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ORIGINAL ARTICLE

The flavor test is a sensitive tool in identifying the flavor sensorineural dysfunction in Parkinson's disease

Anna De Rosa[1] · Immacolata Cristina Nettore[2] · Elena Cantone[1] · Luigi Maione[2] · Silvio Desiderio[2] · Silvio Peluso[1] · Francesco Saccà[1] · Fiore Manganelli[1] · Dario Bruzzese[3] · Annamaria Colao[2] · Giuseppe De Michele[1] · Paolo Emidio Macchia[2]

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Abstract

Gustatory perception has been poorly explored in Parkinson's disease (PD). Aim of this study was to assess the flavor ability in PD patients, using the "flavor test" (FT), a new standardized and validated tool to examine the flavor perception. Thirty-eight patients (17 F and 21 M) and 36 control subjects (15 F and 21 M) comparable for age and gender were enrolled. All the subjects underwent the flavor test (FT), the Sniffin' Sticks test (SST), and the gustometry test (GT), based on the basic four tastants ("salty," "sour," "sweet," and "bitter"). PD patients presented a FT score significantly lower than controls ($p < 0.001$). Olfaction (SST) was impaired in PD in comparison with controls ($p < 0.001$), and the patients also showed a mild reduction of basic tastant identification at the GT ($p = 0.08$), with a trend toward statistical significance. There was no correlation between SST, FT, and GT. GT performance was negatively correlated with disease severity ($p = 0.004$) and stage ($p = 0.024$). The SST and FT resulted abnormal in PD in comparison with controls, independently of disease duration and severity. The ability to identify the basic four tastants was correlated with the disease severity and stage in PD patients suggesting that it might occur later in the course of the disease. FT might be a sensitive tool in identifying the sensorineural perception dysfunction in PD, even in the early stage and regardless of the disease severity.

Keywords Parkinson's disease · Taste · Olfaction · Flavor test

Introduction

Although the cardinal motor features (i.e., tremor, rigidity, and akinesia) are considered the paradigmatic clinical characteristics in Parkinson's disease (PD), a broad spectrum of non-motor symptoms, including cognitive, sleep and behavior disorders, and sensory and autonomic dysfunction, is frequently observed [1]. Olfaction impairment has been recently included as supportive criterion for the diagnosis of PD [2] and represents the most common sensory disturbance in this degenerative disorder [1]. Hyposmia is documented in the early phase of the disease, affects more than 90% of the patients and has been described both in familial and sporadic PD [3]. It is considered a prodromal marker of PD and is associated with an increased risk to develop the disease in the general population [4]. According to Braak's staging, olfaction dysfunction is related to the early presence of Lewy bodies (LB) pathology and neuronal loss in the olfactory bulb [5], which subsequently spread to other limbic and cortical areas of the olfactory system [6].

The olfaction dysfunction is considered a remarkable and well-characterized non-motor symptom in PD, whereas the gustatory perception based on the evaluation of the basic sense of taste (sweet, salt, sour, bitter, and umami) has been poorly explored so far, and the results of the few studies performed on the topic are mixed [7]. One possible reason may be the heterogeneity of the assessment methods and the lack of validated tests.

Anna De Rosa, Immacolata Cristina Nettore and Elena Cantone contributed equally to this work.

✉ Anna De Rosa
anna_derosa@libero.it

1 Department of Neurosciences and Reproductive and Odontostomatological Sciences, Federico II University, Via Pansini 5, 80131 Naples, Italy

2 Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

3 Department of Preventive Medical Sciences, Federico II University, Naples, Italy

Flavor perception is a complex sensory experience determined by olfaction, mostly via the retro-nasal airflow undertaken by volatile substances chewed or dissolved in the oral cavity. This information is implemented by different stimuli present in the mouth, including texture and viscosity of food [8]. Flavor impairment ultimately enables food recognition, oral intake identification, and enjoyment of food [9].

