SHORT COMMUNICATION

Olfactory Functions in Parkinson's Disease and Alzheimer's Disease

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Abstract

The aim of this investigation was to compare olfactory functions of patients suffering from Parkinson's disease (PD) and Alzheimer's disease (AD). Olfactory threshold, odor identification ability and odor memory performance were assessed in 21 non-demented PD patients and in 22 AD patients. Both patient groups were impaired in relation to an age-matched control group for the measure of odor identification. AD patients showed a higher olfactory threshold and poorer odor memory performance. **Chem Senses 22: 105–110, 1997.**

Introduction

Parkinson's disease (PD) and Alzheimer's disease (AD) are common neurodegenerative disorders in the elderly population. Over the past two decades it has become clear that olfactory functions are compromised in both disorders (Doty, 1991).

In PD olfactory impairment is well established. Earlier studies have found decreased olfactory threshold and impaired discrimination ability (Ansari and Johnson, 1975; Ward *et al.*, 1983; Quinn *et al.*, 1987). Since then, odor identification has also been found to be impaired, and furthermore the impairment was independent of age, disease duration, disease severity, anti-Parkinson medication and neuropsychological measures (Doty *et al.*, 1988, 1989, 1992a). Olfactory performance and nigro-striatal dopaminergic degeneration as measured with 2-β-carbomethoxy-3-β-(4-iodophenyl)-tropane single photon emission computer tomography have also been shown to be independent (Lehrner *et al.*, 1995a). Further studies demonstrated that the severity of olfactory dysfunction differed with certain subtypes of PD and atypical Parkinsonian syndromes (Stern *et al.*, 1994; Wenning *et al.*, 1995).

Initial investigations of AD patients reported alterations in the ability to detect and identify odorants (Doty *et al.*, 1987) as well as odor memory (Knupfer and Spiegel, 1986; Moberg *et al.*, 1987). There is, however, no equivocal agreement about whether olfactory dysfunction in AD is correlated with disease progression (Koss, 1986; Warner *et al.*, 1986; Koss *et al.*, 1987, 1988; Rezek, 1987; Serby *et al.*, 1991). Studies comparing olfactory functions in AD patients and PD patients found similiar deficits for odor identification and olfactory threshold in both patient groups

(Corwin *et al.*, 1985; Kesslak *et al.*, 1988; Doty *et al.*, 1991), implying a somewhat similar etiology for the olfactory impairment in both disorders.

The goal of this study was to compare olfactory threshold and odor identification ability in AD patients and non-demented PD patients, and to assess odor memory for the first time in PD patients and compare it with the performance of AD patients. Another aim of this investigation was to determine whether olfactory functions are correlated with disease progression in AD and PD.

Methods, results and discussion

Twenty-two patients (2 males, 20 females) who fulfilled the NINCDS–ADRDA (7) criteria for probable Alzheimer's disease (McKhann *et al.*, 1984) and 21 non-demented patients with Parkinson's disease [13 males, 8 females; mean disease duration (SD) 78 ± 46 months; mean age at onset 61.0 ± 9.4 years; mean Hoehn and Yahr stage 2.44 ± 1.1; all PD patients were taking anti-Parkinson medication] were investigated. Cognitive status was assessed by means of Mini Mental Status (MMS) testing.

Patient groups differed significantly concerning age ($F = 4,87$, d.f. = 2.59, $P < 0.011$). *Post hoc* analysis (Scheffe's, $P < 0.05$) showed that AD patients were significantly older than controls and PD patients. The ages of PD patients and controls were not significantly different.

The demographic characteristics are presented in Table 1.

Olfactory testing was performed using an olfactory testing procedure which had previously been used in HIV-infected patients (Lehrner *et al.*, 1995b). In short, the olfactory testing procedure consisted of an olfactory threshold detection task (1-butanol, ascending staircase, two-bottle, forced-choice method), an odor identification task (20 everyday odors were to be identified) and an odor recognition memory task (retention time 15 min) (Lehrner, 1993b).

