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Olfactory Performance in AD, aMCI, and Healthy Ageing: A Unirhinal Approach

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Abstract

Olfactory dysfunction constitutes one of the earliest signs of Alzheimer's disease (AD) and has been shown in individuals with amnestic mild cognitive impairment (aMCI). Whether the severity of olfactory impairments in aMCI patients parallels those in AD has not been clearly established. In addition, given reports of asymmetries in neuropathological burden in early AD, functional asymmetries in olfactory performance may enhance early detection if olfactory function is assessed unirhinally. We compared AD, aMCI, and healthy participants on olfactory identification and memory assessed unirhinally. Olfactory identification was most proficient in the healthy participants and least proficient in AD, although this disparity did not depend on nostril side. Nevertheless, when only the worst nostril of each participant was included in the analysis, aMCI patients outperformed their AD counterparts. In contrast, when only the best nostril of each participant was included in the analysis—often regarded as an estimate of birhinal performance—this difference between aMCI and AD dissipated. Olfactory memory did not differ significantly across the groups, perhaps reflecting a floor effect. The findings support the hypothesis that unirhinal olfactory assessment may assist in differentiating between demented and nondemented individuals.

Key words: Alzheimer's disease, functional brain asymmetry, mild cognitive impairment, olfaction

Introduction

Patients diagnosed with probable Alzheimer's disease (AD) show marked deficits on tests of olfactory functioning, and these deficits are present very early in the course of the disease (Warner et al. 1986; Nordin and Murphy 1998; Murphy 1999; Devanand et al. 2000; Wilson et al. 2007). Medial temporal lobe (MTL) structures, such as the piriform cortex, the amygdala, and the entorhinal cortex, play important roles in primary and associative olfactory processes. With characteristic neuronal atrophy in AD first appearing in the transentorhinal region (Braak H and Braak E 1995), the observed olfactory deficits in AD are unsurprising (see Ferreyra-Moyano and Barragan 1989, for a seminal work on the involvement of olfactory regions in prodromal AD). Indeed, studies have shown that olfactory identification and episodic olfactory recognition are robustly correlated with volumetric measures of MTL structures (Murphy et al. 2003).

The hypothesis that olfactory deficits in AD are directly related to the underlying neuropathology in regions affected in the earliest stages of the disease implies that olfactory dysfunction may be apparent during the prodromal phase of AD. Indeed, several studies in recent years have shown that people with amnestic mild cognitive impairment (aMCI), an etiologically diverse quasi-clinical entity with an estimated annual risk of escalation to AD approximating 12% (Petersen et al. 1999), show deficits in olfactory identification (e.g., Peters et al. 2003; Eibenstein et al. 2005; Djordjevic et al. 2008). Furthermore, olfactory deficits in aMCI patients have been found to predict who will later meet clinical criteria for AD (Devanand et al. 2000; Albers et al. 2006).

Recently, Wilson et al. (2007) followed a group of aged community-dwelling individuals with no cognitive impairment for a period of up to 5 years. Of the original cohort, 30% met criteria for MCI during the follow-up phases; participants whose scores on olfactory identification were below average were twice as likely to subsequently meet MCI

criteria compared with those with olfactory identification scores above average. These authors thus showed that olfactory deficits can be detected even before patients are classified as cognitively impaired by objective criteria and that impaired olfactory identification and accelerated rate of cognitive decline might be associated with conversion to AD status (see also Tabert et al. 2005).

It is well established that olfactory dysfunction in general, especially if coupled with one or more Apolipoprotein E-epsilon4 alleles, predicts cognitive decline (Graves et al. 1999). In addition, although a number of studies on olfaction have recently included both participants with AD and participants with aMCI, whether or not their olfactory identification deficits are similar in severity is yet to be established clearly. In addition, although a deficit in episodic olfactory recognition is documented in AD (Nordin and Murphy 1998; Sundermann et al. 2006), the extent to which this deficit is present in aMCI patients is unclear. Crucially, however, not all patients with aMCI will subsequently meet clinical criteria for AD. Research therefore needs to characterize the olfactory profile of aMCI patients using methods that seek to differentiate patients whose deficits represent the prodromal phase of AD and patients whose deficits represent a different etiology. Understanding the nature of olfactory dysfunction in aMCI patients is important in attempting to establish its relevance as a reliable marker of preclinical dementia (Nordin and Murphy 1996; Peters et al. 2003; Eibenstein et al. 2005; Tabert et al. 2005).