The aim of this study was to assess the flavor ability using a newly developed test [9] in PD patients and control subjects (Ctrl) in comparison with the results of Sniffin' Sticks test (SST) [10, 11] and gustometry [12].

Methods

Subjects

The study setting was a university-based movement disorders clinic. The local Ethics Committee approval for the study was obtained (Comitato Etico Università Federico II, reference number 121/16) and all participants signed an informed consent, according to the declaration of Helsinki.

Thirty-eight patients (17 F and 21 M) affected by PD and 36 Ctrl (15 F and 21 M) selected among spouses and not consanguineous caregivers, comparable for age, sex, and education were enrolled. PD diagnosis was made according to the Movement Disorders Society criteria for PD [2]. All the patients were negative at the screening for the G2019S and R1441C/G/H mutations of *LRRK2* gene. The subjects with onset age before 40 years were screened and resulted negative for *PRKN* and *PNK1* genes mutations. All the patients and the Ctrl underwent the Mini-Mental State Examination (MMSE), and the subjects with a score < 24/30 were excluded. A questionnaire explored the presence of smoking, alcohol abuse, head injury, and concomitant diseases such as endocrine, metabolic and cerebrovascular diseases, seasonal allergies, rhinosinusitis, and drug intake. The questionnaire included a section for the patients only concerning the onset and typology of motor symptoms (i.e., tremor, akinesia, gait disorder), the most affected side, the current pharmacological therapy for PD, the presence of motor fluctuations, dyskinesias, sleep, neuropsychiatric and autonomic disorders. All patients were assessed by the motor section of the Unified PD Rating Scale (UPDRS-III) in "on" state, whereas the disease stage was evaluated by the Hoehn and Yahr (HY) scale. PD cohort was tested on dopaminergic medication.

We did not include individuals receiving any drugs known to interfere with the ability to taste or smell such as antithyroid drugs, antibiotics, griseofulvin, lithium, penicillamine, procarbazine, rifampin, anxiolytics, antipsychotics, antiepileptic drugs, antidepressants, amiodarone, digoxin, and chemotherapeutic drugs. Subjects with history of head trauma, previous maxilla-facial surgery, and chronic or acute rhinonasal infection detected at ear, nose, and throat evaluation were excluded. It was forbidden to eat, smoke, or chew gums before the assessment.

Characteristics of the enrolled subjects are shown in Table 1.

Evaluation of flavor and taste

Prior to the evaluation of chemosensory functions, all the subjects were invited to self-define their ability in sensorineural perception on an arbitrary scale (0 = minimum; 10 = maximum) to define their ability to identify food (flavor), to recognize the basic taste (sweet, bitter, salty, sour), and to assess the ability to smell (odor).

The flavor test was previously developed, validated, and patented (patent no. 0001426253, category A61B500 of the Italian Ministry for the Economic Development) [9]. Briefly, it consists of a series of 20 aromatic extracts, corresponding to flavors present in the usual Italian diet. Each extract, kindly provided by the manufacturer GIOTTI (Enrico Giotti spa, Scandicci, Firenze, Italy), has been previously tested and marketed for alimentary use in accordance with Italian and EU current regulations (European Food Safety Authority Regulation EC n. 178/2002; EC n. 854/2004; Italian G.U. n. 139/2004). Each tastant, originally stored in a 30-mL amber bottle, was diluted in distilled water according to the manufacturer's instructions, stored at 4 °C in single-use aliquots after preparation, and kept at room temperature for 20 min before administration. An aliquot of approximately 0.5 mL of each tastant was administered in the oral cavity using a 3-mL Transfer Pipet (Falcon, A Corning Brand) and left for approximately 5 s; the mouth was then rinsed twice with distilled water before the administration of the following tastant. At each administration, participants were invited to identify the aromatic by making a choice from five proposed items. A total of 21 aromatics (including one blank) were administered sequentially. The flavor score (FS) was calculated as the sum of correctly identified aromatics and ranged from 0 to 21. According to the distribution of FS in normal population,

