatively poorly on an olfactory discrimination task, they may still demonstrate normal performance on multi-choice olfactory identification (Bahar-Fuchs et al. 2007). Therefore, the results obtained by Luzzi et al. (2007) do not seem to definitively support their conclusions.

Limitations of the Current Study and Directions for Future Research

A limitation of the current study was that the distracter classification in the olfactory identification task did not always conform to the desired hierarchy, precluding a more meaningful interpretation of the difference in committing the two related types of errors. The design of the distracters in the current olfactory task relied on raters' judgments of similarity of odor labels to the target items. Refining the semantic olfactory identification procedure will enable researchers in future studies to improve the analysis of error types committed at different stages of AD. In addition, olfactory discrimination was not assessed in the current study, and therefore could not be statistically controlled. To confirm our assertion—that semantic deficits underlie the tendency of AD and aMCI patients to select unrelated distracters—future research should include concurrent measures of olfactory identification and discrimination. Nevertheless, our observations are unlikely to be ascribed to perceptual deficits, as MCI patients have been found to perform similar to control participants on olfactory discrimination (Djordjevic et al. 2008). Importantly, the current study failed to find clear support for a unirhinal assessment approach, as no nostril effects were found. Elsewhere, we have reported on the potential contribution of a unirhinal olfactory assessment approach to the differentiation between aMCI and AD patients (Bahar-Fuchs et al. 2007). More studies are required to explore whether a unirhinal olfactory assessment method offers a reliable advantage on the more traditional birhinal approach in the context of early and preclinical AD. Finally, the sample used in the current study was small, reducing the statistical power to detect effects. The trends observed in this study have nevertheless shown moderate effect sizes.

Conclusions

In conclusion, the pattern of errors that AD patients commit in olfactory identification tasks suggests a decline in olfactory-mediated access to semantic knowledge. Our study showed this semantic decline is present in aMCI patients, a subgroup of whom likely represent the prodromal stage of the AD. Assessing olfactory identification in early and preclinical AD may be a useful way to demonstrate early semantic decline. Future research will uncover whether this demonstration may, in turn, facilitate differentiation between olfactory identification deficits associated with AD and those associated with other conditions causing cognitive decline.

References

Adlam AL, Bozeat S, Arnold R, Watson P, Hodges JR (2006) Semantic knowledge in mild cognitive impairment and mild Alzheimer's disease. Cortex 42(5):675–684

Alathari L, Trinh Ngo C, Dopkins S (2004) Loss of distinctive features and a broader pattern of priming in Alzheimer's disease. Neuropsychology 18(4):603–612

Albers MW, Tabert MH, Devanand DP (2006) Olfactory dysfunction as a predictor of neurodegenerative disease. Curr Neurol Neurosci Rep 6(5):379–386

Bacon AW, Bondi MW, Salmon DP, Murphy C (1998) Very early changes in olfactory functioning due to Alzheimer's disease and the role of apolipoprotein E in olfaction. Ann N Y Acad Sci 855:723–731

Bahar-Fuchs A, Savage G, Rowe C, Moss S (2007) Decline of olfactory identification in MCI and AD: evidence for the breakdown of olfactory "semantics". J Int Neuropsychol Soc 13 (Suppl 2):102

Barbarotto R, Capitani E, Jori T, Laiacona M, Molinari S (1998) Picture naming and progression of Alzheimer's disease: an analysis of error types. Neuropsychologia 36:397–405

Collie A, Maruff P, Shafiq-Antonacci R, Smith M, Hallup M, Schofield RP et al (2001) Memory decline in healthy older people: implications for identifying mild cognitive impairment. Neurology 56:1533–1538

Collins AM, Loftus EF (1975) A spreading activation of semantic processing. Psychol Rev 82:407–428

Delis D, Kramer J, Kaplan E, Ober B (2000) CVLT-II: California Verbal Learning Test Adult Version, 2nd edn. The Psychological Corporation, San Antonio

