Parkinson disease in Elder: lessons from odor detection thresholds on olfacto-trigeminal interaction

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Keywords: Pathology (Elderly with Parkinson disease), odor detection thresholds, olfacto-trigeminal interaction, abnormalities, diagnosis.

Summary:

Objectives: Human nasal chemosensation is mediated by two separate, though interacting sensory pathways: the trigeminal and olfactory systems. Trigeminal sensitivity and olfacto-trigeminal interactions have not yet been well studied in idiopathic Parkinson's disease (IPD). The aim of this study was to assess odor detection thresholds in elderly IPD patients, and compare them to the odor detection thresholds of healthy controls. Finally, we investigated potential interactions between trigeminal and olfactory sensitivity.

Methods: 89 IPD patients aged over 65 and 89 matched healthy participants were enrolled in the study. Odor detection thresholds to 3 stimuli differentially activating olfactory and trigeminal afferents (Phenyl-ethyl alcohol, n-Butanol and Pyridine) were assessed, using an ascending staircase, binary forced-choice procedure.

Results and conclusion: Detection threshold scores were able to discriminate between elderly IPD and controls. Pyridine was less effective than the two other odorants, suggesting that trigeminal pathway is less impaired than the olfactory system. We found that the detection thresholds were significantly different between IPD patients with good autonomy, and patients with impaired autonomy.

Keywords: Pathology (Elderly with Parkinson disease), odor detection thresholds, olfacto-trigeminal interaction, abnormalities, diagnosis.

Introduction

The impairment of olfaction is now increasingly recognized as a neurodegenerative diseases feature [1] and a prominent early-appearing feature of idiopathic Parkinson's disease (IPD)[2]; and the American Academy of Neurology even recommends an olfactory evaluation of patients, as part of the basic clinical evaluation[3]. Although lots of studies have investigated olfaction in IPD patients, the vast majority of them have mainly focused on relatively young patients (<65 years), while elderly IPD (>65 years) have hardly been investigated.

It is well known that the vast majority of odorants activate both olfactory system (mediated by the first cranial nerve (CN I)) and trigeminal system (mediated by CN V). These two systems closely interact with each other, resulting in the global nasal chemosensory experience [4, 5]. While the decrease in olfactory sensitivity is well recognized in IPD regardless of age; in contrast, trigeminal sensitivity appears to be preserved in elderly with IPD patients [6]. Hence, it can be hypothesized that trigeminal sensitivity is less affected in IPD as compared to pure olfactory sensitivity.

The purposes of the present study were thus; (1) to assess nasal chemosensory perception deficits in elderly patients with IPD relative to matched healthy control participants, on the basis of odorants detection thresholds; (2) to investigate a possible interaction between olfactory and trigeminal systems, using odorants that are known to differentially activate the olfactory and trigeminal systems; and (3) to explore potential links between chemosensory detection thresholds.

Materials and Methods

The study is analytical, cross-sectional and aims to evaluate the olfactory detection thresholds in Parkinson's disease patients and matched healthy controls. It was conducted according to the Declaration of Helsinki on Biomedical Research Involving Human Subjects.

During enrollment and data collections from October 2011 to May 2014, participants and their relatives were given detailed information about all testing procedures and their consents were collected prior to participating in the study.

Participants

In total, 178 subjects were enrolled in the present study: 89 elderly patients with Parkinson disease (IPD) aged 65 and over [74.80 ± 6.76 years; range: 65 - 90 years] and healthy controls matched for gender [79.80 ± 8.82 years; range: 65 - 93 years].

All participants had no history of nasal/sinus and oral/throat diseases, neither head injury nor stroke within six months prior to the olfactory tests. Furthermore, they had no acute upper respiratory disease at the moment of testing. Participants in both groups did not have any history of active smoking or less than 20 packs/year of tobacco consumption during the past 10 years. Additionally, during the testing period, participants were free of untreated patent depression [evaluated by Mini-Geriatric Depression Scale [7]].

Neurocognitive [Folstein's Mini-Mental State Examination (MMSE) [8] and clock drawing [9]] tests were performed to exclude mild cognitive impairment or moderate and severe dementia [10].