Table 1 Clinical characteristics of the studied subjects

	PD ($n = 38$)	Ctrl ($n = 36$)	p value
Gender	17 F/21 M	15 F/21 M	1.000
Age median (range)	63.5 (32–71)	63.5 (42–79)	0.922
MMSE median (range)	28 (24–30)	29 (24–30)	0.230
UPDRS III median (range)	25 (5–48)	–	–
HY median (range)	2 (1–3)	–	–

PD, Parkinson's disease patients; *Ctrl*, control subjects; *MMSE*, Mini-Mental State Examination; *UPDRS-III*, Unified Parkinson's Disease Rating Scale-III; *HY*, Hoehn and Yahr scale individuals with FS ≤ 3rd percentile were considered have complete sensorineural disability, and those with FS ≤ 10th percentile having decreased sensorineural ability (Nettore et al. Submitted).

The gustometry test (GT) was based on the basic four tastant assessment: (1) 10 g/L (29 mM) sucrose, for "sweet;" (2) 324 mg/L (1 mM) quinine hydrochloride, for "bitter"; (3) 1.0 g/L (17 mM) sodium chloride, for "salty;" (4) 192 mg/L (1 mM) citric acid, for "sour" [12]. These substances were dissolved in distilled water and a drop of approximately 20 μL of each solution was applied on the upper surface of the tongue. Before application of each taste solution, the mouth was rinsed twice with distilled water. After presentation of the stimulus, each subject was invited to pick one of the five descriptors (sweet, sour, salty, bitter, water). Each solution was applied four times in non-repetitive order. The taste score was calculated as the sum of correctly identified tastants and ranged from 0 to16. Hypogeusia was defined as a gustative score (GS) < 9, corresponding to the 10th percentile in the studied population [12].

Evaluation of olfaction

To assess olfactory performance, all subjects underwent the SST (Burghart Medical Technology), in which 16 odorants are presented in felt-tip pen-like sticks [10]. Olfactory testing was performed in a quiet room with adequate ventilation. The SST consists of three olfactory subtests: odor threshold (T), odor discrimination (D), and odor identification (I), as previously described [10]. The TDI score is determined by the results of the three subtests. According to previously established normative data, the TDI score was considered abnormal if it was lower than the 10th percentile for the corresponding age range [10].

Statistical analysis

Differences in non-parametric data between PD patients and control were analyzed using the Mann-Whitney *U* test. Qualitative data were compared by the Fisher's exact test. The relationship between variables was examined using the Spearman's correlation coefficient. A *p* value < 0.05 was considered statistically significant. The Statistical Package for the Social Sciences software for Windows (version 20.00, SPSS, Chicago, IL, USA) was used for the statistical analyses.

Results

At time of the screening in the PD group the median age at onset was 54.5 years (range, 32–71), the median disease duration was 7.5 years (range, 1–36), the median HY score 2 (range, 1–3) and the median UPDRS-III score 25 (5–48) (Table 1).

Flavor, taste, and olfactory functions

FS values are shown in Fig. 1a. FS was significantly lower ($p < 0.001$) in PD subjects (median = 7.0) when compared with Ctrl (median = 13.0). According to the distribution of FS in normal population, about 80% of patients had some degrees of alterations in flavor perception. Among the controls, only 20% present a reduction in sensorineural perception ($p < 0.001$).

A list of the tested aromatic substances is shown in the Table 2. When compared with Ctrl, PD patients have a significant reduction in the ability to recognize the following flavors: tea, licorice, lemon, coffee, and onion. FS was not correlated with TDI score (rho, 0.209; $p = 0.222$) or with GT (rho, 0.104; $p = 0.536$).

The GT results were not statistically different between the two groups, even if the score was lower in PD with a trend toward the statistical significance ($p = 0.08$) (Fig. 1 b). In particular, PD patients were less able to identify the basic taste "bitter" ($p < 0.01$).

