Research Article • DOI: 10.2478/s13380-011-0026-1 • Translational Neuroscience • 2(3) • 2011 • 233-240

Translational Neuroscience

VERSITA

ODOR IDENTIFICATION AND COGNITIVE ABILITIES IN ALZHEIMER'S DISEASE

Mladenka Tkalčić[1,*],
Nika Spasić[1],
Matea Ivanković[1],
Alessandra Pokrajac-Bulian[1],
Daša Bosanac[2]

[1]*Department of Psychology, Faculty of Humanities and Social Sciences, University of Rijeka, Slavka Krautzeka b.b., 51000 Rijeka, Croatia*

[2]*Psychiatry Hospital Lopača, Lopača 11, 51218 Dražice, Croatia*

Abstract

Research results indicate systemic odor identification deficits in patients with Alzheimer's disease (AD). The aims of this study were: 1) to compare the ability to identify different odors and to compare cognitive status among patients with AD, patients with vascular dementia (VaD) and a comparison group of elderly persons; 2) to test the efficiency of olfactory and neuropsychological measures to classify patients and 3) to relate the odor identification ability with cognitive functioning for each group, respectively. The participants were 15 patients with AD, 11 patients with VaD and 30 non-demented elderly persons, age range 58 to 90. To assess olfactory function, we used the Scandinavian Odor-Identification Test. To assess cognitive functions, we used the Dementia Rating Scale-2, the Clock Drawing Test, the Boston Naming Test and the Category Fluency Test. The ANOVA showed that patients with AD correctly identifed significantly fewer odors presented to them compared to patients with VaD and control group. Patients with AD achieved significantly lower scores on all neuropsychological measures compared to the control group and differ in the DRS-2 total score, initiation/perseveration, constructive and naming abilities comparing to patients with VaD. Discriminant analysis showed that category fluency and olfactory identification were the best predictors of AD. Significant correlations were found between the olfactory and initiation/perseveration, memory and animal naming abilities for patients with AD. Differences among patients with AD, VaD and elderly persons exist in their abilities to identify odors. The findings suggest that olfactory functional testing in combination with memory testing are important.

Keywords

• Odor identification • Cognitive abilities • Alzheimer's disease • Vascular dementia • Non-demented elderly persons

Received 05 September 2011
accepted 09 September 2011

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia among people over the age 65 that involves the impairment of cognitive domains (e.g., reduced memory, language, executive functioning, visuospatial skills), and other areas of global functioning, including olfactory detection and identification [1-3].

Several different odor identification tests have been developed for use in clinical settings to detect olfactory disfunction. One of the first and the most widely used was The Smell Identification Test, formerly denoted UPSIT, developed by Doty *et al.* [4]) Studies that have used this and other similar tests reported olfactory impairments, especially odor identification deficits in AD [1,5,6]. Other reports describe that olfactory brain regions were subject to AD neuropathology, including cell loss, amyloid plaques and neurofibrillary tangles [3,7,8]. Wilson *et al.* [9] found that the density of tangles present in the central olfactory system, the entorhinal cortex and CA1/subiculum region of the hippocampus, was inversely related to odor identification ability. It is not suprising that olfactory deficit are apparent even in the earliest stages of AD given that the earliest pathologic changes in AD appear to take place within the transentorhinal and entorhinal cortex [2,5,7,10,11]. This area of the brain is important both for memory consolidation and the processing of olfactory information [2]. According to these findings some authors have proposed a relationship between the course of AD and the appearance of olfactory deficits that might appear even before cognitive deficits [3,12]. Therefore assessment of olfactory functions may be the method of choice for early identification of patients with memory deficits [2,3,8]. Schubert *et al.* [3] found a strong association between olfactory impairment and 5-year incidence of cognitive impairment, which is consistent with the results found in other longitudinal studies.

Olfactory deficits have been observed in non-AD dementias including vascular dementia, dementia with Lewy bodies, Huntington's disease, frontotemporal dementia and Parkinson's disease [13-16].

AD and VaD are the most common forms of dementia but often difficult to differentiate [17]. VaD refers to a cumulative decline in cognitive functioning secondary to multiple infarctions, ischemic injury or hemorrhagic lesions [10]. AD and VaD are quite heterogeneous and can overlap in their clinical presentations [10]. There is no clear consensus concerning the cognitive function or tests that best discriminate between these two type of dementia [17] which brings into question the utility of odor identification test in combination with cognitive tests for differential diagnosis. Cognitive assessment frequently forms a part of the diagnostic

* *E-mail: mladenka.tkalcic@ffri.hr*

process but olfactory function assessment does not.