Patient Group

The IPD patients group included 47 women and 42 men, who were diagnosed according to the United Kingdom Parkinson Disease Society Brain Bank (UKPDSBB) diagnostic criteria [11]. Elderly IPD patients are defined as older than 70 years [12, 13]. We defined three groups of

patients: 2 groups of patients, older than 70: (1) early onset elderly IPD consisting primarily of patients whose first clinical signs appeared before the age of 70 [12, 14], referred to "IPD_1's group" throughout the manuscript (45 out to 89 IPD); (2) late onset IPD patients (occurring after 70), referred to "IPD_2's group" throughout the manuscript (23 out to 89 IPD). Moreover, we defined as a third group (3) IPD patients aged between 65 and 70 years, referred to "IPD_0's group" (21 out to 89 IPD). "Unified Parkinson's Disease Rating Scale" (UPDRS) (part III) [15] and 'Hoehn and Yahr' (HY) scale [16] [somewhat modified into 5 stages: HY_1, HY_2, HY_3, HY_4, HY_5] evaluations were used to assess (i) severity progression of motor (symptom) impairment and relative level of disability; and (ii) global clinical autonomy of the IPD's patients respectively.

At the time of olfactory testing, most of the patients were being treated with L-Dopa (85 of 89 IPD) or some other antiparkinsonian drugs either alone or in a combination of two or more treatments [Dopamine receptor agonists or anticholinergic antiparkinson agents or selective monoamine oxidase B (MAO_B) inhibitors (45 out of 89 IPD), catechol-O-methyl transferase (COMT) inhibitors (39 out to 89 IPD) and cranial electrostimulation (7 out to 89 IPD)].

1.2. Control Group

None of the control subjects had a medical history of Parkinsonism, or any other major neurological disorder. Otherwise, participants in this group were in a good state of autonomy.

2. Olfactory Testing

2.1. Stimuli

Olfactory detection thresholds were determined for three odorants known to differentially activate the olfactory and trigeminal systems based on the previous data [17]. Phenyl-ethyl alcohol (PEA) was chosen to activate almost exclusively the olfactory system; n-Butanol was

118 considered to activate both olfactory and trigeminal systems [6]. Finally, Pyridine was used to
119 be specifically activating trigeminal afferents [5].

120

121 2.2. Procedure

122 Successive dilutions of odorants by a factor 2 were realized with distilled water as solvent.
123 This yielded a geometric series starting from solutions of pure n-Butanol until the 20th
124 dilution, pure PEA until the 23rd dilution or pure Pyridine up to the 26th dilution.

125 The odorant stimulus was presented in a white glass bottle (7.5 cm high, opening diameter: 1
126 cm) filled with 4 ml of liquid. The bottle was presented for 3 seconds, medially 1 cm under
127 both nostrils using a holder to avoid any olfactory or thermic interference with the
128 experimenter's hand. Odor thresholds were assessed using an ascending staircase, binary
129 (stimulus vs. blank) forced-choice procedure, with inter-trial intervals of 90 seconds. The two
130 bottles were presented to the subject in random order. After sniffing each stimulus, the
131 participant was asked to identify the one who smelled stronger. An incorrect choice led to
132 increase the concentration of the stimulus in the next trial. The dilution step at which the
133 odorant stimulus was first detected correctly three times in a row was recorded as the
134 detection threshold (Table 1).

135

136 3. Data Analysis

137 Statistical analyses were performed using Statview (SAS Institute Inc., Version 9.2).
138 The Shapiro-Wilks test was used to test each variable for normality. As some variables were
139 not normally distributed, therefore, nonparametric test procedures (with post-hoc tests when
140 necessary) were used to compare odor detection thresholds. We investigated for a possible
141 order effect of odor (PEA and pyridine) presentation's sequence. Multivariate analyses have

142 been conducted, to account for other parameters in our data (age, sex and order of
143 presentation of PEA's stimuli).

144 In IPD patients, Spearman correlation analyses between odor thresholds were performed.
145 In all cases, the alpha level was set at $p < 0.05$.
146 Sensitivity and specificity of each odorant to discriminate between IPD patients and healthy
147 controls were assessed using Receiver Operating Characteristic (ROC) curves [18]. The area
148 under the ROC curve (AUC) was calculated using SPSS software [19].
149 Youden's index (Youden Index= Sensitivity + Specificity - 1) was used to define the optimal
150 cut-off points.

