ORIGINAL CONTRIBUTION

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Just noticeable difference in olfaction: a discriminative tool between healthy elderly and patients with cognitive disorders associated with dementia*

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SUMMARY

Olfactory dysfunction appears to be one of the earliest signs of several age-related neurodegenerative disorders, including Alzheimer's disease (AD) or Parkinson's disease (PD). To rate performance and olfactory deficits in patients with cognitive disorders, various olfactory tasks have been used such as odor detection, discrimination, recognition memory, identification and naming but no study has been focused on just noticeable difference (JND), a sensitive tool of detection. The aim of this study was to investigate and compare variations in JNDs in healthy elderly and in patients with cognitive disorders associated with dementia. The results showed significantly higher olfactory JNDs in a population with cognitive disorders associated with dementia - i.e. a lower olfactory detection performance - compared to a control population paired in age, gender and education level. Additionally, the findings of the present study showed strong correlations between cognitive performances and JND scores in the control population contrary to the patient population. These findings are discussed in relation to the relevance of using olfactory JNDs in the diagnosis of dementias.

Key words: *just noticeable difference, olfactory sensitivity, dementia, Alzheimer's disease, cognitive disorders*

INTRODUCTION

Treatment of olfactory information involves "peripheral" and "central" levels, which determine the global olfactory performance. The "peripheral" level corresponding to the olfactory epithelium is implied in the olfactory sensibility estimated by the measure of the detection threshold (the lowest concentration that a subject can detect) or the just noticeable difference (JND or differential threshold), the smallest difference that a subject can detect between two olfactory stimulations. The "central" level refers to a higher degree of treatment (localized on different regions of the brain) and involves more complex cognitive components such as the ability to differentiate the quality of odorants (discrimination), to recognize odor targets previously smelt (memory), or to give the name of an odorant in a list of words (identification). During ageing, degenerative changes occur in neuroreceptors in the nasal cavity [(1)], in neurons of the olfactory bulb [(2)] as well as in cerebral regions such as thalamus, hypothalamus and hippocampus [(3)]. The neurotransmitter pathways can also be affected [(4)]. All these physiological changes of the olfactory structures occurring at both "peripheral" and "central" levels are characterized by a decrease of the olfactory sensitivity (i.e. a gradual increase of the detection threshold) [(5-7)] and a decrease of the discrimination, memory and identification abilities [(7-12)]. Several studies have reported the decrease of the ability to smell as common in older age and as an early sign of age-related neurodegenerative disorders, including Alzheimer's disease (AD) [(13-15)] and Dementia with Lewy bodies (DLB) [(16)]. In these pathologies, the olfactory dysfunctions seem to increase with the severity of dementia [(16)]. Specifically, the histopathological lesions in AD such as senile plaques and neurofibrillary tangles in the olfactory structures, i.e. olfactory bulb [(17,18)], pyriform cortex [(19)] and entorhinal cortex [(18)], are known to lead to a decrease in recognition memory, odor identification and discrimination at moderate stage of disease. Deficits in olfactory detection were also described at earlier stage of AD [(21,21)]. Similar impairments have been reported in PD, before the apparition of the resting tremor [(22)]. In the DLB, lesions observed in anterior olfactory nucleus and in amygdala are responsible for a more severe deficit of olfactory sensitivity than in AD [(16,23)]. Thus, although

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research on various types of dementia suggest that discrimination, memory and identification olfactory abilities decrease, the possible effects on detection capacities are discussed [24-26]. However, the published works have used the absolute detection thresholds preferentially to the differential threshold. In sensory perception, the differential threshold, also called just noticeable difference (JND), is defined by the level at which an increase in a detected stimulus can be perceived or the smallest change in stimulation that a subject can detect. JND might be a more sensitive measure for assessing the quality of olfactory perception in different manners such as comparative assessment between single molecule and mixtures [27], clinical test [28] or damages to the olfactory system [29], than the most frequently measured absolute threshold [15]. The aim of the present study was to investigate and compare, in subjects with cognitive disorders and in a healthy comparison group, the olfactory detection abilities using JNDs and to assess their potential utility as a complementary tool in the diagnosis of dementia.

