New test of odor pleasantness in Parkinson's disease

Kristyna Pospichalova, MSN[a,b]
Jan Vodicka, MD[b,c]
Ales Kopal, MD[d]

[a] Clinic of Internal Medicine, Department of Cardiology, Hospital of Pardubice, Pardubice, Czech Republic
[b] Faculty of Health Studies, University of Pardubice, Pardubice, Czech Republic
[c] Department of Otorhinolaryngology and Head and Neck Surgery, Hospital of Pardubice, Pardubice, Czech Republic
[d] Department of Neurology, Hospital of Pardubice, Pardubice, Czech Republic

Correspondence to: Kristyna Pospichalova
E-mail: pospichalova.k@gmail.com

Summary

The New Test of Odor Pleasantness (NTOP) evaluates the hedonicity of olfactory stimulants. The aim of this study was to compare results of the NTOP, the Sniffin' Sticks test, and the Odorized Marker Test (OMT) in patients with Parkinson's disease (PD).
The study sample comprised 30 PD patients (mean age 71±7.36 years) and the control group made up of 31 non-PD subjects (mean age 68±12.39 years). Sociodemographic data, medical history and tests of cognitive function were investigated. Olfaction was evaluated using the NTOP, Sniffin' Sticks test and OMT.
The PD patients, compared with the control group, recorded significantly lower scores on all three tests: NTOP (p=0.00), Sniffin' Sticks (p=0.02), OMT (p=0.00).
The NTOP was the test preferred by 55% of the subjects. This preference was more marked in the PD group.
This study shows that the NTOP is a valuable method within the complex array of olfactory screening tools used in PD.

KEY WORDS: hedonicity, olfaction, Parkinson's disease, pleasantness

Introduction

Parkinson's disease (PD) is a systemic disease characterized by various motor (bradykinesia, resting tremor, slowness of initial movement, rigidity, postural instability) and non-motor symptoms. The latter consist of autonomic failure, cognitive impairment, psychiatric symptoms and sensory deficits (visual, olfactory and somatosensory system deficits) (Jörg and Gerhard, 1987; Bodis-Wollner, 1990; Doty et al., 1991; Ferrer, 2011). The motor symptoms of PD are due to the loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to reduced dopaminergic input to the striatum and is accompanied by adaptive responses in the internal and external globus pallidus, subthalamus, substantia nigra pars reticularis and thalamus. This degeneration, associated with the deposition of α-synuclein in the olfactory bulb, anterior olfactory nucleus and limbic rhinencephalon, leads to hyposmia in the early stages of PD (Ferrer, 2011). The basis of olfactory dysfunction in PD is multifactorial. Interestingly, most olfactory dysfunction is due to pathology not only in the olfactory bulb, but also in brain regions associated with cholinergic, serotonergic and noradrenergic function (Doty, 2012). It is well established in the literature that PD is associated with olfactory deficits; dysfunctions have been described in odor detection (Ansari and Johnson, 1975; Quinn et al., 1987; Murofushi et al., 1991; Hudry et al., 2003; Bohnen et al., 2010), discrimination (Ward et al., 1983; Hudry et al., 2003; Bohnen et al., 2010) and identification (Doty et al., 1988; Hudry et al., 2003; Bohnen et al., 2010), and also in odor recognition memory (Hudry et al., 2003; Bohnen et al., 2010). Symptoms of olfactory impairment may precede motor symptoms by years (Haehner et al., 2007; Bohnen et al., 2008; Doty, 2012).
The identification of odorants is a process that involves odor recognition and comparison with previous experience, which is under the control of the hippocampus.
The hippocampus is equally important in the discrimination of odors (Bohnen et al., 2010). Discrimination is also subject to the influence of the amygdala, the structure involved in emotional processing (Bohnen et al., 2008). Selective hyposmia in PD is more robustly correlated with hippocampal dopaminergic activity