The prevalence of olfactory impairment and cognitive impairment increase with age [3]. Among elderly persons without manifest cognitive impairment, difficulty in identifying odors predicted subsequent development of mild cognitive impairment (MCI) , a risk factor for developing AD [15]. Neuropsychological research has made considerable progress in defining different patterns of relatively preserved and impaired cognitive abilities that distinguish between AD and other age-associated neurodegenerative disorders [10]. For this purpose olfaction has gained increased attention in the clinical setting. Measurement of changes in olfaction and cognition play an important role in the early detection of AD, in differentional diagnosis and in the monitoring of therapy effectiveness [12].

To conclude, research show that olfactory identification deficit in patients with AD is a systematic phenomenon. Olfactory identification deficits were more pronounced in patients with AD compared to those in other age-associated neurodegenerative disorders. This is primarily because the central olfactory structures responsible for complex olfactory functioning in patients with AD are impaired. The relationship between olfactory identification function and cognitive abilities in patients with AD and other type of dementia still remains unresolved.

Therefore, the aims of this study were: 1) to compare the cognitive status and the ability to identify different odors among patients with AD, patients with VaD, and a comparison group of elderly persons; 2) to test the efficiency of olfactory and neuropsychological measures to classify patients according to the existing diagnosis and 3) to relate the odor identification ability with the cognitive functioning for each group, respectively.

2. Experimental Procedures

The local Ethics Committee of the Department of Psychology at the Faculty of Humanities and Social Sciences, University of Rijeka, approved this study.

2.1. Participants

Participants were 56 elderly people. Among them were 15 patients (73% female) who were diagnosed with probable Alzheimer's disease (AD) and 11 patients (73% female) who were diagnosed with vascular dementia (VaD), their ages ranging from 58 to 89 (Mean=77.80, SD=7.17). All patients had 8 to 12 years of education. Diagnoses were made by a neurologist and a psychiatrist based on all available clinical data. As control/comparison, a group of 30 elderly persons (67% female) who were not diagnosed with dementia participated, their ages ranging from 68 to 90 (Mean=79.80, SD=5.95). Most participants of the control group (93%) had 8 to 12 years of education.

2.2. Materials and procedure

2.2.1. Odor identification

Scandinavian Odor-Identification Test – SOIT [18] was used to assess odor identification ability. The SOIT uses natural oils as odor stimuli. 16 stimuli represent a wide range of aromatic qualities such as floral (lilac, violet), citrus (lemon, orange), non-citrus fruity (apple), sweet (almond, anise, vanilla), woody (juniper berry, tar), spicy (cinnamon, clove), minty (peppermint, pine-needle), and pungent (ammonia, vinegar). Five millilitres of the stimulus were placed in a 10 ml amber glass jar and presented birhinally 1-2 cm under the participant's nose for as long as required to accomplish the task. Participant was provided with a written list of the four response alternatives and his/her task was to choose the most appropriate answer among these four-alternatives. Where appropriate, the investigator read the list to the participant. We used this response paradigm to limit the cognitive and emphasize the sensory components of task. The 16 stimuli were presented in an order uniquely randomized for each participant with a 30-second pause between each stimuli to avoid the adaptation effect. In Table 1 basic descriptive data for this scale are presented.

The cut-off scores obtained from the normative data for diagnosing olfactory status in the age group of 55 to 74 for hyposmia is 8 to 10 and for anosmia is less than 7 correctly identified stimuli [18]. In our sample, the average result on SOIT for the control group is 9.43 (SD=2.65), for the patients with VaD 6.09 (SD=2.30) and for the patients with AD 3.33 (SD=3.16). According to the normative data, persons from the control group were mildly hyposmic, and both groups of patients with AD and VaD were anosmic. Because olfactory function declines in old age, our control group, with ages ranging from 69 to 90, on average scores lower than the normative sample, which represents the results from a sample of younger people. Furthermore, the SOIT test is culturally valid for Scandinavian population and Croatian people may have found some presented stimuli unfamiliar (e.g. *anise*). Therefore caution is needed when interpreting absolute scores. Because the main aim of this study was *to compare* odor identification ability among three groups of participants and not odor identification ability *per se*, the application of this test was reasonable and valid.

2.2.2. Neuropsychological battery

The neuropsychological battery assesses the following domains: global cognitive function, attention, initiation/perseveration, constructive abilities, reasoning, nonverbal and verbal memory, language and executive abilities. We selected cognitive tests to cover a broad range of cognitive abilities commonly affected by dementia. Descriptive data (mean, standard deviation and score range) of applied measures are presented in Table 1.

Dementia Rating Scale-2 – DRS-2 [19,20] provides and index of cognitive function in people with known or suspected dementia. The 36 test items are arranged hierarchically, from difficult to easier items. A global measure of dementia severity is derived from subscales of specific cognitive capacities. The subscales include measure of *attention* (e.g., digit span; 37 maximum points), *initiation and perseveration* (e.g., performing alternating movements, semantic fluency; 37 maximum points), *construction* (e.g., copying designs, writing name; 6 maximum points), *conceptualization* (e.g., similarities; 39 maximum points), and *verbal and nonverbal short-term memory* (e.g., sentence recall, design recognition; 25 maximum points). One point is given for each

item performed correctly. The maximum total score is 144. Instead of using a suggested cutoff score (e.g. 137 proposed by Mattis, 1988), we interpreted results by taking into consideration the participants ages and levels of education.