Finally, TDI score resulted significantly lower ($p < 0.001$) in PD group (median = 14.0) than in control (median = 25.0) (Fig. 1c). Indeed, in comparison with the Ctrl, olfaction resulted abnormal in 84% of the PD and in 14% of Ctrl. Compared with the Ctrl, PD patients showed a lower rate of correct answers for peppermint, considered a compound with putative trigeminal stimulation; for coffee, which is an aromatic with pure odorant properties; and for banana, orange, cinnamon, lemon, apple, pineapple, rose, and fish (Table 3).

TDI score was significantly lower in male than in female PD patients ($p = 0.030$), whereas FT ($p = 0.213$) and GT ($p = 0.848$) scores were not influenced by the gender.

Answers of self-assessment questionnaires are shown in Fig. 1d–f. In contrast to the results of the objective evaluation of chemosensory functions, PD patients evaluated their own capacity to discriminate flavor (Fig. 1d) and taste (Fig. 1 e) similarly to control, whereas they were conscious to have a reduction in odor perception ($p < 0.001$) (Fig. 1f).

PD patients presented no significant differences in flavor, taste, and olfactory perception in relation to the following parameters: age at exam, age at onset, disease duration, MMSE, subtype (tremor-dominant or akinetic-rigid), most affected side, l-dopa dose, dyskinesias, self-reported sleep and autonomic disorders.

Only GT score resulted negatively correlated with the UPDRS-III score (rho − 0.458; $p = 0.004$) and the HY scale score (rho − 0.366; $p = 0.024$).