than with activity in other areas (amygdala, ventral striatum) (Bohnen et al., 2008). Westermann et al. (2008) found reduced neuronal activity in the amygdala and hippocampus in a study using a functional imaging technique to investigate the cerebral olfactory system in patients with PD.
Hudry et al. (2003) were the first to consider aspects of odor processing other than deficits in odor identification, which had already been reported in PD. They simultaneously investigated intensity, familiarity, pleasantness and edibility judgments, and their study showed impairment of these four olfactory tasks in PD patients (Hudry et al., 2003).
A study by Sienkiewitcz et al. (2005) indicated that dopaminergic transmission in the basal ganglia may be involved in the processing of pleasant and unpleasant stimuli. Olfactory assessment can be difficult in some situations, e.g. in patients with dementia and/or from different cultural backgrounds. Major parts of olfactory tests (e.g. University of Pennsylvania smell identification test, the odor identification part of the Sniffin' Sticks test) are based on odor identification and require certain levels of cognitive abilities. The patient's evaluation of odor pleasantness may be particularly valuable in assessing olfaction in PD.
On the basis of these considerations, we decided to implement our New Test of Odor Pleasantness (NTOP) in patients with PD. The original Test of Odor Pleasantness (TOP) with 14 odorants, on which the NTOP is based, has similar characteristics to other olfactory tests (Vodicka et al., 2010). We set out to determine whether the NTOP, compared with other olfactory tests, would give us valid results concerning olfactory function. Our aim was thus to establish whether this tool, for rating the pleasantness of odors, would be suitable for use in patients with PD.

Materials and methods

Preliminary study

In the preliminary study we tested 83 healthy subjects (58 females) aged between 61 and 95 years (mean age 74.4 years) using the NTOP. The aim was to identify the hedonic evaluation category most frequently chosen for each stimulant included in the NTOP for the age band of 61 years and older. The odorants used in the test are listed in table I. The examination procedure is described in detail in the following section.

Main study

We included 30 subjects (15 females and 15 males) with PD. All fulfilled the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria for PD. Their mean age was 71.1 years (range 55–81 years). The control group consisted of 31 (20 females and 11 males) non-PD subjects with a mean age of 68 years (range 39–89 years). The patients were recruited in cooperation with the Department of Neurology of the Hospital of Pardubice and examinations were conducted at the Department of Otorhinolaryngology and Head and Neck Surgery of the same hospital.
The study purpose and procedures were explained to all the participants and each participant read and signed a consent form. The study was performed in accordance with the Declaration of Helsinki, and was approved by the ethics committee of Pardubice Hospital, Czech Republic.

General design

The study was designed to compare the scores recorded by the entire study population on three olfactory tests, and to examine differences between these scores and correlations between the olfactory tests; it was also designed to compare the results recorded in the PD group with those of the control group. A further aim was to compare, between the patients and the controls, the correlation between the subjects' present mood and the results of the NTOP.

Procedure

The examination session usually took between 30 and 40 minutes, and was conducted in a quiet, ventilated and temperature-controlled room. The session was divided into three parts.
During the first part, the participants were questioned about their personal medical history, negative health behaviors (i.e. smoking, drinking alcohol), working environment, and any chronic medication use and diseases or olfactory disorders they had experienced. They were also asked to provide a subjective evaluation, using a visual analog scale (VAS), of their olfaction, sense of taste and nasal patency. The final question was about their mood, which was also rated using a VAS.
The olfactory tests were used in the second part of the examination session. For the purposes of this study we used the NTOP, the Sniffin' Sticks test (identification part, 16 items), and the OMT to evaluate the respective olfactory functions.
The NTOP comprises 32 odorants (Table I) contained in a pen-like device. The subjects were asked to classify each odor as: pleasant, neutral, unpleasant or fetid. This scale was asymmetric (Vodicka et al., 2010). Subjects were assigned one point, if their answer matched those given by the healthy subjects in the preliminary study (Table I). The total score was calculated by summing the assigned points.
The Sniffin' Sticks test (odor identification part) also involves the use of a pen-like odor dispensing device, which contains 16 odors. In this case, too, the participants were required to categorize each odor according to a list of four options, and they scored one point for each correct answer. The technique was described by Hummel et al. (1997).
The OMT is a two-part screening test in which six pens are used (containing the smell of licorice, lemon, cinnamon, peach, apple and strawberry). In the first part of the test, subjects are asked to spontaneously