Olfactory bulb efferent neurons project directly to primary olfactory areas in the cortex without synapsing in thalamic nuclei (Allison 1954; Mirza et al. 1997). The olfactory system, in contrast with the other senses, is primarily processed ipsilaterally with only minor contralateral projections via the anterior commissure (Shipley and Ennis 1996). Some studies have found evidence for hemispheric lateralization of olfactory functioning (Dade et al. 1998; Herz et al. 1999; Broman et al. 2001; Homewood and Stevenson 2001; Royet et al. 2003; Doty and Kerr 2005), but the evidence is inconsistent. The task of identifying possible lateralization of olfactory cognitive tasks is complicated by important aspects of the olfactory stimulus and, in particular, its hedonic value and trigeminal impact. Nevertheless, researchers tend to concur that perceptual functions, such as intensity judgments and quality discrimination, are better performed when stimuli are presented to the right nostril and thus right hemisphere (Zatorre and Jones-Gotman 1990) and that odor naming may be better when stimuli are presented to the left nostril and thus left hemisphere (Brand and Jacquot 2001; Broman et al. 2001; Homewood and Stevenson 2001; Murphy et al. 2003).

To date, research on olfactory processing in AD or MCI has employed a birhinal testing procedure in which both nostrils are assessed simultaneously. One potential shortcoming of the birhinal procedure is that any asymmetries in nostril performance are masked, with decisions primarily derived from the nostril that is functioning better (Hornung et al. 1990; Betchen and Doty 1998; Good et al. 2003). It has been suggested that AD-related neurodegeneration in the MTL may progress asymmetrically, becoming more symmetrical by the time the disease is expressed clinically. Whether early neurodegeneration in AD affects more significantly medial temporal structures in a particular hemisphere is unknown, and reports have been published supporting both predominantly left (Bottino et al. 2002) and predominantly right hemisphere involvement (Pantel et al. 2003). Alternatively, it is possible that early neurodegeneration in AD is asymmetrical, with the more affected side varying stochastically between individuals. In either case, any hemispheric asymmetry in neurodegeneration could plausibly manifest as functional asymmetry in ipsilateral nostril performance but only if performance were to be assessed unirhinally. Therefore, beyond the potential differences in the severity of olfactory dysfunction between aMCI and AD patients, unirhinal olfactory testing may assist in identifying people with aMCI who are more likely to meet clinical criteria for AD.

Consistent with this notion, speculations regarding hemispheric asymmetry in neuropathology led to the adoption of a unirhinal assessment approach in studies on olfactory function in Parkinson's disease (Doty et al. 1992; Zucco et al. 2001) as well as in schizophrenia (Good et al. 2002, 2003; Roalf et al. 2006). Roalf et al. compared the olfactory performance of patients with schizophrenia to that of their first-degree relatives as well as to healthy controls. Unlike previous studies using a birhinal assessment approach, using a unirhinal procedure, these authors observed that the olfactory impairment of their patients was similar to that of their relatives. These authors underscored the potential relevance of unraveling asymmetries in performance to the diagnostic process.

In the current study, we compared the performance of AD, aMCI, and healthy control participants on measures of odor identification and episodic olfactory recognition. We predicted that AD patients would perform less proficiently than aMCI patients on olfactory identification and subsequent memory for the odors, who will in turn perform less proficiently than control participants. Furthermore, we predicted that asymmetry in neurodegeneration in the MTL may manifest in asymmetrical performance on unirhinal olfactory assessment; consistent hemispheric asymmetry will lead to consistent differences between performance on the left and right nostrils, whereas random hemispheric asymmetry will manifest by inconsistencies in the side of the best- and worst-performing nostril.

Materials and methods

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 National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association 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 standard deviation or more below the relevant normative data, in the context of normal nonmemory test scores. Healthy control participants from the large-scale longitudinal Melbourne Healthy Aging Study (MHAS; Collie et al. 2001; Weaver 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; this participant was excluded from analyses. 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 consented to participate in the olfactory testing separately from their consent to participate in the PiB study or the MHAS study. Where capacity to consent was uncertain, consent was also obtained from the primary carer, usually a spouse. This project was conducted with the approval of the Monash University Standing Committee on Ethics in Research Involving Humans.