As shown in Table 1, the score range indicates a large variability within two groups of patients, for which we corrected for age and education level [21]. When we compare these results of our participants' average score with normative data for DRS-2, we find that patients with AD and VaD had significant impairment of global cognitive functioning. The comparison group on average had mild impairment of their cognitive functioning. Of course, one must keep in mind that this normative data are not adjusted for the Croatian elderly population.

Clock Drawing Test – CDT [22] is a screening instrument for dementia as well as for visuo-spatial, constructional, and executive difficulties. In other words, CDT depends on multiple cognitive domains. Clock-drawing is a practical test which can be useful for clinicians as a screen for cognitive impairment in old age and possibly as a marker of change in cognitive status as well as in distinguishing normal elderly from patients with dementia, especially those with AD [23].

There are a number of versions and scoring systems of this test. In this study, the participant was provided a sheet with a printed empty circle (10 cm in diameter), representing the shape of the clock face. The participant was asked to write the numbers and draw the hands for "10 after 11," a commonly used time setting. The scoring system used in this study is a simple 4-point system: 1 point for all numbers (1-12) present and in the correct sequence; 1 point for correct spatial orientation and placement of numbers, 1 point for correct drawing of the hour hands and 1 point for the placement of the hands pointing to the correct numbers (correct time setting). A test score less than 3 indicates a significant impairment of aforementioned cognitive function. According to these criteria all groups of patients expressed impairment of cognitive functioning. These results are compatible with the results on the DRS-2 test.

Boston Naming Test – BNT [24] is a 60-item test used to assess visual naming ability using black and white drawings of common objects. The participant was asked to name drawings of objects with increasing difficulty, ranging from simple, high-frequency vocabulary words (e.g., comb) to rare words (e.g., abacus). Scores included the number of spontaneously produced correct answer, the number of cues given, the number of correct responses after semantic hinting, and the number given after phonemic hinting. The total of correct responses is the sum of the number of spontaneously given correct responses and the number of correct responses given after a stimulus hint. Heaton *et al.* [cited in 23] suggest that T scores lower than 40 are considered "impaired." Poor performance on the BNT can occur in a variety of clinical conditions. For example, patients with AD tend to show impairment on the BNT, more so than patients with vascular dementia [23,25]. The average results on BNT for all three participants' groups were low. This may be due to the rigorous scoring procedure originally proposed by authors of this scale [24]. Due to lack of appropriate normative data in general and for Croatian population specifically we cannot make definitive conclusions on the participants' naming abilities.

Category Fluency Test – CFT (semantic fluency), which measures executive function, language, and semantic memory, is an integral component of the neuropsychological assessment, especially when evaluating for dementia syndromes [26]. In this test, the patient is asked to name as many things within a specified category that come to mind within a one-minute interval. The most common category tested, and the one that we used in our study, is "animals." The total of correct responses is the sum of all admissible words for the semantic category. In patients with AD, semantic fluency is affected more that phonemic fluency, reflecting a disorganization or a degradation in semantic knowledge [23]. Patients with AD and VaD on average named relatively few animals but each group of patients showed great individual differences in scores.

All participants were evaluated by a clinical interview and a battery of neuropsychological measures, including odor identification test. Evaluation was carried out individually at a hospital or in nursing home settings by a trained senior graduate psychology student. Patients with AD or VaD were evaluated at the Lopača Psychiatry Hospital, the Rab Psychiatry Hospital and the Centre for Intensified Care for Patients with Alzheimer Disease in Pula. Non-

Table 1. Descriptive statistics of the SOIT, DRS-2, CDT, BNT and CFT for the three participants' groups.

		AD	VaD	Control
		N=15	N=11	N=30
SOIT	Mean	3.33	6.09	9.43
	SD	3.16	2.30	2.65
	Range	0-9	2-9	0-14
DRS-2	Mean	60.00	79.45	130.47
	SD	36.36	34.50	11.52
	Range	2-117	8-115	86-149
CDT	Mean	0.27	0.82	2.83
	SD	0.80	1.08	1.32
	Range	0-3	0-3	0-4
BNT	Mean	10.67	14.82	16.43
	SD	6.90	6.40	8.58
	Range	0-21	0-27	14-17
CFT	Mean	2.40	5.36	13.60
	SD	3.02	2.94	5.48
	Range	0-9	1-10	7-29

demented elderly persons were evaluated in nursing homes in Rijeka and Pula.