identify the odorants. In the second part they have to categorize each odorant according to four options. The subjects scored 1 point for each odor correctly identified. If they were unable to identify the odorant, or if they incorrectly identified an odorant, they scored 0 points. In the second part, they scored 1 point for the correct categorization of an odorant. The technique and evaluation were described by Vodicka et al. (2007).

The third part of the examination session was devoted to evaluation of the subject's cognitive state using the Mini-Mental State Examination test (MMSE) (Folstein et al., 1975), and the Clock Drawing Test (CDT) (Shulman et al., 1993).

Finally, every participant was asked to state which of the tests they had found easiest and had preferred (subjective assessment).

Statistics

All the data were analyzed using NCSS9 statistical analysis and graphics software (NCSS, Kaysville, Utah, USA), STATISTICA 12.0 (StatSoft, Tulsa, Oklahoma, USA), and MS Office Excel 2007 (Microsoft Corporation, Redmond, Washington, USA). The qualitative parameters were analyzed using the

Table I – Substances and category of hedonic evaluation categories.

Item	Substance	Concentration	Dilution	Producer	Category
1	rum aroma	100		AROO s.r.o.	Pleasant
2	pineapple aroma	100		AROO s.r.o.	Pleasant
3	fish composition	100		Aroma a.s.	Stink
4	babirusa celebes	100		Aroma a.s.	Pleasant
5	propyl acid	100	distilled water 1:25		Stink
6	almond aroma	100		Dr. Oetker	Pleasant
7	butenol-1	100	distilled water 1:25		Stink
8	formic acid	98	distilled water 1:25		Neutral
9	lemon aroma	100		AROO s.r.o.	Pleasant
10	cherry aroma	100		AROO s.r.o.	Pleasant
11	valeric acid	100	distilled water 1:100	BASF	Stink
12	oleic acid	100		Chemapol	Stink
13	coconut aroma	100		Kovandovi	Pleasant
14	distilled water	100			Neutral
15	vanilla aroma	100		AROO s.r.o.	Pleasant
16	diesel fuel	100		OMV	Stink
17	valeraldehyde	97	distilled water 1:125		Stink
18	Elvie perfume	100		Avon	Pleasant
19	octanoic adic	100			Stink
20	acetic acid	100	distilled water 1:4		Stink
21	deer aroma	100		Aroma a.s.	Pleasant
22	cyclohexanone	100	distilled water 1:1	Apolda	Stink
23	propylene glycol	100	distilled water 1:1	Gemed	Neutral
24	N-caproic acid	100	distilled water 1:4	Reachim	Stink
25	Vivien de saixe perfume	100		NO II	Pleasant
26	pelargonic acid	100	distilled water 1:5		Stink
27	cat aroma	100		Aroma a.s.	Stink
28	musk aroma	100		Aroma a.s.	Stink
29	strawberry aroma	100		AROO s.r.o.	Pleasant
30	ethylether acetate	100		Penta	Stink
31	ethyl propionate	100	distilled water 1:20	Lachema NP Brno	Stink
32	benzaldehyde	100	distilled water 1:100		Stink

Abbreviations: VAS=visual analog scale; NTOP=New Test of Odor Pleasantness; OMT=Odorized Marker Test

X^2 procedure, Pearson's chi-square or Fisher's exact probability test, while Student's t-test and the Mann-Whitney U test (for non-parametric data) were used for inter-group comparisons of olfactory tests. A probability level less than 0.05 was considered significant. The study is reported according to STARD guidelines (Bossuyt et al., 2003).

