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Validation of a new scale to assess olfactory dysfunction in patients with Parkinson's disease

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ABSTRACT

Bakckground: Olfactory dysfunction is present in up to 90% of Parkinson's disease (PD) patients. It is usually evaluated by means of objective standardized tests; however no self-administered scales have been developed for olfactory dysfunction bedside assessment. We present validation of a new scale to assess this symptom in PD patients.
Methods: Seventy-five PD patients and 25 control subjects were evaluated using a Hyposmia Rating Scale developed in-house, combined with the extended Sniffin' Sticks test.
Results: Total score of the 6-item Hyposmia Rating Scale showed significant correlation with threshold, discrimination, identification and total Sniffin' Sticks test scores ($r = 0.53$; $r = 0.60$; $r = 0.57$; $r = 0.65$ respectively, $p < 0.001$ for all values). Area under the curve of the receiver operating curve for the ability of Hyposmia Rating Scale to discriminate patients with Sniffin' Sticks test total scores below or above the cut-off point was 80 ± 6% ($p < 0.001$). Considering Sniffin' Sticks test as the gold standard method for olfactory dysfunction detection, an affirmative response to a single screening question about smelling ability problems showed 35% sensitivity (95%CI = 23–47%) and 100% specificity. The best cut-off point for Hyposmia Rating Scale was 22.5 with a sensitivity of 70% (60–81%) and a specificity of 85% (65–100%).
Conclusion: The Hyposmia Rating Scale here presented may offer a simple, cost-effective, time-saving and reliable approach to evaluate olfactory dysfunction in PD patients.

1. Introduction

Olfactory dysfunction in Parkinson's disease (PD) was first described by Ansari and Johnson [1] in 1975. Since then it has been recognized as one of the most frequent symptoms after bradykinesia, present in up to 90% of PD patients, competing in frequency with resting tremor [2–4]. It has also been observed to precede motor features by as much as a decade, or even longer, and is considered a predictor for developing PD [5,6].

Degree of olfactory dysfunction does not seem to vary in great measure with disease duration, stage or extent of motor involvement, nor does it improve with antiparkinsonian medication [7]. It is bilateral (in spite of asymmetric anatomical and functional basal ganglia disruption) and is infrequently found in other parkinsonian syndromes, such as essential tremor [8], progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy [9], PARKIN [10] or MPTP induced parkinsonism [11], and helps when attempting to distinguish idiopathic PD from these entities.

Olfactory dysfunction can be assessed by means of comprehensive and reliable objective tests, like the University of Pennsylvania Smell Identification Test (UPSIT) [12] or the Sniffin' Sticks Test (SST) [13]. Nonetheless, these tests may not be readily available to most clinicians or neurologists, or be practical for use in large populations and are time-consuming. We validated a self-administered scale specifically developed for olfactory dysfunction assessment in patients with PD.

2. Methods

Protocol was first approved by the local IRB and both study patients and controls gave written informed consent prior to study entry.

2.1. Population

Seventy-two unselected consecutive PD patients were recruited from a tertiary outpatient Movement Disorders clinic. A group of 25 age and gender-matched healthy controls were selected among patient relatives.

Patients and control subjects with history of chronic sinusitis; long term, or significant exposure to volatile substances such as pesticides, herbicides, metallic dusts, acid fumes, industrial solvents or thinners, cleaning products or sawdust were excluded; as were individuals who had suffered severe head trauma with loss of consciousness, referred history of drug abuse, or who had undergone nasal surgery

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Table 1
Characteristics of PD patients and healthy controls.

	Healthy controls ($n = 25$)	PD patients ($n = 72$)
Males	9 (36)	40 (56)
Age	60.9 ± 2.4	65.3 ± 1.3
Self–reported olfactory dysfunction	0	21 (29)[a]
Olfactory scale score	58.1 ± 0.4	49.9 ± 1.4[a]
Sniffin' Stick Test		
Threshold	6.5 ± 0.5	3.6 ± 0.3[a]
Discrimination	12.2 ± 0.4	8.6 ± 0.3[a]
Identification	12.8 ± 0.3	7.9 ± 0.4[a]
Total	31.5 ± 0.8	20.2 ± 0.9[a]
UPDRS II + III	–	19.7 ± 1.7
UPDRS IV Dyskinesias	–	17 (24)
UPDRS IV Fluctuations	–	16 (22)
PD duration	–	4.9 ± 0.5
Age at PD onset	–	60.3 ± 1.5
Antiparkinsonian medications		
Levodopa	–	36 (50)
Dopamine agonists	–	37 (51)
MAO-b inhibitors	–	27 (38)
COMT inhibitors	–	3 (4)
Amantadine	–	7 (10)

[a] <0.001 vs Healthy controls (*T*-test o ChiSq-test).

to correct a deviated septum or other plastic surgery procedures, or were current smokers. PD patients with dementia detected applying the Addenbrook Cognitive Evaluation (ACE) or patients treated with functional brain surgery were not included in the analysis.