151

Results

Statistical analyses

According to the Mann-Whitney-Wilcoxon test, mean olfactory detection thresholds (PEA, n-Butanol, Pyridine) were found to be lower in (i) IPD patients as compared to (ii) healthy matched controls (all p value < 0.001) [Table 2].

The multivariate analysis confirmed a significant difference in the mean detection threshold for PEA between IPD patients (*PEA thresholds scores* = 13.73 ± 7.69 [0; 23]) and controls (*PEA thresholds scores* = 21.84 ± 2.07 [9; 23]) (F= 88.711; p < 0.000), having considered the PEA and trigeminal-like stimuli (n-Butanol or Pyridine) order presentation effect as statistically significant. Indeed, we found a significant reduction of the detection thresholds scores for PEA if the *above* trigeminal-like stimuli were presented before PEA (*PEA thresholds scores* = 16.99 ± 7.30) compared to if PEA is presented before trigeminal-like stimuli (*PEA thresholds scores* = 18.86 ±6.40) (F= 4.919 ; p= 0.028).

The multivariate analysis indicated that the 'age' variable had no impact on the value of odor detection thresholds when compared between IPD patients and controls (p= 0.791; 0.822 and 0.207 for PEA, n-Butanol, and Pyridine, respectively).

Moreover, the IPD group (IPD_0, IPD_1, IPD_2) had no significant effect on the mean odor detection thresholds (p= 0.664, 0.271 and 0.486 for PEA, n-Butanol and Pyridine, respectively).

Interestingly, we found that odor detection threshold performances were significantly affected by the autonomy status of patients (evaluated on Hoehn and Yahr's scale). Indeed, patients with benign IPD (honeymoon phase corresponding to HY_1 and HY_2) had significantly better olfactory detection threshold performances as compared to patients with malignant IPD

(corresponding to HY_3, HY_4 and HY_5); [$p< 0.005$ for odor (PEA, n-Butanol and Pyridine) thresholds)] [Figure 1]. On contrast, no significant difference was observed when the 5 different Hoehn and Yahr's stages were considered separately; although the p-values were close to significance between stages 2 and 3 ($p= 0.065$, 0.085 and 0.088 for PEA, n-butanol and pyridine, respectively).

Finally, we found a significant difference for the n-butanol detection threshold between patients treated with COMT inhibitors drugs (e.g., Entacapone) associated or not with other drugs and patients without COMT inhibitors drugs (Table 3). This was not true considering thresholds to PEA and Pyridine. L-dopa, dopamine agonists and deep brain stimulation had no effect on odor detection thresholds.

Correlation analysis results

We found a significant correlation between the different odor detection thresholds performances [PEA– n-Butanol ($p<0.001$, $r=0.78$); PEA-Pyridine ($p<0.001$, $r=0.78$); and n-Butanol-Pyridine ($p<0.001$, $r=0.81$))] according to Spearman correlation.

Receiver operating characteristic (ROC) curves and Odors threshold's cut-off points

The ability of each odor to discriminate between IPD and controls was assessed using ROC curves. We found that detection threshold scores to n-Butanol and PEA had good discrimination performances, with sensibility and specificity of respectively 66% and 89% for n-Butanol (area under the curve (AUC) = 0.800), and 72% and 92% for PEA (AUC = 0.881). The pyridine's detection thresholds discrimination performance was lower (Sensitivity: 44%, Specificity: 96%, AUC = 0.693) (Figure 2). The threshold scores associated with the highest Youden index were 20 for PEA, 19 for n-Butanol and 22 for Pyridine (Figure 2).

Discussion

This study shows that similarly as for younger IPD patients (less than 65 years), elderly IPD patients show impaired olfactory detection when compared to healthy subjects. We observed significantly lower mean odor detection performances to the 3 odorants in IPD patients as compared to healthy elderly controls. Because the odorants used in the present study activate the olfactory and/or trigeminal systems, the results suggest that the overall nasal chemosensory sensitivity is more affected in elderly patients with IPD as compared to healthy controls.