Results

Eighteen members of the PD group reported that their olfaction was normal, while 10 reported a decreased sense of smell, and two that they had lost their sense of smell. In the control group, 24 subjects reported normal olfaction and seven a decreased sense of smell.

The two study groups were not statistically different with regard to age (p=0.24), subjective evaluation of olfaction on VAS (p=0.17), subjective evaluation of nasal patency on VAS (p=0.89), MMSE results (p=0.32), level of education (p=0.25), or smoking habits (p=0.23).

Statistically significant positive correlations between VAS rating of olfaction (subjective evaluation) and all three olfactory tests were found in the PD group (Table II). This was not the case with the control group.

A negative correlation between the MMSE and CDT performances was found (r = –0.66). Overall, the number of subjects evaluated using the MMSE and CDT was 56 (28/28 subjects); two subjects from each group were not willing to participate in this part of the examination.

Table III shows the correlations between the three olfactory tests used in this study.

In the subjects overall (n=60), the correlation coefficient (r) was higher than 0.25 on a level of significance of 0.05, which demonstrates a significant mutual correlation between all three tests (Sniffin' Sticks, TOP and OMT). Figures 1, 2 and 3 show the comparisons, between the PD patients and the controls, of the points scored on the three olfactory tests.

The Mann-Whitney U test was used to analyze the differences in the olfactory test scores between the PD patients and the controls. A significant difference was found for each of the three tests: NTOP (p<0.001), Sniffin' Sticks (p<0.02), and OMT (p<0.001). The PD subjects showed significant impairment in olfactory identification and judgment of pleasantness, as compared to the control group.

The correlation between mood (evaluated on VAS) and NTOP score was not statistically significant for any group (control group r = –0.14; PD r = –0.27).

Discussion

The first to explore the concept of measuring the pleasantness of odorants was Henion (1971), followed by Moskowith et al. (1974) and Doty (1975). The purpose of Doty's study was to investigate the relationship between physical concentration and perceived intensity and pleasantness for a number of chemically and perceptually different stimuli. For this purpose, a modified procedure for judging the affective attributes of a stimulus was chosen. An odor was assigned a positive number in proportion to its pleasantness, and a negative number in proportion to its unpleasantness. If it was neutral, it was reported as zero. The results of that experiment showed that the pleasantness of olfactory stimuli varies with their physical concentration; pleasantness and intensity are closely related psychological dimensions for some odorants. The rating scale used by Distel et al. (1999) for judging pleasantness was similar to the one used in Doty's study. Pleasantness was rated on an 11-point scale, ranging from very unpleasant at –5, through neutral at zero, to pleasant at +5.

Table II – Correlation of subjective olfaction abilities as rated on VAS and olfactory tests in the PD group (p<0.05), n=30

Variable	VAS	NTOP	Sniffin' Sticks	OMT
VAS	1.00	0.43	0.56	0.40
NTOP	0.43	1.00	0.60	0.61
Sniffin' Sticks	0.56	0.60	1.00	0.69
OMT	0.40	0.61	0.69	1.00

Abbreviations: VAS=visual analog scale; NTOP=New Test of Odor Pleasantness; OMT=Odorized Marker Test

Table III – Correlation of olfactory tests (p<0.05), n=60

Variable	TOP	Sniffin' Sticks	OMT
NTOP	1	0.51	0.47
Sniffin'Sticks	0.51	1	0.50
OMT	0.47	0.50	1

Abbreviations: VAS=visual analog scale; NTOP=New Test of Odor Pleasantness; OMT=Odorized Marker Test