2.2. Evaluation

All subjects were evaluated using both the in-house developed "Hyposmia Rating Scale" (HRS) and the extended version of the SST (Burghart Messtechnik, Wedel, Germany) [13]. HRS and SST were administered to selected patients on the morning after taking prescribed medication in on-state.

The SST [13] consists of 3 subsets of tests assessing different olfaction modalities, including threshold (using n-butanol), discrimination and identification, administering odors contained in felt-tip whiteboard markers. It establishes partial and total scores, generating an overall assessment of olfactory function. Subset scores range from 0 to 16, with a maximum total score of 48.

First patients were asked to answer: "yes", "no", or "don't know", to a single question: *"Are you experiencing problems with your sense of smell?"* After which 15-Likert type questions referring to the frequency with which certain odors were perceived were administered. Odors evaluated included: freshly brewed coffee, baked bread/pastries, flowers, freshly cut grass, natural gas (mercaptans), burning paper/cardboard/wood, incense or air fresheners, sewage/garbage, smog, perfume, bleach, ammonia, perspiration, paint thinner, home-cooked food, cigarette smoke, dirty clothes and deodorant. Patients were asked to rate the frequency of their perceptions as 'always'/'sometimes'/'only after being made aware of'/'never' (which corresponded to 4, 3, 2 or 1 points respectively) or 'unfamiliar'.

A discrimination index [14] was used to select items better correlating with SST. Briefly, percentage average score difference was calculated for each HRS question between two groups formed by 27% of PD subjects with highest or lowest total SST score respectively. Items were ordered according to discrimination index. Total scores for sets of consecutive items were calculated (the first included the single item with highest discrimination index, the second, the first and second items with highest discrimination scores and so on).

Area under the curve (AUC) of the receiver operating characteristic curve (ROC) for discriminating patients with SST above or below cut-off values considered normal for each set of items were calculated, and those generating highest AUC of the ROC curve were then selected for further testing.

2.3. Statistical analysis

Sample size calculation was performed according to Carley et al. [15]. Thus, for 80% sensitivity and specificity in olfactory dysfunction detection and ≤6.5% standard error of the mean, we estimated 75 PD patients would be needed. Twenty-five healthy controls would be enough to detect a 20% difference in SST with respect to PD patients, allowing a maximum standard deviation of 40% for each group.

Demographic data from both groups was analyzed applying a *T*-test for independent samples or a Chi-square test.

HRS internal consistency was assessed using Chronbach's alfa. Floor and ceiling effects in PD patients were calculated. Internal validity was assessed by correlating HRS scores with SST values using Spearman's rank coefficient, also used to assess correlations with HRS score and age. To assess HRS differences between male and female subjects, a Chi-square test was used. HRS diagnostic accuracy was tested calculating AUC of the ROC curves in PD patients with and without hyposmia, for which SST cut-off values were needed. These were obtained analyzing SST distribution in healthy subjects and from ROC curves, subsequently identifying optimal values discriminating between PD patients and healthy controls.

Sensitivity and specificity for HRS and the question "*Are you experiencing problems with your sense of smell* ?" were calculated taking SST as the gold standard.

Finally, characteristics between patients with or without olfactory dysfunction were analyzed using *T*-test for independent samples or the Chi-square test.

Table 2
Discrimination index for HRS items.

Smell	Discrimination index
Natural gas (mercaptans)	33
Perspiration	16
Garbage	13
Home cooked Food	11
Perfume	9
Flowers	8
Freshly cut grass	7
Coffee	7
Burnt paper	7
Incense	6
Bleach, amonnia	5
Paint thinner	5
Baked pastries	5
Smog	3
Tobacco smoke	0

3. Results

Seventy-five PD patients and 25 healthy subjects were recruited; demographic data are shown in Table 1.