Devanand DP, Michaels-Marston KS, Liu X, Pelton G, Padilla M (2000) Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow up. Am J Psychiatry 157:1399–1405

Djordjevic J, Jones-Gotman M, De Sousa K, Chertkow H (2008) Olfaction in patients with mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 29:693–706

Doty RL (ed) (1995) Handbook of olfaction and gustation. Marcel Dekker, New York

Doty RL, Shaman P, Dann M (1984) Development of the University of Pennsylvania smell identification test: a standardized microencapsulated test of olfactory function. Physiol Behav 32(3):489–502

Doty RL, Marcus A, Lee WW (1996) Development of the 12-item cross-cultural smell identification test (CC-SIT). Laryngoscope 106(3 Pt 1):353–356

Duff K, McCaffrey JR, Solomon SG (2002) The pocket smell test: successfully discriminating probable Alzheimer's dementia from vascular dementia and major depression. J Neuropsychiatry Clin Neurosci 14:197–201

Eibenstein A, Fioretti AB, Simaskou MN, Sucapane P, Mearelli S, Mina C et al (2005) Olfactory screening test in mild cognitive impairment. J Neurol Sci 26(3):156–160

Engen T (1987) Remembering odors and their names. Am Sci 75:497–503

Finton MJ, Lucas JA, Graff-Radford NR, Uitti RJ (1998) Analysis of visuospatial errors in patients with Alzheimer's disease or Parkinson's disease. J Clin Exp Neuropsychol 20:186–193

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(3):189–198

Garrard P, Lambon Ralph MA, Patterson K, Pratt KH, Hodges JR (2005) Semantic feature knowledge and picture naming in dementia of Alzheimer's type: a new approach. Brain Lang 93 (1):79–94

Good KP, Martzke JS, Milliken HI, Honer WG, Kopala LC (2002) Unirhinal olfactory identification deficits in young male patients with schizophrenia and related disorders: association with impaired memory function. Schizophr Res 56:211–223

Graves AB, Bowen JD, Rajaram L, McCormick WC, McCurry SM, Schellenberg GD et al (1999) Impaired olfaction as a marker for cognitive decline: interaction with apolipoprotein E epsilon4 status. Neurology 53:1480–1487

Hodges JR, Salmon DP, Butters N (1992) Semantic memory impairment in Alzheimer's disease: failure of access or degraded knowledge? Neuropsychologia 30:301–314

Hodges JR, Graham N, Patterson K (1995) Charting the progression in semantic dementia: implications for the organisation of semantic memory. Memory 3:463–495

Joubert S, Felician O, Barbeau EJ, Didic M, Poncet M, Ceccaldi M (2008) Patterns of semantic memory impairment in mild cognitive impairment. Behav Neurol 19(1–2):35–40

Kjelvik G, Sando SB, Aasly J, Engedal KA, White LR (2007) Use of the brief smell identification test for olfactory deficit in a Norwegian population with Alzheimer's disease. Int J Geriatr Psychiatry 22(10):1020–1024

Koss E, Weiffenbach JM, Haxby JV, Friedland RP (1988) Olfactory detection and identification performance are dissociated in early Alzheimer's disease. Neurology 38(8):1228–1232

Luzzi S, Snowden SS, Neary D, Coccia M, Provinciali L, Lambon Ralph AM (2007) Distinct patterns of olfactory impairment in Alzheimer's disease, semantic dementia, frontotemporal dementia and corticobasal degeneration. Neuropsychologia 45:1823–1831

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS–ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–944

Meyers J, Meyers K (1995) Rey complex figure test and recognition trial. Psychological Assessment Resources, Odessa

Moreaud O, David D, Charnallet A, Pellat J (2001) Are semantic errors actually semantic?: evidence from Alzheimer's disease. Brain Lang 77:176–186

Morgan CD, 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, Bacon AW, Bondi MW, Salmon DP (1998) Apolipoprotein E status is associated with odor identification deficits in nondemented older persons. Ann N Y Acad Sci 855:744–750