Materials

The olfactory identification task utilized a subset of 10 items from the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al. 1984). The 10 items that were selected were "menthol, clove, leather, strawberry, lilac, pineapple, smoke, soap, natural gas, and pizza." These odors, apart from pizza, have been found by Tabert et al. (2005) to be most predictive of progressive conversion across healthy aging, MCI, and AD states when compared with the overall UPSIT. In addition, we substituted pizza for Tabert et al.'s lemon because of widespread detection difficulties with the latter during pilot testing. To facilitate examination of error types in olfactory identification, we varied the extent to which the distracters were related to the target. The following additional 10 items from the complete UPSIT were selected to be used as distracters in the olfactory memory task: "bubble gum, cherry, motor oil, mint, banana, onion, liquorice, cinnamon, petrol, and chocolate."

Neuropsychological assessment

All participants underwent a neuropsychological evaluation that included the Mini-Mental Status 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 J and Meyers K 1995), and subtests of the Delis-Kaplan Executive Function System verbal fluency (Delis et al. 2001).

Procedure

The 10 items in the olfactory identification task were presented to each patient in a different randomized order. 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 first nostril of presentation was counterbalanced between participants. For each item, the participants were asked to read aloud the 4 listed alternatives (e.g., clove, cinnamon, gingerbread, and gasoline). Immediately after the odor-impregnated strip was scratched with a pencil to release the odorant, participants were instructed to position the card close to their open nostril and inhale as soon as they could before the odor faded. They were then asked to decide on the most likely label for the odor, with the list remaining in view.

Immediately after the 10 target items were presented in the identification phase, the odor memory task was presented. All participants were presented with 20 odors: 10 targets and 10 distracters. Participants decided whether or not the odor had been presented previously. Odors in the memory phase were presented in a quasi-randomized order: The original order in which target odors were presented was preserved in the memory phase and interspersed with distracters. A similar procedure was used by other authors in assessing episodic odor recognition memory (Nordin and Murphy 1998; Gilbert and Murphy 2004; Sundermann et al. 2006). For each participant, the same procedure was repeated approximately 1 week later using the other nostril.

Data analysis

From the neuropsychological measures, 2 composite scores were calculated to represent episodic memory and nonmemory domains. The composite episodic memory score was calculated by computing the average of the z scores, generated using the HC group as the reference, for RCFT long delayed recall and CVLT-II long delayed recall. The nonmemory composite score was derived from the average scores on verbal fluency, DS, DS-C, RCFT copy tests, and BNT.

Olfactory identification performance was represented by the number of odors out of 10 that were correctly identified. For the olfactory memory analyses, sensitivity scores were

calculated by subtracting the false alarm rate from the hit rate, and specificity scores were computed by subtracting the miss rate from the correct rejection rate. Areas under the normal curve were then calculated for the hit and false alarm rates, and these indices were used to generate the discrimination score (d') for each nostril (z_{hit}–z_{fa}) as described by Sundermann et al. (2006), consistent with signal detection theory (Stanislaw and Todorov 1999). The d' scores represent the ability of a person to discriminate previously presented stimuli from novel stimuli, with scores of 0 representing chance levels of discrimination and higher scores representing better discrimination.

A pair of analyses of variance (ANOVAs) was first conducted to ascertain whether the disparities across groups in olfactory identification differed between the left and right nostrils. The first ANOVA compared HC with aMCI, and the second ANOVA compared aMCI and AD. This approach was used to ensure that the number of analyses was less than the number of groups, primarily to preserve the family-wise Type I error rate while circumventing the need to include a Bonferroni adjustment—sometimes considered too strict when the sample size is small (see Olejnik et al. 1997; Noble 2006). Next, this pair of ANOVAs was repeated, except the best and worst, rather than left and right, nostrils were compared. Finally, the same strategy was applied to examine whether olfactory memory varied across the groups.