3.1. Sniffing' sticks test cut-off values

In healthy controls, 25th percentile of total SST score was 29. AUC of the ROC curve assessing total SST score ability to discriminate between PD and healthy controls was 90 ± 3% ($p < 0.001$). Cut-off value set at 28.4, showed 82% sensitivity and 85% specificity for discriminating PD from controls. Fifty-nine (82%) PD patients and 4 (16%) healthy controls scored < 28.4.

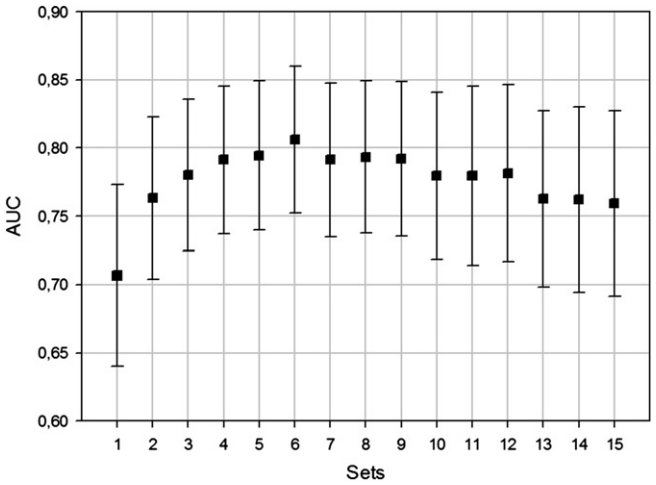

Fig. 1. AUC for the ROC curve of each set of hyposmia-related items. Shown are: AUC ± standard error of the mean. Sets were constructed by considering growing number of hyposmia items in ascending order (i.e. the first one included the single item with highest discrimination index, the second set included the first and second items with highest discrimination scores and so on).

Table 3
Sensitivity and specificity of the single question "are you experiencing problems with your sense of smell?" or the 6-item HRS for the evaluation of hyposmia taking SST as the gold-standard method.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Single question	35%	100%	100%	25% (13–38)
6-item HRS	70% (60–80%)	85% (65–100%)	95% (90–100%)	38% (20–55%)

95% confidence intervals are shown into brackets.

3.2. Item selection

Discrimination indexes for the 15 items are shown in Table 2. As can be seen in Fig. 1, the set containing the 6 items with highest discrimination score (i.e. natural gas, perspiration, garbage, home-cooked food, perfume and flowers) offered the highest AUC. The final 6-item Hyposmia Rating Scale is shown in Appendix 1.

3.3. HRS clinimetric properties

Five (7%) patients failed to answer, 1 and 3 (4%) failed to answer 2 questions. Cronbach's alpha was 0.89. A floor effect of 1.4% was observed, while the ceiling effect was 40% (i.e. 29 subjects had HRS scores gt; 95% of the maximum score), and mean time required for completion of full HRS was 3.42 min (95% CI: 2.18–5.30).

HRS score correlated significantly with SST threshold score ($r = 0.53$ $p < 0.001$), discrimination score ($r = 0.60$ $p < 0.001$), identification score ($r = 0.57$ $p < 0.001$) and total score ($r = 0.65$ $p < 0.001$). It also showed significant correlation with age ($r = -0.33$ $p < 0.001$). Chi-square tests revealed no significant differences between male and female HRS scores ($p = 0.62$).

HRS cut-off point set at ≤ 22 points yielded 70% sensitivity and 85% specificity compared to SST as gold standard (Table 3).

3.4. Diagnostic validity of self-reported smelling capacity based on answering single screening question

When asked *"Are you experiencing problems with your sense of smell?"*, 34 patients (47%) responded negatively, 21 (29%) affirmatively and 17 (24%) were not sure. Taking SST score < 28.4 as gold standard for olfactory dysfunction detection, sensitivity was 35% and specificity was 100% for an affirmative response (Table 3). Combining of question and HRS score did not yield better results than HRS result alone.