Nagy E, Loveland KA (2001) Olfactory deficit in Alzheimer's disease? [Letter to the editor]. Am J Psychiatry 158:1533–1533

Nordin S, Murphy C (1996) Impaired sensory and cognitive olfactory function in questionable Alzheimer's disease. Neuropsychology 10(1):113–119

Patterson K (2007) The reign of typicality in semantic memory. Philosophical transactions of the Royal Society of London Series B. Biol Sci 362:813–821

Peters MJ, Hummel T, Kratzsch T, Lotsch J, Skarke C, Frolich L (2003) Olfactory function in mild cognitive impairment and Alzheimer's Disease: an investigation using psychophysical and electrophysiological techniques. Am J Psychiatry 160(11):1995–2002

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV et al (2001) Current concepts in mild cognitive impairment. Arch Neurol 58(12):1985–1992

Rogers TT, Hodges JR, Patterson K, Lambon Ralph MA (2004a) Object recognition under semantic impairment: the effects of conceptual regularities on perceptual decisions. Lang Cognitive Proc 18(5–6):625–662

Rogers TT, Lambon Ralph MA, Garrard P, Bozeat S, McClelland JL, Hodges JR et al (2004b) Structure and deterioration of semantic memory: a neuropsychological and computational investigation. Psychol Rev 111(1):205–235

Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G et al (2007) Imaging beta-amyloid burden in aging and dementia. Neurology 68(20):1718–1725

Saxton J, Ratcliff G, Munro CA, Coffey EC, Becker JT, Fried L et al (2000) Normative data on the Boston Naming Test and two equivalent 30-item short forms. Clin Neuropsychol 14:526–534

Serby M, Corwin J, Conrad P, Rotrosen J (1985) Olfactory dysfunction in Alzheimer's disease and Parkinson's disease. Am J Psychiatry 142(6):781–782

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

Ska B, Poissant A, Joanette Y (1990) Line orientation judgment in normal elderly and subjects with dementia of Alzheimer's type. J Clin Exp Neuropsychol 12:695–702

Stevenson RJ, Boakes RA (2003) A mnemonic theory of odor perception. Psychol Rev 110(2):340–364

Szeszko PR, Bates J, Robinson D, Kane J, Bilder RM (2004) Investigation of unirhinal olfactory identification in antipsychotic-free patients experiencing a first-episode schizophrenia. Schizophr Res 67(2–3):219–225

Tabert MH, Liu X, Doty RL, Serby M, Zamora D, Pelton GH et al (2005) A 10-item smell identification scale related to risk for Alzheimer's disease. Ann Neurol 58(1):155–160

Wang QS, Tian L, Huang YL, Qin S, He LQ, Zhou JN (2002) Olfactory identification and apolipoprotein E epsilon 4 allele in mild cognitive impairment. Brain Res 951(1):77–81

Warner MD, Peabody CA, Flattery JJ, Tinklenberg JR (1986) Olfactory deficits and Alzheimer's disease. Biol Psychiatry 21 (1):116–118

Warrington EK, Crutch SJ (2007) A within-modality test of semantic knowledge: the size/weight attribute test. Neuropsychology 21:803–811

Weaver Cargin J, Maruff P, Collie A, Masters C (2006) Mild memory impairment in healthy older adults is distinct from normal aging. Brain Cogn 60:146–155

Wechsler D (1997) WAIS-III Administration and Scoring Manual. The Psychological Corporation, San Antonio

Wilson RS, Schneider JA, Arnold SE, Tang Y, Boyle PA, Bennett DA (2007) Olfactory identification and incidence of mild cognitive impairment in older age. Arch Gen Psychiatry 64(7):802–808

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO et al (2004) Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 256(3):240–246

Yaffe K, Petersen RC, Lindquist K, Kramer J, Miller B (2006) Subtype of mild cognitive impairment and progression to dementia and death. Dement Geriatr Cogn Disord 22(4):312–319