3. Results

Analysis of variance (ANOVA) revealed that the three groups did not differ in terms of age (p=0.79) and educational level (p=0.77). There were no significant differences of gender proportions across groups. The distribution of measured variables was normal. Since the clinical samples are small, the variances within each sample significantly differ, and therefore we apply non-parametric and parametric statistical procedures. Because the results of non-parametric and parametric test coincide, we present only the results of parametric statistics.

3.1 Differences in olfactory and cognitive functioning among participants' groups

By analyzing variance (ANOVA) of the results for SOIT and the neuropsychological tests for all three groups, we find that all the results are significant at p<0.001. Table 2 outlines the descriptive statistics, F-ratios, and significant post-hoc comparisons of the three groups with respect to the SOIT and neuropsychological results.

As can be seen in Table 2, employing the Newman-Keuls post-hoc test, patients with AD correctly identified significantly fewer presented odors compared to both the control group of elderly persons and the patients with vascular dementia.

Furthermore, patients with AD achieved significantly lower scores on all neuropsychological tests in comparison to the control group of elderly persons. Similarly, patients with VaD achieved significantly lower results on almost all neuropsychological measures, with the exception of BNT, in comparison to the control group.

However, obtained results indicated that patients with AD significantly differed in the DRS-2 total score. Compared with patients with VaD, they also differed in subscales measuring initiation and perserveration, and constructive abilities. Further, they had significantly lower BNT scores compared to patients with VaD.

To conclude, persons diagnosed with dementia achieved significantly lower scores on almost all applied measures in comparison to elderly people who are not diagnosed with dementia, indicating a significant impairment in cognitive functioning. More important, patients with AD significantly differed from patients with VaD in odor identification and overall index of cognitive functioning, particularly in initiation, perseveration, as well as constructive and visual naming ability.

In order to characterize *the neuropsychological profile* of the sample groups and visually present obtained differences in applied cognitive measures, we calculated a z-score for each variable which indicates the relative degree of deviation from normal in SD units, allowing comparison across different cognitive tests (Figure 1).

Cognitive disabilities of patients with AD and VaD showed a similar pattern. As expected, patients with AD expressed lower results on all applied measures compared to patients with VaD. Yet because AD and VaD diagnoses are difficult to differentiate, we set out to verify that the neuropsychological test can indeed provide a valid mode of classification of patients with various forms of dementia.

3.2. Patients' classification on the basis of applied olfactory and cognitive measures

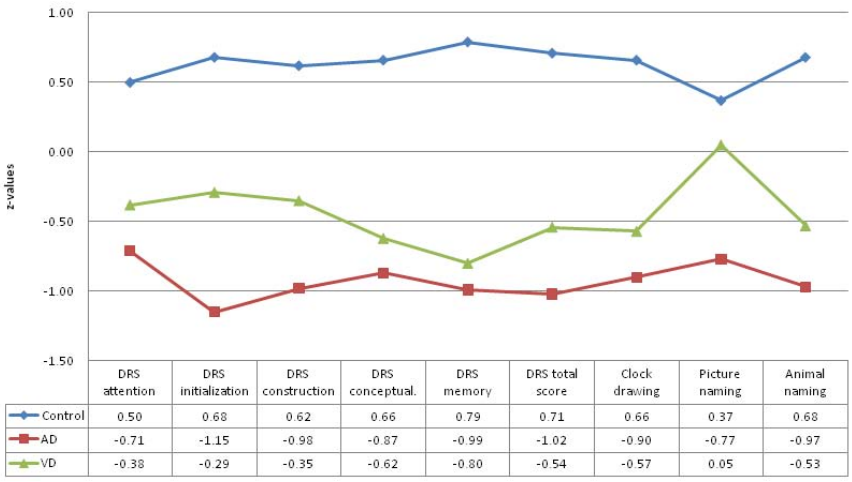
To test if olfactory and neuropsychological tests discriminate well between patients with AD and VaD, we conducted a standard discriminant analysis. In our discriminant analysis the diagnoses AD and VaD serve as the dependent variable and olfactory identification score, DRS-2 total score, clock drawing, naming and category/semantic fluency (animal naming) scores as predictor variables. When we calculated a single discriminant function, the value of this function was not significantly different for AD patients and VaD patients (chi-square = 8.27, df = 5, p =0.142). The correlation between predictor variables and the discriminant function suggested that *animal naming and olfactory identification* were the best indicators of different diagnoses. Overall the discriminant function successfully predicted

Table 2. Mean, standard deviation and F-ratio of measured variables for AD, VaD and control groups.