4. Discussion

We have developed a simple, affordable, time-saving self-administered scale that reliably evaluates hyposmia in PD. HRS was superior in terms of clinimetric properties in comparison to the single screening question "Are you experiencing problems with your sense of smell?" (Table 3) which is the tool most often used at patient bedside or in clinic to begin olfactory function evaluation. Our results showed that the question alone lacked sensitivity although the result was slightly higher than the 20% reported by Shu [16] and Murphy [17] for a healthy population, and the possibility of hyposmia with a negative response is high, a positive response can still be considered trustworthy. In contrast, HRS exposed individuals to readily recognizable every day odors, specifically including many that elderly or homebound patients would be familiar with, thus allowing more reliably olfactory function evaluation. Certain limitations of the HRS should be mentioned. A moderate ceiling effect was observed, generated by the fact that many patients assigned higher scores to certain questions regardless of olfactory capacity (i.e. denied having a problem related to a particular odor), causing a fall in specificity when trying to improve sensitivity by raising cut-off points. Nonetheless, selecting 22.5 as the cut-off point allowed good discrimination between PD patients with normal or abnormal SST results, with acceptable sensitivity and specificity.

The premotor phase of PD is a period during which the pathological process has started, but motor signs required for clinical diagnosis are absent. Ability to identify this phase may be critical for the development and eventual use of neuroprotective therapy [18]. Proposed PD staging systems have suggested that degeneration may occur initially in areas outside the substantia nigra, suggesting non-motor manifestations may be markers of presymptomatic PD [19]. Decreased olfaction has recently been demonstrated to predict PD in prospective pathological studies, although lead time may be relatively short and positive predictive value not as high as expected [20]. Nevertheless, the presence of idiopathic REM sleep behavior disorder with olfactory impairment might represent clear PD premotor phase [21]. The combination of olfactory dysfunction with certain brain imaging studies has also been explored with presymtomatic diagnostic purposes [22–26]. HRS showed good clinimetric properties, is simple to administer, and saves time and resources, making it an important tool for hyposmia diagnosis in PD, especially when objective tests are not available. Interestingly, this scale offers the possibility of over-the-phone hyposmia screening in unselected populations. Further studies should focus on the validity of the HRS scale administered to patients with suspected premotor PD.

In summary, this 6-item self-administered Hyposmia Rating Scale reliably evaluated hyposmia in comparison to SST as gold standard. In contrast, a simple question on self-perceived olfactory capacity lacked sensitivity. Thus, use of the HRS is favored over a single question in early stages of hyposmia evaluation in PD patients.

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Appendix

Hyposmia rating scale

1. When going to a florist; the scent of flowers:
   - ☐ I am always aware of it, without others remarking on it.
   - ☐ I am sometimes aware of it, without others remarking on it.
   - ☐ I am only aware of, if asked by others whether I can smell it
   - ☐ I am never aware of, even after being asked by others if I can smell it
   - ☐ I am unfamiliar or have never smelt fresh flowers.
2. If I am close to a gas leak, the smell of unburned gas:
   - ☐ I am always aware of it, without others remarking on it.
   - ☐ I am sometimes aware of it, without others remarking on it.
   - ☐ I am only aware of, if asked by others whether I can smell it
   - ☐ I am never aware of, even after being asked by others if I can smell it
   - ☐ I am unfamiliar or have never smelt it

3. If I am close to garbage, sewage or other foul smelling materials:
   - ☐ I am always aware of it, without others remarking on it.
   - ☐ I am sometimes aware of it, without others remarking on it.
   - ☐ I am only aware of, if asked by others whether I can smell them
   - ☐ I am never aware of, even after being asked by others if I can smell them
   - ☐ I am unfamiliar or have never smelt garbage or other foul odors
4. The scent of perfume on someone I approach to hug or embrace:
   - ☐ I am always aware of it, without others remarking on it.
   - ☐ I am sometimes aware of it, without others remarking on it.
   - ☐ I am only aware of, if asked by others whether I can smell it
   - ☐ I am never aware of, even after being asked by others if I can smell it
   - ☐ I am unfamiliar or have never smelt perfume
5. In closed or confined spaces (elevators etc), the smell of stuffiness or strong body odor:
   - ☐ I am always aware of it, without others remarking on it.
   - ☐ I am sometimes aware of it, without others remarking on it.
   - ☐ I am only aware of, if asked by others whether I can smell it
   - ☐ I am never aware of, even after being asked by others if I can smell it
   - ☐ I am unfamiliar or have never smelt it
6. The smell of home cooking:
   - ☐ I am always aware of it, without others remarking on it.
   - ☐ I am sometimes aware of it, without others remarking on it.
   - ☐ I am only aware of it, if asked by others whether I can smell it
   - ☐ I am never aware of it, even after being asked by others if I can smell it
   - ☐ I am unfamiliar or have never smelt the smell of home cooked food.

Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.parkreldis.2011.12.001.

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