Results

Demographic characteristics are presented in Table 1, indicating that participants in the 3 groups did not differ significantly on mean age, educational attainment, or gender ratio. As expected, the HC group demonstrated better performance on the MMSE than the aMCI participants ($P < 0.01$), who in turn showed better performance than the AD group ($P = 0.05$). As Table 1 shows, the composite episodic memory score varied across the groups, $F_{2,32} = 41.2$, $P < 0.001$, $\eta^2 = 0.72$. Post-hoc analysis with Bonferroni adjustment confirmed that the HC group obtained greater scores than the aMCI group ($P < 0.001$). The difference between the aMCI and AD groups was not significant. Analysis of variance also showed that the groups differed on the nonmemory composite score, $F_{2,32} = 11.6$, $P < 0.01$, $\eta^2 = 0.42$. Post-hoc analysis with Bonferroni adjustment indicated that the AD group performed more poorly than the HC group ($P < 0.001$). The difference between the aMCI and HC groups was not significant.

Table 1 Demographic characteristics and episodic memory performance in the different groups

	HC (n = 10)	MCI (n = 13)	AD (n = 14)
Age	73.0 (5.3)[a]	74.5 (7.1)[a]	74.1 (10.2)[a]
Education	13.0 (2.3)[a]	14.8 (5.9)[a]	13.8 (4.5)[a]
% Male	30[a]	54[a]	50[a]
MMSE	29.5 (0.8)[a]	25.6 (2.4)[b]	23.3 (3.3)[c]
Composite episodic memory z score	0.1 (0.8)[a]	−2.4 (1.2)[b]	−3.6 (0.9)[b]
Composite nonmemory z score	−0.02 (0.7)[a]	−1.2 (1.2)[a]	−2.9 (1.9)[b]

Figures in the same row that do not share a superscript are statistically different. Data are means and standard deviations unless otherwise specified.

The correlation between olfactory identification and episodic olfactory recognition was low and not significant, measuring $r(37) = 0.17$, $P > 0.05$, for the left nostril, and $r(37) = 0.28$, $P > 0.05$, for the right nostril. The correlation between scores obtained on the left and right nostrils was high for olfactory identification, $r(37) = 0.53$, $P < 0.05$, but low for memory, $r(37) = 0.17$, $P > 0.05$. The correlation between scores obtained on the best and worst nostril was high for olfactory identification, $r(37) = 0.84$, $P < 0.01$, as well as for olfactory memory $r(37) = 0.59$, $P < 0.01$. For all ANOVAs, the residuals did not diverge appreciably from normality, and no violations of sphericity were uncovered.

Olfactory identification and episodic olfactory recognition scores for the left and right nostrils and for the best and worst nostril appear in Table 2.

Olfactory identification

A 2×2 ANOVA was conducted to ascertain whether the difference between HC and aMCI on olfactory identification differs between the left and right nostrils; olfactory identification was more proficient in HC compared with aMCI, $F_{1,21} = 12.14$, $P < 0.01$, $\eta^2 = 0.36$. Nostril side did not affect olfactory identification, $F < 1$, and did not interact with this difference between the groups, $F_{1,21} = 1.17$. This analysis was repeated, except aMCI was compared with AD instead. Olfactory identification performance was better in aMCI compared with AD, $F_{1,25} = 4.44$, $P < 0.05$, $\eta^2 = 0.15$ but not between left and right nostrils, $F < 1$. This disparity between aMCI and AD did not interact with nostril side, $F < 1$.

This pattern of observations implies that differences across the groups were independent of nostril side. Nevertheless, more informative results emerge when the best and worst nostrils are differentiated. First, a 2×2 ANOVA was undertaken to establish whether or not the difference between HC and aMCI on olfactory identification differed between the best and worst nostrils. In this instance, the disparity between HC and aMCI on olfactory identification, although significant $F_{1,21} = 12.1$, $P < 0.01$, $\eta^2 = 0.36$, did not differ between best and worst nostrils, $F < 1$. In contrast, when the same analysis was repeated, but applied to compare aMCI and AD groups, a different pattern emerged. The disparity between aMCI and AD on olfactory identification, $F_{1,25} = 4.4$, $P = 0.04$, $\eta^2 = 0.15$, did differ significantly between