METHODS

Participants

Two participant groups were recruited in this study: a group of patients (mean age = 78 years) and a control group (mean age = 77 years 10 months). Both groups (N=15) were matched for age (t = 0.094, *ns*), gender (i.e. 6 females and 9 males in each group) and education level. The participants of the patient group were recruited from the neurology department of an university hospital. All patients had a dementia according to the DSM-IV diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, fourth edition). Standard criteria were used for diagnosis of a specific dementing illness. Exclusion criteria were the same for both groups, i.e. traumatic brain injury, progressive psychiatric illness, history of brain or nasal surgery, smoking, nasal congestion at the time of tests and participants did not have any disorders of comprehension instructions. Healthy volunteers of the control group were non-smokers and none of them had a nasal/sinus disease, a neurological or a psychiatric history.

Neuropsychological Evaluation

All controls and patients underwent the RAPID neuropsychological battery [30], including the following tests: the Memory Impairment Screen (MIS) [31,32], the Isaacs Set Test (IST) [32,33], the Mini-Mental State Examination (MMSE) [34], the Free and Cued Selective Recall Test (FCSRT) [35], the Trail Making Test (TMT) forms A and B [36], the Crossing-Off-Test (COT) [37], a test for picture naming [30], a test for copying geometric figures as part of the cognitive evaluation battery and a test for matching categories [38]. All these tests were normalized on a cohort of healty controls according to age and level of education [30].

Olfactory tests

The odorant used was the butanol ($C_4H_{10}O$) (Table 1), a neutral smell with middle trigeminal properties [39]. Dilution series (factor 2) were prepared in deionized water. After successive dilutions (Table 2), the full series included steps 1 to 11 (step 1 as the highest concentration). Four mL of each concentration were placed in a glass tube (7.5 cm high, 1 cm in diameter at the opening). Step 6 was used as the reference concentration. Ten concentrations (steps 1 to 5 and steps 7 to 11) were presented in a randomized order into 5 series. A total of 50 trials were performed, i.e. 5 trials for each stimulus comparison. A rest period of 1 minute was observed between the series. The full experiment lasted about 30 minutes. All concentrations were compared to the step 6 (as referent) in a classical two alternative forced-choice task. A rack with the reference tube and another tube, more or less concentrated, was presented to the subject who had to report, which one was more concentrated.

JND calculations

The JND was calculated by using the following equations commonly performed in obtaining upper and lower limits [40].

Upper Limit
$$S_U = \left(Cu + \frac{D}{2}\right) - \frac{\left(\sum_{i=1}^{p} Ui\right)}{n} D \quad (1)$$

Lower Limit
$$S_L = \left(CL + \frac{D}{2}\right) + \frac{\left(\sum_{i=1}^{p} Li\right)}{n} D \quad (2)$$

Differential Threshold
$$\Delta L = \frac{SU - SL}{2} \quad (3)$$

C_U: Maximum stimulus compared, C_L: Minimum stimulus compared, U_i: Total number of judgments that belong to the high limit in the "*i*" th stimulus comparison, L_i: Total number of judgments that belong to the "low" limit in the "*i*" th stimulus comparison, *n*: Number of trials performed in each stimulus comparison, *D*: Step size of comparison stimulus, *p*: Total number of comparison stimulus. For each concentration tested, the discrimination threshold was defined as the stimulus magnitude of the comparison at which the proportion of correct responses was equal to 0.75.

Statistical analysis

The Student t-test (independent) was used to compare the demographic, neuropsychological and olfactory variables of both patient and control groups. The Spearman's correlation coefficient was performed to study the relation between olfactory and cognitive performances. The significance threshold was set at 0.05. The non-significant analyses were noted as ns.

RESULTS

Olfactory performances

The results are presented in Figure 1. The statistical analysis showed a significant difference between both populations (patient and control groups) for JNDs measures [t = 2.328, $p < 0.02$] indicating higher JNDs for the patients. Additionally, when the four patients with vascular dementia were excluded from the patient group (N = 11) the statistical difference was strongly increased [t = 3.974, $p < 0.0006$].

Table 1. Properties of butanol.

Chemical	Company	CAS*	Molecular formula	Mol wt	Density g/cm^3	Mol/cm^3
Butanol	Sigma	71-36-3	$C_4H_{10}O$	74.12	0.81	10.9×10^{-3}

* The American Chemical Society's Chemical Abstracts Service (CAS) registry number

Table 2. Concentrations of butanol obtained by successive dilutions (factor 2).