Odor threshold testing took place during the 15 min retention interval of odor recognition testing. Beginning at the lowest concentration, subjects sampled the head space of the butanol and control bottles in ascending concentrations. Their task was to indicate which bottle contained the butanol solution or smelled stronger. The threshold was defined as the butanol concentration correctly chosen over water in four consecutive trials. The corresponding number of the concentration bottle was taken as the threshold value. High corresponding numbers meant a low threshold.

For the memory recognition test patients were presented with 10 common household odorants at intervals of 30 s. After a retention interval of 15 min, the memory recognition test took place. For each of the 20 stimuli (10 'old', from the initial inspection set, and 10 'new') the subjects were asked to decide whether the odorant was 'old' (i.e. from the inspection set) or 'new'. All odorants were presented in random order. On the basis of signal detection theory a hit-rate and a false alarm-rate were derived and the memory measure A' was calculated thereafter (Pollack and Norman, 1964).

After deciding whether an odor was 'old' or 'new', the subject was required to identify the odor from a four-item word list presented as a little booklet. The highest possible score for the identification measure was 20.

Because the AD patients were significantly older than the PD patients and controls, all subsequent statistical comparisons among groups employed analysis of covariance (ANCOVA) using age as a covariate and disease group as the independent variable. For the olfactory threshold a one-way ANCOVA revealed significant differences between groups ($P < 0.003$). *Post hoc* analysis (Scheffe's, $P < 0.05$) showed that controls have a significantly lower threshold than AD patients and a marginally significantly different threshold ($P < 0.073$) to PD patients. For the measure of odor identification a one-way ANCOVA revealed significant differences between groups ($P < 0.001$). *Post hoc* analysis (Scheffe's, $P < 0.05$) showed that controls

Table 1 Demographic characteristics of subjects groups

	Mean age (SD)[a]	Range	Male/female	MMS (SD)	Range
PD (n = 21)	67.9 (10.2)	45–85	13/8	27.2 (2.3)	22–30
AD (n = 22)	77.4 (8.8)	63–94	2/20	16.9 (4.2)	12–23
Controls (n = 19)	67.8 (15.1)	48–94	4/15	28.1 (1.4)	25–30

[a]One-way analysis of variance revealed significant differences between groups ($P < 0.011$). *Post hoc* analysis (Scheffe's, $P < 0$ 05) showed that AD patients were significantly older than PD patients and controls.

performed significantly better. Both patient groups did not differ significantly.

Odor memory performance was analysed using a one-way ANCOVA. Analysis revealed significant differences between groups ($P < 0.030$). Post hoc analysis (Scheffe's, $P < 0.05$) showed that only AD patients performed at a significantly lower level than controls. Both patient groups were not significantly different. Moreover, a one-way ANCOVA with hit-rate as the dependent variable revealed significant group differences ($P < 0.001$). *Post hoc* analysis showed that AD patients had a significantly lower hit-rate than controls and PD patients. No other differences were significant. A one-way ANCOVA with false alarm-rate as the dependent variable revealed significant group differences ($P < 0.012$). *Post hoc* analysis showed that PD patients had a significantly higher false alarm-rate than controls and AD patients. No other differences were significant (see Table 2).

For the PD patients Pearson correlation coefficients computed between the olfactory test scores and the Hoehn and Yahr stage, mini-mental-status (MMS) score, chronological age, age at onset and disease duration were all non-significant (all $P > 0.20$; Bonferroni correction for inflated alpha level). In order to evaluate whether a relation existed between the stage of the disease as measured with the MMS and the degree of olfactory impairment, the AD patient group was split into two groups: MMS < 19 ($n = 11$) and MMS ≥ 19 ($n = 7$). Mann–Whitney *U*-tests were performed for olfactory threshold, odor identification, odor memory (A') test scores between the split patient groups. No statistically significant differences were apparent for olfactory threshold and odor identification (all $P > 0.35$). However, for A' a trend was seen ($U = 57.0$, $P < 0.084$).