The application of pleasantness rating scales in PD subjects was first described by Hudry et al. (2003). In their study, 12 odorants were evaluated for intensity, pleasantness, familiarity and edibility using linear rating scales (segmented and numbered from 1 to 10). The study was performed in 24 subjects with PD and 24 control subjects in two sessions. The results showed severely impaired olfactory ability in PD, in all olfactory judgments (Hudry et al., 2003). Conversely,

in the present study, 32 odorants were used and the scale was asymmetrical (pleasant, neutral, unpleasant, very unpleasant). In order to oblige subjects to focus only on the hedonic character of the odorant we did not examine other olfactory characteristics (intensity, familiarity and edibility). The NTOP is based on the TOP, which consisted of 14 odorants. The TOP was developed by the Department of Analytical Chemistry at the Faculty of Chemical Technology, University of Pardubice. Fourteen pens were filled with various substances (Vodicka et al., 2010). In developing the new test, we were careful to retain a balance of pleasant, unpleasant, neutral and trigeminal stimulants. The odorants were selected on the basis of the empirical experience of chemists, who provided expert opinion on their hedonic tone. The NTOP is solely a pleasantness rating instrument. Odorant discrimination and identification are two tasks that involve perceptual and cognitive processes and they are dependent on the state of the individual's short-term memory. Common discrimination and identification in olfactory tasks can be affected in vulnerable groups with memory impairment, e.g. elderly people, but also in groups of children and adolescents, who are less familiar with the odors (Zucco et al., 2014), and can also be a limitation for PD patients. Discrimination can involve detecting differences in the pleasantness, intensity and quality of an odor, while identification of an odor is an even more demanding task, which requires intact discriminative abilities, as the presented stimulus has to be differentiated. Once an odor has been recognized, it has to be linked to

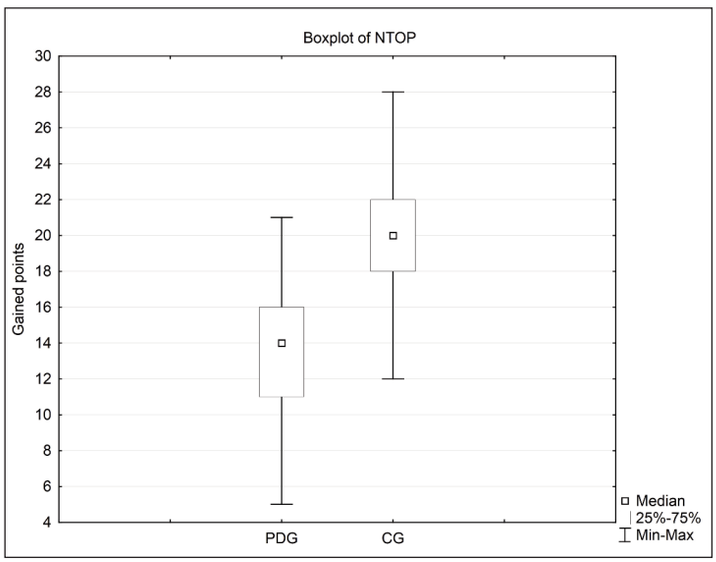

Figure 1 - Boxplot of the results of the NTOP in the PD group (PDG, n=30) and control group (CG, n=30).

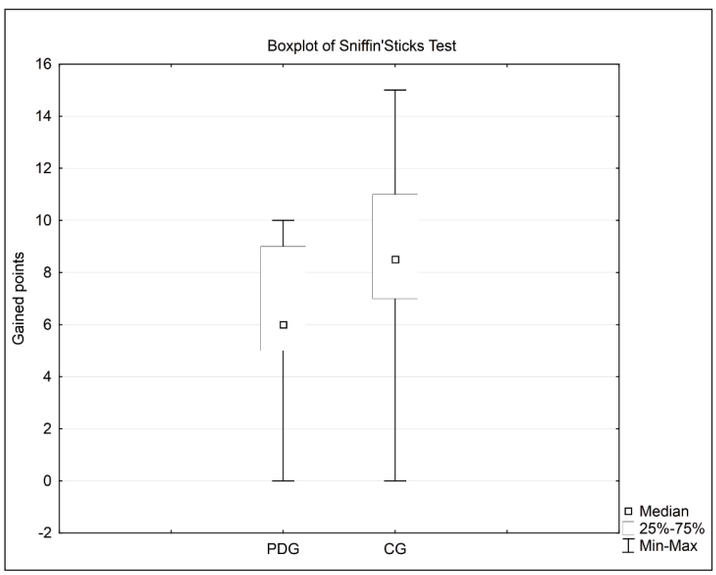

Figure 2 - Boxplot of the results of the Sniffin' Sticks (identification part) in the PD group (PDG, n=30) and control group (CG, n=30).