		Butanol	
Dilution Step	Concentration (% v/v)	g/cm^3	Mol/cm^3
1 Pure liquid	100	0.81	10.9×10^{-3}
2	50	0.405	5.45×10^{-3}
3	25	0.2025	2.725×10^{-3}
…	…	…	…
10	0.195	1.579×10^{-3}	2.125×10^{-5}
…	…	…	…

Table 3. Cognitive performances (Control group vs Patient group).

	Control group (n=15)		Patient group (n=15)		Student-t test (independent)
Neuropsychological tests	m	σ	m	σ	p
MIS	7.5	0.7	4.5	2	0.0001***
IST	27.66	1.91	21.33	7.51	0.003**
MMSE (max. 30)	27.7	1.32	20.6	4.57	0.0001***
COT	114.4	21.33	120.61	43.49	0.08
FCSRT					
FR (max. 48)	18.06	3.49	5.30	4.38	0.0001***
TR (max. 48)	47.33	0.72	26.61	9.52	0.0001***
TMT					
Form A	41.26	9.43	109.86	87.68	0.005**
Form B	174.06	31.05	345.71	115.49	0.0001***
Picture naming (max. 30)	29.8	0.41	26.86	3.18	0.001**
Copying geometric figures	6	0	5.9	0.3	0.13
Matching categories (max. 10)	10	0	9.46	0.91	0.03*

MIS: Memory Impairment Screen; IST: Isaacs Set Test; MMSE: Mini Mental State Examination; COT: Crossing-Off Test; FCSRT: Free and Cued Selective Recall Test; FR: Free recall; TR: Total Recall; TMT: Trail Making Test. m: mean ; σ: standard deviation ; p: p-value. (* p<0.05; ** p<0.01; *** p<0.0001).

Cognitive performances

Results are reported in Table 3. Significant differences between the patient and control groups were observed for the following tests: MIS ($p < 0.0001$), IST ($p < 0.003$), MMSE ($p < 0.0001$), free recall of the FCSRT ($p < 0.0001$), total recall of the FCSRT ($p < 0.0001$), TMT form A ($p < 0.005$), TMT form B ($p < 0.0001$), picture naming ($p < 0.001$) and test for matching categories ($p < 0.03$). Only the results obtained at both COT ($p < 0.08$) and copying geometric figures ($p < 0.13$) tests did not differ significantly between both populations. Overall, it can be considered that the patient group had significantly lower cognitive performances than the control group.

Correlations between cognitive and olfactory performances

The results are reported in Table 4. For the control group, the data clearly indicated that whatever the neuropsychological test, cognitive and olfactory performances were correlated, especially in the case of IST ($p < 0.005$) and COT ($p < 0.001$), expect in the case of picture naming ($p < 0.07$). In contrast, for the patient group no significant correlation was found between cognitive and olfactory performances.

DISCUSSION

The findings of the present study are in agreement with several published papers showing that several neurological diseases

Table 4. Correlations between performance on neuropsychological tests and JNDs.

	Controls (n=15)		Patients (n=15)	
Neuropsychological Tests	r_s	p	r_s	p
MIS	0.53	0.04 *	0.52	0.07
IST	0.75	0.005 **	0.11	0.39
MMSE (max. 30)	0.53	0.04 *	0.23	0.39
COT	0.84	0.001 **	0.08	0.39
FCSRT				
FR (max. 48)	0.58	0.03 *	0.52	0.07
TR (max. 48)	0.53	0.049 *	0.23	0.42
TMT				
Form A	0.58	0.03 *	0.01	0.96
Form B	0.68	0.01 *	0.16	0.68
Picture naming (max. 30)	0.48	0.07	0.12	0.9
Copying geometric figures	0.43	0.09	0.20	0.26
Matching categories (max. 10)	0.53	0.04 *	0.30	0.26

MIS: Memory Impairment Screen; IST: Isaacs Set Test; MMSE: Mini Mental State Examination; COT: Crossing-Off Test; FCSRT: Free and Cued Selective Recall Test; FR: Free recall; TR: Total Recall; TMT: Trail Making Test
m: mean ; σ: standard deviation ; p: p-value. (* p<0.05; ** p<0.01; *** p<0.0001)