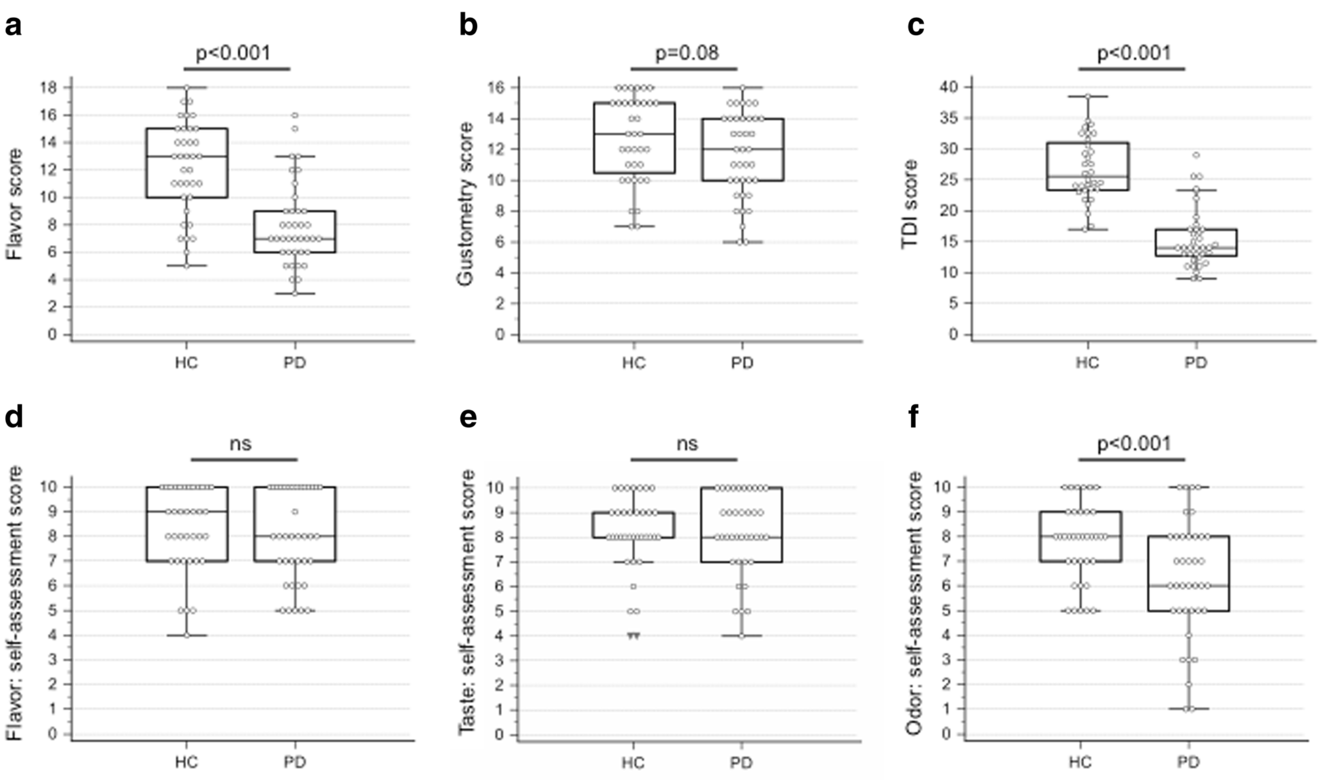

Fig. 1 **a** Flavor test results in Parkinson's Disease (PD) patients and healthy controls (HC). **b** Gustometry test results in PD patients and HC. **c** TDI score in PD patients and HC. **d**–**f** Answers of self-assessment questionnaires about the own ability to discriminate flavors, tastes, and odors. The central boxes represent the values from the lower to upper quartile (25° to 75° percentile). The middle lines represent the median. The vertical lines extend from the minimum to the maximum value, excluding outside and far out values which are displayed as separate points. Ns, not significant

Discussion

Taste is commonly confused with flavor, which represents the combined sensory experience of olfaction and gustation. Gustatory signals originate in the oral cavity and are triggered by water-soluble compounds that contact the apical tips of the epithelial cells of taste buds. By contrast, olfactory signals are generated by neurons in a specialized patch of nasal epithelium and are triggered by volatile compounds. Although the peripheral sensory organs for taste and smell are quite distinct, their signals are integrated in the orbitofrontal cortex (OFC) and other cortical areas to generate flavors and mediate food recognition [13]. The OFC displays multimodal responses to both gustatory and olfactory stimuli, allowing their integration in the flavor of food [14].

On our knowledge, flavor perception has not been previously investigated in PD and a few data about this topic are available so far. Different evaluation tools to assess the taste have been used in the previous studies with conflicting results.

A significant impairment of the taste threshold assessed by electrogustometry (EGM) was observed [15]. The finding was related neither to disease duration and stage nor to olfaction dysfunction, measured by the University of Pennsylvania Smell Identification Test (UPSIT). Similar results were reported in another study in which EGM threshold was significantly impaired in PD group, without a clear correlation between taste and olfaction impairment [16]. In the same direction were the results by Cecchini et al. [17]. The authors, using the taste strip test, that assesses the perception of the four taste solutions (sweet, sour, salty, bitter), found a lower score in PD patients, in particular for the "salty" taste. The correlation between Taste Strip Test score and SST score and disease duration resulted at the limit of statistical significance.

In this work, flavor perception has been studied by a standardized and validated test [9] to assess retronasal olfactory function in 38 patients affected by PD in comparison with 36 controls. Gustometry has also been performed.

We found a dramatic decrease of flavor perception in PD (Fig. 1 A). The patients showed a reduced identification for tea, licorice, lemon, onion, and particularly poor for coffee.