Our results show that olfactory threshold (marginally significant) and odor identification are impaired in PD and AD. These results corroborate previous studies (Doty, 1991) indicating that the olfactory deficit is a robust finding in PD and AD. The finding that odor memory is compromised in AD is also in accordance with earlier reports (Knupfer and Spiegel, 1986; Moberg *et al.*, 1987). That we could only find a marginally significantly higher olfactory threshold for PD patients was surprising and may be due to the low reliability of butanol threshold testing. Doty *et al.* (1995) presented a test–retest correlation coefficient (Pearson *r*) of 0.49 for this testing procedere.

The new finding that odor memory is intact in non-demented PD patients, although these patients had poor odor identification abilities, is puzzling. However, a similar finding was obtained in a study assessing olfactory functions in HIV-infected patients (Lehrner *et al.*, 1995b). Our data suggest that intact memory performance is not dependent on the correct naming of odors. Support for the notion that the olfactory system is capable of odor memory processes without adequate verbal labeling comes also from an earlier study with healthy students (Lehrner, 1993b). The

Table 2 Mean olfactory performance among PD patients ($n = 21$) and AD patients ($n = 22$)

	Mean threshold[a,b]	Mean identification[c]	Mean odor memory (A')[d]	Mean hits	Mean false alarms
PD patients	4.9	7.0	0.69	0.75	0.49
	(2.5)	(2.7)	(0.16)	(0.15)	(0.25)
	0–10	1–10	0.22–0.92	0.5–0.9	0–1.0
AD patients	3.9	7.0	0.57	0.40	0.28
	(2.6)	(2.7)	(0.19)	(0.30)	(0.26)
	0–8	3–11	0.22–0.91	0.0–0.9	0–0.9
Controls	6.5	12.4	0.76	0.67	0.27
	(1.4)	(3.0)	(0.19)	(0.25)	(0.24)
	3–10	8–18	0.22–0.94	0–1.0	0–0.9
P-value	0.003	0.000	0.030		

[a]Figures in parentheses indicate SD. Figures given below indicate range.

[b]One-way analysis of covariance (ANCOVA) revealed significant differences between groups ($P < 0.003$). *Post hoc* analysis (Scheffe's, $P < 0.05$) showed that controls have a significantly lower threshold than AD patients and a marginally significantly different threshold ($P < 0.073$) than PD patients.

[c]One-way ANCOVA revealed significant differences between groups ($P < 0.000$). *Post hoc* analysis (Scheffe's, $P < 0.05$) showed that controls performed significantly better. The two patient groups did not differ significantly.

[d]One-way ANCOVA revealed significant differences between groups ($P < 0.030$). *Post hoc* analysis (Scheffe's, $P < 0.05$) showed that only AD patients performed significantly below controls. Both patient groups were not significantly different.

dissociation of odor memory performance and odor identification in PD patients may suggest that different underlying neural structures are responsible for specific olfactory subfunctions. An alternative explanation for our finding might be that the odor memory test did not have sufficient discriminative power. However, this seems unlikely since a very similar study found differences between children, young adults, middle-aged adults and elderly persons (Lehrner, 1993a). Moreover, recognition memory was previously shown to be robust and not to be affected in other modalities in a PD population. Thus recognition memory for visual stimuli was not impaired in non-demented PD patients (Flower *et al.*, 1984), further indicating preserved recognition memory functions.

The analysis of the false alarm-rate showed that PD patients had a somewhat different response criterion than controls, implying different motivational factors concerning the odor memory task. In contrast, in AD patients the main difference lies in a less pronounced hit-rate, indicating a more conservative response approach to the memory test. As was expected and has been previously found, olfactory functions and age, age at onset, disease duration and disease severity were not correlated (Doty, 1991), indicating that in PD disease progression and olfactory dysfunction are not associated.