Table 2 Unirhinal scores on olfactory identification and memory by group

	Identification			Memory (d')		
	HC	aMCI	AD	HC	aMCI	AD
Left nostril	7.2 (1.1)	4.8 (1.6)	3.5 (2.1)	0.58 (0.56)	0.16 (1.6)	0.18 (0.77)
Right nostril	6.5 (2.0)	4.9 (1.7)	3.8 (1.8)	0.51 (0.60)	0.76 (0.76)	0.36 (1.08)
Best nostril	7.6 (1.2)	5.5 (1.1)	4.8 (1.8)	0.90 (0.51)	0.98 (0.70)	0.70 (0.80)
Worst nostril	6.1 (1.7)	4.1 (1.8)	2.5 (1.4)	0.18 (0.36)	−0.06 (0.81)	−0.16 (0.87)

Data are means and standard deviations.

the best and worst nostrils, $F_{1,25} = 5.09$, $P = 0.03$, $\eta^2 = 0.16$. As Table 2 reveals, AD patients performed more poorly than aMCI patients on olfactory identification on the worst nostril, but no group differences were found when the best-nostril score was used.

Olfactory memory

A 2×2 ANOVA was undertaken to determine whether the difference between HC and aMCI on olfactory memory differs between the left and right nostrils; however, the main effects of group, $F < 1$, and nostril side, $F_{1,21} = 1.51$, $P > 0.05$, did not reach significance. The interaction was also not significant, $F_{1,21} = 2.49$, $P > 0.05$. Similarly, when aMCI was compared with AD, the main effects of group, $F < 1$, and nostril side, $F_{1,21} = 3.44$, $P > 0.05$, were not significant; similarly, the interaction was not significant, $F < 1$.

The pattern did not change when best and worst nostrils were compared. That is, the disparity between best and worst nostril on olfactory memory did not differ between HC and aMCI, $F_{1,21} = 1.64$. Similarly, the disparity between best and worst nostril on olfactory memory did not differ between aMCI and AD, $F < 1$.

Discussion

Consistent with results demonstrated in numerous studies using a birhinal procedure, AD patients, as well as participants classified as aMCI, demonstrated significant deficits in olfactory identification ability when compared with healthy elderly people. These results extend the numerous studies that have documented a profound deficit in olfactory identification in AD as well as align with several recent reports that have demonstrated a deficit in people with aMCI (Devanand et al. 2000; Peters et al. 2003; Djordjevic et al. 2008), some of which represent the preclinical phase of AD (Griffith et al. 2006).

Importantly, we detected a difference between the AD and aMCI groups using a unirhinal procedure. Specifically, when performance on only the worst nostril of each participant was considered, olfactory identification was more proficient in aMCI compared with AD. In contrast, when performance on only the best nostril was considered, often regarded as an estimate of birhinal performance (Hornung et al. 1990), this disparity subsided. Thus, the current study tentatively suggests that to differentiate aMCI from AD, unirhinal assessments might be more informative than birhinal assessments. Unirhinal olfactory assessment did not, however, differentiate HC from individuals with aMCI, suggesting that although asymmetry in olfactory performance may be useful in distinguishing demented from nondemented older adults with cognitive impairment, it may not be useful in differentiating healthy individuals from individuals with aMCI.

To the extent that performance on olfactory identification in AD reflects neurodegeneration burden in the olfactory network (Murphy et al. 2003), the current findings suggest that the burden of neurodegeneration in the olfactory network may actually be symmetrical in nondemented older adults with aMCI but that it becomes more asymmetric as patients develop dementia. The finding that AD and aMCI patients could be better differentiated when scores from the best and worst nostrils were considered rather than scores on the left and right nostrils also supports the proposition that although degeneration might be more severe on one side, the direction of this asymmetry varies between individuals. Because the unirhinal procedure used in the current study did not yield differences between the aMCI and HC group, our findings do not support, however, the propositions of Bottino et al. (2002) and Pantel et al. (2003), who suggested that neurodegeneration is already asymmetrical in MCI patients and that it becomes symmetrical by the time clinical dementia develops. Importantly, unlike the studies cited above, we did not obtain MRI data and were unable to test the hypothesis that asymmetrical olfactory performance in AD patients reflects asymmetry in neurodegeneration. Further imaging studies of olfaction are needed to determine whether AD patients with asymmetrical olfactory performance display corresponding asymmetric structural changes.