It is well known that olfaction decreases with age [20]. Similarly, it has been shown that trigeminal sensitivity also decreases with age [21]. However, these two senses seem to be even more affected in IPD patients. Hence, it has been proposed that an olfactory test should be systematically used in the clinical workup of IPD patients [1, 22]. In the present study we found that olfactory thresholds testing using PEA, n-Butanol and Pyridine may be useful in the diagnosis of IPD in the elderly, with IPD patients exhibiting higher odor thresholds as compared to healthy controls. We found that the optimal cutoff value allowing the detection of IPD was 20 (out of 23) for PEA; 19 (out of 20) for n-Butanol and 22 (out of 26) for Pyridine.

The ROC curves revealed that pyridine*'s* detection threshold (AUC= 0.693) was less discriminant as compared to n-Butanol (AUC= 0.800) and to PEA (AUC= 0.881). Having an AUC of less than 0.7, the discrimination performance of pyridine detection threshold appeared to be poor and not sensitive enough to allow for an adequate discrimination between IPD elderly patients and healthy controls. A possible explanation for this finding is that trigeminal sensitivity could be less impaired in elderly with IPD than olfactory sensitivity as compared to healthy controls. This is in line with a previous study [6].

We found highly significant correlations between pairwise odor thresholds. These significant correlations between the PEA, n-butanol and pyridine detection thresholds could be supported by the existence of a close interaction between the trigeminal and olfactory systems. However, the underlying mechanisms are not yet fully understood [4].

We noticed that a suppression-like interaction mechanism seems to be present between trigeminal and olfactory systems because we found a significant decrease of PEA detection thresholds whenever n-Butanol or Pyridine (with pronounced trigeminal component) were presented to subjects during testing before PEA (having almost no trigeminal effect and mainly olfactory component) ($p = 0.028$). These results are in agreement with those of Schriever et al. [23], who also found a decreased olfactory response due to trigeminal activation. This effect appears to be mediated in the olfactory periphery by neuropeptides such as calcitonin gene-related peptide (CGRP) [23]. Importantly, this stimuli order effect was not significantly affecting the results, as revealed by a multivariate analysis.

Moreover, in the IPD patients, we found that patients with benign IPD (honeymoon phase), had significantly better detection thresholds to the three odorants, than patients with malignant IPD showing a loss of autonomy (more gait and balance difficulties, more depression, cognitive problems, swallowing difficulties and autonomic dysfunction). Stern et al. have also shown subtle olfactory test differences between benign IPD and malignant IPD patients using University of Pennsylvania Smell Identification Test (UPSIT) [24], which is an olfactory test based on identification of odor and not on detection thresholds. They found a significantly higher USIPT score in benign IPD patients compared to patients with malignant IPD. However, most of the previous publications found that the olfactory loss appears to be relatively stable over time and is unrelated to the magnitude of IPD motor symptoms (degree of tremor, rigidity, bradykinesia, or gait disturbance) [25]. But some of these surveys included

early-onset IPD patients, with more or less preserved autonomy or with average Hoehn and Yahr score (disease stage) less than 3 [25, 26]. Our findings indicate that even though the olfactory dysfunctions are set up at early PD stage [26, 27], the patients may have a sustained slightly decrease of odor (PEA, n-butanol and pyridine) detection thresholds scores with 'inflection Point' upon HY_2 allowing to discriminate between benign IPD and malignant IPD patients, even if the conventional Hoehn and Yahr's scale does not. Our findings are in agreement with those of Meusel et al, who showed, an overall decreasing olfactory function in 19 PD patients at 5-year intervals [26]. This is likely to be pathology's reflection on olfactory and trigeminal pathways.

The severity of the olfactory loss may therefore be used as an indicator of overall disease progression in elderly IPD patients. Nevertheless, it would be interesting to evaluate the progression of olfactory function in parallel of the progression of the disease in future studies. Olfactory dysfunction is a clinically significant problem, with a high burden on quality of life [1], and is likely to grow in prevalence due to demographic shifts and improvement of life expectancy (in general and in IPD patients). For these reasons, we think that olfactory evaluation should be integrated to the clinical follow-up of elderly IPD patients.