As recently reported [18], in our study gustometry did not show a significant taste reduction in PD compared with controls. No correlations with gender, disease duration, and l-dopa dose were found. However, GT score negatively correlates with the severity and the stage of disease (UPDRS-III score, HY scale score). As previously hypothesized [19], this finding may suggest that taste impairment might appear late during the course of the disease and might be a marker of

Table 2 Percentage of correct answers performed at the flavor test by PD patients and control subjects. *p* value has been calculated by Fisher's exact test. Significant values are in bold

Flavor	PD (%)	Ctrl (%)	*p* value
Almond	63	83	0.068
Smoke	53	67	0.244
Vanilla	34	50	0.238
Mushroom	37	53	0.242
Chocolate	13	22	0.368
Mint	50	72	0.060
Peach	55	72	0.153
Tea	47	78	**0.008**
Water	53	72	0.979
Licorice	37	95	**< 0.001**
Lemon	18	47	**0.008**
Hazelnut	31	55	0.059
Banana	60	78	0.135
Coffee	24	67	**< 0.001**
Onion	37	80	**< 0.001**
Cheese	5	14	0.255
Roast beef	66	75	0.451
Garlic	21	28	0.592
Honey	13	14	1.000
Mustard	34	39	0.809
Fish	42	64	0.068

Table 3 Percentage of correct answers performed at Sniffin' Sticks test by PD patients and control subjects. *p* value has been calculated by Fisher's exact test. Significant values are in bold

Odors	PD (%)	Ctrl (%)	*p* value
Orange	47	80	**< 0.001**
Leather	34	53	0.087
Cinnamon	42	69	**0.006**
Peppermint	47	72	**0.010**
Banana	50	80	**0.001**
Lemon	24	47	**0.024**
Liquorice	24	19	0.783
Trementin	45	42	1.000
Garlic	55	72	0.064
Coffee	16	58	**< 0.001**
Apple	5	28	**0.009**
Cloves	60	67	0.431
Pineapple	34	61	**0.008**
Rose	45	67	**0.026**
Aniseed	24	25	0.791
Fish	53	75	**0.017**

motor progression. This hypothesis is in contrast with the results of a previous small prospective study reporting a slight but not significant reduction in both gustatory and olfactory function in PD patients between the first and the second assessment over 5 years [19].

Moreover, we observed a lower recognition for the "bitter" among the four basic tastes, in contrast with previous data [17]. Interestingly, our finding is supported by the observation that the cortical taste receptors mainly involved in the reception of bitterness are downregulated in PD [20].

Olfactory dysfunction is frequently observed in PD, reported in preclinical stage of disease, regardless of dopaminergic treatment, and often associated with REM behavior disorder [6]. Moreover, idiopathic olfaction impairment is considered a factor risk for PD development and for higher progression of mild cognitive impairment and dementia [6].

The results of our study are in agreement with previous reports that attempted to characterize the olfactory function in PD [21–24]. As expected, the olfaction was abnormal in PD in comparison with controls and more impaired in men than in women [25]. We confirmed that the degree of smell loss was unrelated to the tremor-dominant or akinetic-rigid subtype of disease [26]. As in a previous study [24], PD patients showed a higher inability to identify correctly specific odors such as coffee.

The lack of correlation between the SST and FT results with the motor signs suggests that these perception defects are not related to the progression of the neurodegenerative process and could be early disease manifestations.

As the flavor is influenced by the olfactory perception, most of our results could be due to the olfactory dysfunction. However, although taste, smell, and other food-related stimuli are all represented and integrated in the OFC, we did not find any significant correlation between FT and SST scores.

In comparison to taste, the decline of the flavor perception in PD patients was noteworthy, suggesting that the FT, similarly to SST, might be a sensitive tool to identify the neurosensory dysfunction in PD, even at the early stage and regardless the severity of the disease. After all, the nucleus of the solitary tract shows the occurrence of LB and Lewy neuritis pathology at the beginning of the neurodegenerative process in PD [27]. The central dysfunction of flavor perception may be due to a damage early originating from the nucleus of the solitary tract in the brainstem and subsequently spreading to thalamus and cortical areas [28].

In conclusion, for the first time, we demonstrated that flavor perception is significantly impaired in PD. The small sample size is a limitation of the study; however, our data suggest that also flavor dysfunction might be an early non-motor marker in PD similarly to olfaction, sleep and mood abnormalities. It will now be interesting to evaluate the flavor perception over the time to compare it with the disease progression in a prospective study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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