These olfactory identification deficits in AD may reflect impairment in semantic processing, a feature acknowledged as cardinal in the early stages of the disease (Joubert et al. 2008). In the early clinical and preclinical stages of AD, the ability of patients to perform verbal semantic memory tasks, such as the BNT or Category Fluency, is relatively preserved. We

propose that, early in the course of the disease, olfactory identification provides a more sensitive test to detect the deterioration of semantic knowledge than do tests in other sensory modalities. Although deficits in new learning and episodic memory continue to be the clinical hallmarks of incipient AD, some researchers have proposed that the inclusion of sensitive measures of semantic decline may improve the identification of people with aMCI who are more likely to meet clinical criteria for AD over time (e.g., Hodges et al. 2006).

Conceivably, differences between the aMCI and AD on olfactory identification can also be ascribed to other cognitive deficits, perhaps executive functioning. AD patients, for example, might not have been able to follow instructions or resist distractions effectively. Nevertheless, these deficits should have compromised performance on both the best and the worst nostrils to comparable degrees, contrary to the findings. Hence, the observation that olfactory identification performance diminishes in AD, compared with aMCI, but only in the worst nostril, indicates this deterioration cannot be solely ascribed to broader cognitive functioning.

Differences between aMCI and healthy controls on olfactory identification, however, did not seem to be confined by nostril side. That is, this disparity did not differ between the left versus right or between best versus worst nostrils. Perhaps, deterioration that differentiates aMCI from healthy controls is bilateral, making unirhinal olfactory assessments less effective in differentiating these groups.

Episodic olfactory recognition

In light of the hallmark episodic memory deficit in early AD, a surprising finding in the current study was that episodic odor recognition did not differ significantly across groups. Indeed, Nordin and Murphy (1996, 1998) did show differences in odor memory between AD and healthy participants. In the present study, however, performance on the olfactory memory test approached floor levels, indicating that the procedure might have been too difficult or long to differentiate the groups. Importantly, unlike in the studies by Nordin and Murphy, we tested olfactory memory in a unirhinal fashion. Bromley and Doty (1995) found that when olfactory memory was assessed unirhinally, healthy participants obtained lower scores than they did when olfactory memory was assessed birhinally. These authors further suggested that olfactory memory is represented centrally and facilitated by bilateral activation. This finding may partially explain the poor performance of healthy participants on unilateral testing of odor memory, who possibly failed to achieve bilateral-level activation required for successful performance.

Limitations

One limitation is that differences between the groups on olfactory identification could be explained by sensory or perceptual level of processing, such as detection and discrimination. Indeed, Luzzi et al. (2007) found that olfactory discrimination was impaired in patients with AD relative to those with semantic dementia. Other researchers have shown, however, that deficits in olfactory identification cannot be explained by deficiencies at the sensory or the perceptual level (Nordin and Murphy 1996; Djordjevic et al. 2008). Nevertheless, because olfactory detection and discrimination were not controlled in the current study, the observed deficits on odor identification cannot definitively be attributed to deterioration in semantic knowledge but could reflect deficits in earlier stages of processing.

This limitation, however, does not nullify the proposition that unirhinal assessments seem more sensitive than birhinal assessments to uncover differences between aMCI and AD patients on olfactory identification. Furthermore, the items from the UPSIT, utilized in this study, are assumed to be presented at a suprathreshold levels to minimize the role of detection in performance on this task (Doty et al. 1984). Some participants, however, did report that items used were not equally salient: Some items, such as lilac and clove, were often reported to be more difficult to detect than other items.

Finally, the current study was based on a small sample of participants in each group, and therefore the findings and their clinical implications are essentially tentative. Replication of these findings in larger sample of participants and the opportunity for follow-up analyses are needed to increase confidence in these findings.

In conclusion, the results of the present study support the hypothesis that functional asymmetries in olfactory performance may assist in differentiating aMCI from AD patients and that these asymmetries can be detected by unirhinal assessment, which can detect performance in the worst nostril. In contrast, the current study did not support the use of unirhinal assessment for differentiating between healthy older adults from individuals with aMCI.

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