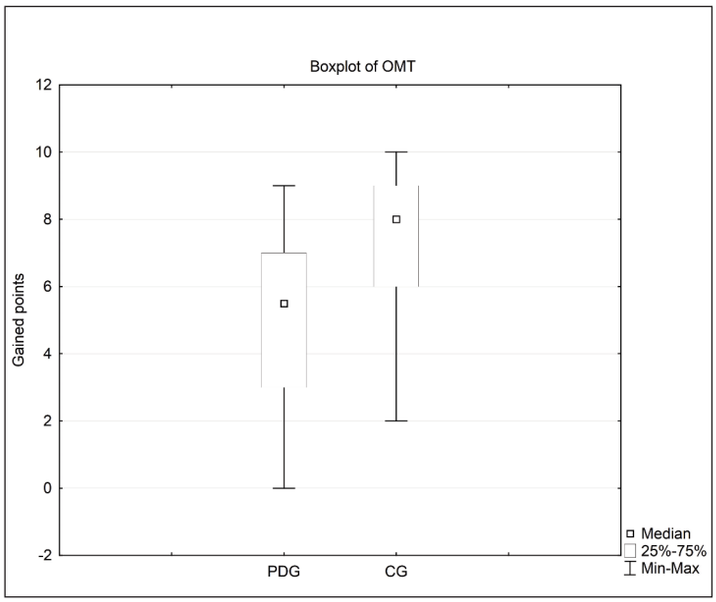

Figure 3 - Boxplot of the results of the OMT (identification) in the PD group (PDG, n=30) and control group (CG, n=30).

information about odor in the semantic memory; this requires knowledge of verbal categories and word meaning in order to attribute and produce a correct label (Zucco et al., 2014). Thus, odor identification tests can be more difficult for patients with PD than tests focusing on the pleasantness of odors. This is in accordance with the results of our study. We asked the subjects to indicate the test they found easiest and preferred, and more than 50% chose the NTOP. The NTOP was especially popular in the PD group (65%). This result could be explained by the fact that the hedonicity evaluation task was easier than the tasks requiring them to identify the odorants by name.

The idea of measuring the ability to judge the hedonic character of odors in PD led us to compare performance on the NTOP between patients with PD and healthy subjects. First of all, the NTOP, Sniffin' Sticks Test and OMT demonstrated significant mutual correlation. The NTOP was thus comparable to other olfactory tests in its ability to examine olfactory function. The results in the PD group, compared with the controls, showed significant impairment of olfactory function. Our study supports the conclusion of a study performed by Hudry et al. (2003), who found that evaluation of pleasantness was disturbed in a PD group.

In our study, we used a four-point rating scale. Subjects were asked to classify odors as pleasant, neutral, unpleasant or fetid. We consider this method of evaluating pleasantness simple yet sufficient to reveal differences in judgements of hedonicity. Our results showed that PD patients recorded lower scores in the evaluation of pleasantness.

Furthermore, we found a slightly negative correlation of mood with NTOP results in both groups. This is contradictory to the results of a study by Mayer and Bremer (1985), in which a moderate positive correlation was found between self-report of mood and performance on selected cognitive and motor tasks.

Hedonicity of taste was also evaluated, but no difference was found between the PD subjects and the control group. Sienkiewicz-Jarosz and collaborators proved that PD is not associated with any major alteration in taste responses to pleasant or unpleasant stimuli (Sienkiewicz-Jarosz et al., 2005, 2013).

The NTOP is a valuable method within the complex array of olfactory screening tools and it is also well received by patients. It is simple for patients and may be a suitable method for evaluating not only patients with PD but also elderly people.

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