Finally, no gender–related differences were apparent for odor detection thresholds comparison (p-values > 0.2); although many studies have shown that women often outperformed men in most subtypes olfactory tests or examinations [24]. One possibility may be related to the advanced age of our population cohort (aged over 65 years) and the fact that olfactory sense sensitivity declines with senescence [28] or some neurodegenerative diseases such IPD. Further studies are warranted to answer this question.

Conclusion

This study highlights the importance of PEA, n-butanol and pyridine detection thresholds to distinguish between elderly Parkinson's patients and matched healthy controls. Interestingly, we found that odor detection thresholds tests are able to distinguish between the earlier IPD patients with good autonomy (honeymoon phase) and other IPD patients with impaired autonomy (becoming malignant IPD).

Our results suggest that both olfactory and trigeminal systems are impaired in elderly IPD patients, although 'pure' trigeminal pathways seem to be less impaired than the olfactory system.

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Conflict of interest statement

The authors have no conflict of interest with regard to this research.

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388 Table 1 : Example of ascending forced choice test's notation

	Dilution	Test 1	Test 2	Test 3
	4	O	X	X
	3	X	O	X
→→→	2	O	O	O
	1	O	O	O

389 †

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391 Table 2:

	Number of subjects (IPD/Controls)	Median (and 25%/75% quartiles) detection threshold values	Mean odor detection threshold ± SD (IPD/Controls)	p-value
PEA	89/89	21 (15/23)	13.73±7.69 / 21.84±2.07	<0.0001
n-Butanol	89/89	19 (14/20)	12.63±7.25 / 19.34±1.71	<0.0001
Pyridine	54/76	25 (14/20)	17.22±9.4 / 24.88±1.67	0.0004

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395 Table 3

	Number of subjects (with/without COMT inhibitor drugs)	Median odor detection threshold values	Odor threshold quartiles values (25%/75%)	p-value
PEA	39/47	16.5	8/20	0.081
n-Butanol	39/47	16	6/20	0.0255
Pyridine	24/27	23	9/26	0.513

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Tables and iconographies' Legends

Iconographies' Legends

Figure 1: Comparison of odor (PEA, n-Butanol, Pyridine) detection thresholds between benign IPD's patients (during "honeymoon"'s period) and malignant IPD patients.

****Footnotes:** - p (Wilcoxon test); value of significance < 0.05

Acronyms: PEA: Phenyl-ethyl alcohol ; BUT: n-Butanol ; PYR: Pyridine .

Figure 2: Receiver Operating Characteristic (ROC) curves.

ROC curves were computed to estimate the discrimination performance (ability to discriminate between IPD patients and controls) of Phenyl-ethyl alcohol (PEA), n-Butanol (BUT) and Pyridine (PYR). The black dot indicates the optimal cut-off value, as defined by the Youden index.

Footnotes: - Optimal cut-off values were (0.08; 0.72), (0.11; 0.66) and (0.04; 0.44) for PEA, n-Butanol and Pyridine respectively. The threshold scores associated with the highest Youden index were 20 for PEA, 19 for n-Butanol and 22 for Pyridine.

Acronyms: *Odorants:* PEA*: Phenyl-ethyl alcohol;* BUT*: n-Butanol;* PYR*: Pyridine.*

AUC: area under the ROC curve.

Legends for Tables

Table 1: Example of ascending forced choice test's notation: the recorded detection threshold was first detected correctly three times in a row.

† Footnotes: O: adequate response ; X: wrong answer

Table 2: Comparisons of Phenyl-ethyl alcohol (PEA), n-butanol and pyridine detection thresholds between idiopathic Parkinson's disease (IPD)'s patients and healthy controls.

‡ **Footnotes**: - SD: standard deviation;

- p (Wilcoxon test); value of significance < 0.05

436 Table 3: Comparisons of Phenyl-ethyl alcohol (PEA), n-butanol and pyridine detection
437 thresholds between idiopathic Parkinson's disease (IPD)'s patients treated with COMT
438 inhibitor drugs (*eg: Entacapone*) and those without COMT inhibitor drugs.
439