The results concerning disease progression and olfactory functions in AD indicate that impaired olfactory threshold and odor identification ability are present early in disease progression, i.e. in mildly demented patients, and that odor memory performance is even more impaired in patients with advanced disease stage.

The underlying neuropathological processes of the olfactory system have been better established in AD than in PD. Earlier studies showed AD-related changes in olfactory receptor neurons (Talamo *et al.*, 1989; Tabaton *et al.*, 1991; Trojanowski *et al.*, 1991; Yamagishi *et al.*, 1994). The olfactory bulb, olfactory anterior nucleus and olfactory related limbic structures such as the piriform cortex, amygdala and hippocampus have all been shown to be prime targets of the hallmarks of AD—neurofibrillary tangles and senile plaques (Averback, 1983; Esiri and Wilcock, 1984; Pearson *et al.*, 1985; Ohm and Braak, 1987; Braak and Braak, 1991; Hyman *et al.*, 1991; Laak *et al.*, 1994). Furthermore, Alzheimer-related changes appear early in the disease process in the entorhinal cortex, which is considered to be a major part of the primary olfactory cortex (Price, 1990; Reyes *et al.*, 1993; Delacourte, 1994).

Thus, it has been suggested on both behavioral and neuropathological grounds that the olfactory system is an early target of AD-related processes and that olfactory functions are compromised early in the course of the disease (Pearson *et al.*, 1985). Our results confirm this view, because mildly and severely demented AD patients performed equally poorly in the olfactory threshold and odor identification tasks. Furthermore, in more advanced patients odor memory had deteriorated, indicating that the memory formation systems entorhinal cortex/hippocampus might be more strongly affected.

In PD there is a lack of information concerning the neuropathological processes of the olfactory system in the course of the disease. An early report demonstrated the presence of Lewy bodies in the olfactory bulb (Daniel and Hawkes, 1992). Pearce *et al.* (1995) subsequently confirmed this report and also found the anterior olfactory nucleus to be affected. Specific alterations in the amygdala were also shown (Braak *et al.*, 1994, 1995). Studies investigating the fate of the olfactory receptors neurons in PD disease are, however, rare and inconclusive (Crino *et al.*, 1995).

Another candidate for the etiology of the olfactory deficit is the nigro-striatal dopaminergic system, which is known to be strongly affected in PD. The olfactory disturbance is, however, unlikely to be associated with nigro-striatal dopaminergic degeneration since olfactory functions have been consistently shown to be independent of motor symptoms, medication, disease duration and disease severity (Doty, 1991). Additionally, a more direct approach, the measurement of nigro-striatal dopaminergic degeneration by means of SPECT with the tracer β-CIT, which detects the loss of dopamine uptake sites in the striatum in PD patients, was not correlated with olfactory functions either (Lehrner *et al.*, 1995a). Moreover, olfactory functions in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinsonism were found to be in the normal range (Doty *et al.*, 1992b). Reports that the administration of MPTP causes nigro-striatal degeneration in primates but spares mesocorticolimbic structures (Burns *et al.*, 1983) give further weight to the hypothesis that the nigro-striatal dopaminergic degeneration is not responsible for the olfactory deficit in PD.

The new finding that odor memory was not impaired in PD is puzzling and might be explained in terms of specific neuropathological alterations in the limbic system. Braak *et al.* (1994) found that Lewy bodies were unevenly distributed in the amygdala, and that the intact amygdala nuclei may contribute to olfactory memory processes.

ACKNOWLEDGEMENTS

We thank Professor K. Jellinger and Dr C. Baumgartner for their helpful criticism of the text. This paper was presented as a poster at the 4th International Congress of Movement Disorders held in Vienna, June 1996.

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Received on July 8, 1996; accepted on August 6, 1996