	AD (1)		VaD (2)		Control (3)		
	Mean	SD	Mean	SD	Mean	SD	F (2,53)
Odor identification	$3.33_{2,3}$	3.16	$6.09_{1,3}$	2.30	$9.43_{1,2}$	2.65	25.94**
DRS_attention	24.07_{3}	11.43	27.09_{3}	11.07	$35.13_{1,2}$	2.24	11.53**
DRS_initiation/perseveration	$12.00_{2,3}$	9.39	$21.82_{1,3}$	10.68	$32.83_{1,2}$	2.82	45.63**
DRS_construction	$2.20_{2,3}$	2.40	$3.64_{1,3}$	2.11	$5.83_{1,2}$	0.75	26.40**
DRS_conceptualization	17.00_{3}	11.01	19.73_{3}	10.59	$34.20_{1,2}$	4.24	28.82**
DRS_memory	5.40_{3}	6.12	7.18_{3}	4.90	$21.80_{1,2}$	3.84	76.12**
DRS_total score	$60.00_{2,3}$	36.36	$79.45_{1,3}$	34.50	$130.47_{1,2}$	11.52	43.59**
Clock drawing	0.27_{3}	0.80	0.82_{3}	1.08	$2.83_{1,2}$	1.32	29.13**
Picture naming	$10.60_{2,3}$	6.90	14.82_{1}	6.40	16.43_{1}	0.86	8.25**
Animal naming	2.40_{3}	3.02	5.36_{3}	2.94	$13.60_{1,2}$	5.48	35.00**

**p<.001

Note. Different numbers subscripts indicate differences between participant groups according to Newman-Keuls post hoc tests (p<.05).



	DRS attention	DRS initialization	DRS construction	DRS conceptual.	DRS memory	DRS total score	Clock drawing	Picture naming	Animal naming
Control	0.50	0.68	0.62	0.66	0.79	0.71	0.66	0.37	0.68
AD	-0.71	-1.15	-0.98	-0.87	-0.99	-1.02	-0.90	-0.77	-0.97
VD	-0.38	-0.29	-0.35	-0.62	-0.80	-0.54	-0.57	0.05	-0.53

Figure 1. Comparison of z-values of avarage results on cognitive measures between patients with AD and VaD and control group.

Table 3. Classification results obtained by discriminant analysis.

		Diagnosis	Predicted Group Membership		Total
			AD	VaD	AD
Original	Count	AD	12	3	15
		VaD	3	8	11
	%	AD	80.0	20.0	100
		VaD	27.3	72.7	100

a 76,9% of original grouped cases correctly classified.

the outcome of 77% of cases, with accurate predictions of 80% of AD patients and 72% of VaD patients (Table 3).

3.3. Relation between olfactory and cognitive abilities

We used Pearson's correlation coefficient to test the relationship between odor identification ability and cognitive function. Additionally, we calculated partial correlation coefficients controlling for age and education given that general olfactory function and cognitive abilities decline in old age and education was likely to co-vary with many cognitive abilities [7].

3.3.1 The relation between olfactory and cognitive abilities in patients with Alzheimer's disease

Significant correlations exist between odor identification ability and initiation/perseveration (r_{15}=0.52, p<0.05), verbal and nonverbal short-term memory (r_{15}=0.64, p<0.01) and category/semantic fluency (r_{15}=0.74, p<0.01).

When controlling age and education the correlations remained significant between odor identification ability and verbal/nonverbal short-term memory (r_{11}=0.56, p<0.05) and category/semantic fluency (r_{11}=0.69, p<0.01).

3.3.2 The relation between olfactory and cognitive abilities in patients with vascular dementia

Significant correlations exist between odor identification ability and constructive ability (r_{11}= 0.61, p<0.05) and conceptualization (r_{11}= 0.60, p<0.05), but controlling age and education, the correlation coefficient was not significant.

3.3.3. The relation between olfactory and cognitive abilities in control group of elderly persons

Almost all correlation coefficients between odor identifaction and cognitive abilities were significant: attention (r_{30}= 0.61, p<0.01), initiation/perseveration (r_{30}= 0.56, p<0.01), conceptualization (r_{30}= 0.55, p<0.01), verbal and nonverbal short-term memory (r_{30}= 0.38, p<0.05), index of general cognitive functioning (r_{30}= 0.61, p<0.01), drawings/picture naming (r_{30}= 0.61, p<0.01) and clock drawing (r_{30}= 0.40, p<0.05). Only the correlation coefficients of odor identification ability, constructive ability, category fluency were not significant.

After controlling for age and education, the previously mentioned significant correlations still remained with the exception of the correlation between odor identification ability and memory and clock drawing.

4. Discussion

The main finding of this preliminary clinical study is that patients with AD have significant impairment on an odor identification task comparing to other two groups of participants. This is in accordance with the results obtained by Knupfer and Spiegel [27] who used a series of experimental olfactory tests to compare patients with AD, VaD and healthy elderly control subjects. The AD patients scored significantly worse on these measures than the VaD patients, who scored below the elderly control subjects. Duff *et al.* [28] also showed that patients with AD scored significantly lower than patients with VaD on the pocket smell test. Although entorhinal cortex or other parts of the olfactory system theoretically could be affected in VaD, they are not consistent sites for vascular damage [28]. The main explanation of obtained results is the existence of amyloid plaques and tangles in the medial temporal lobe that exert a significant influence on olfactory identification ability even in elderly participants who are not diagnosed with dementia [7]. This could explain mild impairment of olfactory function in elderly control subjects as well as the slight decrease in their overall cognitive functioning measured with DRS-2.