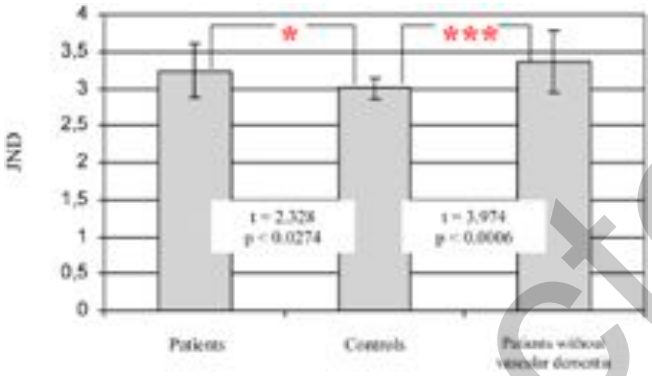

Figure 1. Just noticeable differences (JNDs) in olfaction obtained with butanol odorant in three populations: Patients (N = 15; patients with cognitive disorders associated with dementia), Controls (N = 15; paired in sex, age and education level with the patient group,) and Patients without vascular dementia (N = 11; four participants with vascular dementia were excluded from the Patients group).

such as dementia are accompanied by olfactory disturbances. Specifically, data showed that JNDs in olfaction were significantly higher in a population with cognitive disorders associated with dementia - i.e. a lower olfactory detection performance - than in a control population paired in age. Aging itself is an important variable affecting olfaction [41]. After the age of 80 years about 70 percent of individuals have a marked impairment of olfactory functions and between 65 and 80 years, 50 percent have a quantifiable deficit [41,42]. Thus, the development of olfactory tools, which can predict dementia and discriminate between normal aging deficit and neurological pathologies are required [43].

Additionally, the findings of the present study showed strong correlations between cognitive performances and JND scores in the control population contrary to the patient population. The strong correlation in the control group was mainly due to the small standard deviation around the mean scores for all cognitive tests showing an homogeneous population. In contrast, the patient group presented a great standard deviation around the mean scores for several cognitive tests while the dispersion of JND scores was weak. Cognitive disturbances in the patient group depend on many factors such as disease duration, medical treatment or specific nervous central structure deterioration, which prevent a correlation between JND and cognitive scores.

Overall, these results suggested that JNDs could be an interesting tool added to classical cognitive evaluation in determining neuropsychological diagnosis in the elderly. Indeed, olfactory detection tests are relevant in the case of patients with dementia insofar as the task did not involve specific cognitive processes. Moreover, these findings are in agreement with a recent published work [44], which suggested that the JND in olfaction could be a more discriminative tool than the classical absolute threshold.

Specifically, in normal elderly population, scores in MMSE,

a marker widely used in cognitive neurology to characterize the overall cognitive efficiency, are correlated with JNDs. Performances in olfactory sensitivity are also highly correlated with memory performance, speed of information processing and executive function. The interest of these results focuses on the parallel evolution of memory scores and olfactory performances, i.e.when cognitive performance declines, olfactory performance declines too. This correlation was not observed in the group of patients who showed cognitive impairment associated with different types of dementia (vascular dementia, degenerative, mixed and possible or probable dementias). However, memory impairment is one of the first symptoms of most neurodegenerative diseases such as ATD [16], and it would be interesting to incorporate into the interview with persons coming in clinical memory consultation, questions concerning the olfactory complaints, which are never expressed spontaneously. In addition, the award of olfactory tests in the neuropsychological assessment could provide valuable information on brain function of patients and could contribute to the differential diagnosis of dementia. Indeed, specific dementia such as vascular dementia [45] could be logically not associated with olfactory sensitivity deficits and could obtain similar thresholds than those of elderly controls. As a consequence, it would be appropriate for further study, to establish a patient population including more subjects and more homogeneous characteristics at the clinical level (i.e., subgroups of patients characterized by a particular type of dementia) to study the performance in terms of olfactory JNDs in comparison with a control group.

Finally, the use of olfactory tests such as JNDs in the diagnosis of neurodegenerative diseases raises a strong interest because of their accuracy added to the non-invasive and low-cost characters of this tool.

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