As expected, patients with dementia (AD or VaD) showed significant impairment in cognitive functioning compared to the elderly control group without dementia. Generally, cognitive impairment of patients with AD and VaD showed similar patterns but some differences emerged. In addition to marked olfactory dysfunction, patients with AD showed significant impairment in general cognitive functioning, especially in initiation and perseveration (e.g., semantic fluency), constructive (e.g., copying designs) and verbal ability (visual naming) compared to patients with VaD. These results were not completely in line with the results of other studies. For example, Lukatela *et al.* [29] found that patients with AD scored less on the DRS-memory scale and conceptualization while the patients with VaD scored less on the construction. But another study by Lukatela *et al.* [30] showed clear separation between the participant groups (AD, VaD, elderly control) on overall BNT accuracy (visual naming ability) with the AD group having the lowest scores. Similar results were obtained in this study. AD and VaD result from a neurodegenerative process associated with aging, but given etiological, neuroanatomical, and functional differences in the brain areas involved (cortical atrophy in AD vs. cortico-subcortical vascular lesions in VaD), differences in the pattern of cognitive functioning are to be expected. Mathias and Burke [17] completed a meta-analysis of research comparing the cognitive abilities of patients with AD and VaD. They argued that because all cognitive tests are limited in their ability to discriminate between AD and VaD, they should be used cautiously and only in conjunction with other information when diagnosing patients. The reason for contradictory results could be in possible mixed dementia, especially in the group of patients with VaD. Neuropathological data has revealed that over 30% of patients whose diagnosis of AD was confirmed at postmortem also had cerebrovascular disease and that 40% of patients diagnosed with VaD confirmed at postmortem showed evidence of AD pathology. There are also similarities in the clinical presentation of AD and VaD, including cognitive decline, functional deterioration, and behavioral symptoms [more details in ref 17]. These are in accordance with the results of discriminant analysis showing that 80% of AD patients and 72% of VaD patients could be accurately classified based on applied neuropsychological measures. This means that about 20% of patients with AD and 30% of patients with VaD are misdiagnosed. Although the discriminant function was not significantly different for AD and VaD patients, as in accordance with Mathias and Burke's assumptions [17], category fluency task (animal naming) and olfactory identification tests were the best predictors of differentiating the diagnoses.

In addition, significant correlation exists between odor identification ability and verbal/nonverbal memory and category (semantic) fluency for patients with AD but not for patients with VaD. Wang *et al.* [31] also showed strong correlation among the olfactory and neurocognitive dementia measures. Similarly, in the control group of elderly persons, the majority of the correlation coefficients between odor identification and cognitive abilities were significant. This is most likely due to the fact that general olfactory function and cognitive abilities simultaneously decline in old age, but according to our results, they decline at different rates for each of our test groups. By reviewing past research, the correlation between memory and olfactory ability in patients with AD was expected. Odor identification relies on sensory, perceptual, and cognitive skills, particularly semantic memory [8]. As mentioned before, the animal naming task measures executive functions, language, semantic memory, and according to Sager *et al.* [32] is moderately to highly effective in identifying dementia. Progressive naming difficulties are one of the main characteristics of AD [30]. In other words, semantic knowledge rather than visual processing is impaired in AD. The impairment in the naming process is due to a loss or a reduction in the availability of the specific semantic attributes that determine conceptual meaning. Patients with AD usually demonstrate impaired semantic category fluency, phonemic category fluency, semantic priming, naming to definition, and recognition of object names [30]. Brickman *et al.* [33] emphasize that category but not letter fluency is typically poorer in elderly compared to younger adults and this pattern of poorer performance on test of category fluency is reproduced in AD with a greater effect. Clark *et al.* [34] found that the category fluency was superior to letter fluency in distinguishing between normal controls and patients with AD based on the fact that impairments in semantic memory processing occur early in the course of AD. Therefore, animal naming would be associated with the temporal part of the brain as well as olfactory function. A disorganization of semantic knowledge might be expected as the disease progress. The results of these studies provide strong evidence that the organization of semantic knowledge is abnormal in patients with AD, particularly in the verbal and olfactory domains [35].

Based on the findings of this study, the use of olfactory tests in combination with other neuropsychological measures, especially those investigating semantic memory ability, could provide useful tools in differential diagnosis of AD [8,36].

We should carefully interpret the results of the present study due to the number of limitations: a) small sample sizes of groups - 15 AD and 11 VaD patients; b) possible mixed diagnosis (overlapping of etiologies and neuropathological substrates as well as symptoms between AD and VaD) or misdiagnosis (control group possibly included some participants whose scores were influenced by preclinical AD changes); c) intragroup variability - large score range; d) gender bias - more female participants; e) cultural specificity and dependency of applied measures, specifically the lack of appropriate normative data for the Croatian population and f) possible influence of cognitive factors on olfactory functioning. This last point may be the most influential in determining our results. Namely, the process of identifying an odor poses sensory and cognitive demands [7], especially possible lexical difficulty in naming an odor for patients with obvious cognitive deficits. But Murphy [8] showed that both lexically based and the non-lexically based olfactory identification tests showed high sensitivity and specificity for the population "at risk" for AD, so the results of this study clearly indicated a true decline in odor

identification ability in patients with dementia, particularly AD patients. Therefore, since the lexical impairments of AD were not responsible for the smell identification deficiency, the odor identification tasks could be useful in diagnosing AD.

To summarize, patients with AD showed clear odor identification deficiency. This is in accordance with the observation that the olfactory disorders are an integral factor of the pathology of AD. Therefore, olfactory functional testing should be an important part of the neurological and neuropsychological assessment. It could give insights into the progression of degeneration in the early as well as late stages of AD and help to better distinguish between AD and VaD. Although patients with VaD also showed odor identification deficiency, their results were less pronounced than in patients with AD. Also, patients with AD differed from patients with VaD in overall cognitive functioning, particularly in initiation and perseveration, constructive and visual naming ability. These results should skeptically be considered because they were not in line with the results of other studies investigating differences in cognitive functioning of patients with AD and VaD [29,30]. The results of discriminant analysis were more intriguing. As Mathias and Burke [17] stated, not all of the tests of the neuropsychological battery can distinguish AD from VaD, yet we found that odor identification ability and category fluency were the best predictors for AD. Recent studies [31,34] report the importance of the assessment of the category/semantic fluency, due to the significant correlation between odor identification ability and memory and category fluency for patients with AD. Considering the limitations and shortcomings of this study, we may suggest that the odor identification test in combination with memory and verbal/category fluency tests should be the integral part of the neuropsychological assessment of the patients having probable AD.

Acknowledgments

We are greatful to prof. Steven Nordin, Umea University, Sweden, for generously offering us the Scandinavian Odor-Identification Test for measuring odor identification ability in our study samples.

Conflict of interest statement. None declared.

References

[1] Doty R. L., Reyes P. F., Gregor T., Presence of both odor identification and detection deficits in Alzheimer's disease, Brain Res. Bull., 1987, 18, 597-600

[2] Laakso M. P., Tervo S., Hanninen T., Vanhanen M., Hallikainen M., Soininen H., Olfactory identification in non-demented elderly population and in mild cognitive impairment: a comparison of performance in clinical odor identification versus Boston Naming Test, J. Neural. Transm., 2009, 116, 891-895

[3] Schubert C. R., Carmichal L. L., Murphy C., Klein B. E. K., Klein R., Cruickshanks K. J., Olfaction and the 5-year incidence of cognitive impairment in an epidemiological study of older adults, J. Am. Geriatr. Soc., 2008, 56, 1517-1521

[4] Doty R. L., Shaman P., Dann M., Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsualted test of olfactory function, Physiol. Behav., 1984, 32, 489-502

[5] Westervelt H. J., Carvalho J., Duff K., Presentation of Alzheimer's disease in patients with and without olfactory deficits, Arch. Clin. Neuropsychol., 2007, 22, 117-122

[6] Westervelt H. J., Bruce J. M., Coon W. G., Tremont G., Odor identification in mild cognitive impairment subtypes, J. Clin. Exp. Neuropsychol., 2007, 22, 925-931

[7] Olofsson J. K., Odor identification in aging and dementia: influences of cognition and the ApoE gene, PhD thesis, Department of Psychology, Umea University, Umea, Sweden, 2008

[8] Murphy C., Loss of olfactory function in dementing disease, Physiol. Behav., 1999, 66, 177-182

[9] Wilson R. S., Arnold S. E., Schneider J. A. et al., The relationship between cerebral Alzheimer's disease pathology and odour identification in old age, J. Neurol. Neurosurg. Psychiatry, 2007, 78, 30-35

[10] Salmon D. P., Bondi M. W., Neuropsychological assessment of dementia, Annu. Rev. Psychol., 2009, 60, 257-282

[11] Thomann P. A., Dos Santos V., Toro P., Schonknecht P., Essig M., Schroder J., Reduced olfactory bulb and tract volume in early Alzheimer's disease – a MRI study, Neurobiol. Aging, 2009, 30, 838-841, 2009

[12] Lange R., Donathan C. L., Hughes L. F., Assessing olfactory abilities with the University of Pennsylvania smell identification test: a rasch scaling approach, J. Alzh. Dis., 2002, 4, 77-91

[13] Gray A. J., Staples V., Murren K., Dhariwal, A., Bentham P., Olfactory identification is impaired in clinic-based patients with vascular dementia and senile dementia of Alzheimer type, Int. J. Geriatr. Psychiatry, 2001, 16, 513-517

[14] McLaughlin N. C. R., Westervelt H. J., Odor identification deficits in frontotemporal dementia: a preliminary study, Arch. Clin. Neuropsychol., 2008, 23, 119-123

[15] Lehrner J., Pusswald G., Gleiss A., Auff E., Del-Bianco P., Odor identification and self-reported olfactory functioning in patients with subtypes of mild cognitive impairments, Clin. Neuropsychol., 2009, 23, 818-830

[16] Mesholam R. I., Moberg P. J., Mahr R. N., Doty R. L., Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases, Arch. Neurol., 1998, 55, 84-90

[17] Mathias J. L., Burke J., Cognitive functioning in Alzheimer's and vascular dementia: a meta-analysis, Neuropsychology, 2009, 23, 411-423

[18] Nordin S., Brämerson A., Lidén E., Bende, M., The Scandinavian odor-identification test: development, reliability, validity and normative Data, Acta Otolaryngol., 1998, 118, 226–234

[19] Mattis S., Dementia rating scale: professional manual, Psychological Assessment Resources, Odessa, 1988

[20] Jurica P. J., Leitten C. L., Mattis, S., Dementia rating scale-2, Professional Manual, Psychological Assessment Resources, Odessa, 2001

[21] Lucas J. A., Ivnik R. J., Smith G. E., Bohac D. L., Tangalos E. G., Kokmnen N. R., et al., Normative data for Mattis Dementia Rating Scale, J. Clin. Exp. Neuropsychol., 1998, 20, 540-545

[22] Shulman K., Clock-drawing: is it the ideal cognitive screening test?, Int. J. Geriatr. Psychiatry, 2000, 15, 548-561

[23] Strauss E., Sherman E. M. S., Spreen O., A compendium od neurology tests: Administration, norms and comentary, Oxford University Press, New York, 2006

[24] Kaplan E., Goodglass H., Weintraub S., The Boston naming test, Lea & Febiger, Philadelphia, 1983

[25] Galić S., Neuropsihologijska procjena: Testovi i tehnike (Neuropsychological assessment: tests and techniques), Naklada Slap, Jastrebarsko, 2002

[26] Brucki S. M. D., Rocha, M. S. G., Category fluency test: effects of age, gender and education on total scores, clustering and switching in Brazilian Portuguese-speaking subjects, Braz. J. Med. Biol. Res., 2004, 37, 1771-1777

[27] Knupfer L., Spiegel R., Differences in olfactory test performance between normal aged, Alzheimer and vascular-type dementia individuals, Int. J. Geriatr. Psychiatry, 1986, 1, 3-14

[28] Duff K., McCaffrey R. J., Solomon G. S., The pocket smell test – successfully discriminating probable Alzheimer's dementia from vascular dementia and major depression, Neuropsychiatry Clin. Neurosci., 2002, 14, 197-201

[29] Lukatela K., Cohen R. A., Kessler H., Jenkins M. A., Moser D. J., Stone W. F., et al., Dementia rating scale performance: a comparison of vascular and Alzheimer's dementia, J. Clin. Exp. Neuropsychol., 2000, 22, 445-454

[30] Lukatela K., Malloy P., Jenkins M., Cohen R., The naming deficit in early Alzheimer's and vascular dementia, Neuropsychology, 1998,12, 565-572

[31] Wang J., Eslinger P. J., Doty R. L., Zimmerman E. K., Grunfeld R., Sun X., et al., Olfactory deficit detected by fMRI in early Alzheimer's disease, Brain Res., 2010, 1357, 184-194

[32] Sager M. A., Hermann B. P., La Rue A., Woodard J. L., Screening for dementia in community-based memory clinics, Wisc. Med. J., 2006,105, 25-29

[33] Brickman A. M., Paul R. H., Cohen R. A., Williams L. M., Mac Gregor K. L., Jefferson A. L., et al., Category and letter verbal fluency across the adult lifespan: relationship to EEG theta power, Arch. Clin. Neuropsychol., 2005, 20, 561-573

[34] Clark L. J., Gatz M., Zheng L., Chen Y-L., McCleary C., Mack W. J., Longitudinal verbal fluency in normal aging, preclinical, and prevalent Alzheimer's disease, Am. J. Alzh. Dis. Other Demen., 2009, 24, 461-468

[35] Chan A. S., Butters N., Salmon D. P., The deterioration of semantic networks in patients with Alzheimer's disease: a cross-sectional study, Neuropsychologia, 1997, 35, 241-248

[36] Morgan C. D., Nordin S., Murphy C., Odor identification as an early marker for Alzheimer's disease: impact of lexical functioning and detection sensitivity, J. Clin. Exp. Neuropsychol., 1995, 17, 793-803