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Accurate Detection of Parkinson's Disease in Tremor Syndromes Using Olfactory Testing

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Key Words

Olfactory testing · Tremor · Parkinson's disease · Essential tremor

Abstract

Background/Aims: The diagnostic value of olfactory testing for the discrimination of tremor-dominant Parkinson's disease (PD) from other tremor disorders remains enigmatic. We evaluated whether olfactory testing can accurately detect PD in tremor patients. **Methods:** A retrospective analysis of 299 consecutive subjects referred for the differential diagnosis of a tremor disorder was done. Olfactory testing was performed using 'Sniffin' Sticks', resulting in a composite TDI score of odor threshold (T), discrimination (D), and identification (I). Receiver operating curve (ROC) plots were used to calculate sensitivity/specificity for the detection of PD. **Results:** Of all subjects, 167 (55.9%) had PD and 85 (28.4%) had essential tremor (ET). The mean TDI score in PD was significantly reduced compared to those in ET and other tremor disorders with no differences between ET and other tremor disorders. ROC analysis revealed strong correlations of TDI scores with PD [area under the curve: 0.85 (95% CI: 0.80–

0.89); $p < 0.001$]. The highest Youden index was observed for a TDI score < 25 (Youden index: 0.58). Using this cutoff score and that generated from normative data of healthy controls, the TDI score provided high sensitivity (negative predictive value) and specificity (positive predictive value) of approximately 80% for detecting PD. **Conclusion:** Olfactory testing is a useful, easily applied and inexpensive diagnostic test which is helpful to detect PD among tremor patients.

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Introduction

Discrimination of tremor-dominant Parkinson's disease (PD) from other tremor disorders such as essential tremor (ET) is often difficult, particularly in the early disease stages with occasional monosymptomatic tremor in PD. Olfactory dysfunction is a characteristic and early feature of PD with more than 95% of subjects presenting with a significant loss of olfactory function independently of the subtype of the disease and thus including the tremor-dominant form of PD [1–5]. Olfactory testing is used in the diagnosis of PD [2, 6, 7]; however, its value in the differen-

tial diagnosis between tremor-dominant PD and other tremor disorders remains unclear. In contrast to patients with various forms of parkinsonism, subjects suffering from most tremor disorders other than PD do not experience an impairment of olfactory function at all or less severe hyposmia compared to PD patients [7–10]. Shah et al. [8] performed odor identification testing using the University of Pennsylvania Smell Identification Test (UPSIT) in ET compared to tremor-dominant PD. They reported high sensitivity and specificity of the standard cutoff values to distinguish PD from ET patients, but no other quantitative measures of the discriminatory power or the optimized cutoff values of UPSIT, e.g. by using the receiver operating curve (ROC) analysis; no diagnostic predictive values were reported, which would be important for diagnostic purposes. The aim of this study was thus to investigate the diagnostic accuracy of psychophysical olfactory testing in differentiating PD from other tremor disorders.

Materials and Methods

Study Population

In this single-center retrospective study, we analyzed data of 302 consecutive subjects admitted to the Department of Neurology for a differential diagnosis of a tremor syndrome and who underwent olfactory testing between September 2004 and October 2009. Final diagnoses were established using available diagnostic criteria for PD [11], ET [12], and other tremor syndromes [12]. Patients not fulfilling these diagnostic criteria ($n = 88$; 29.4%) underwent functional brain imaging using standard ^{18}F -dopa positron emission tomography or DAT-SCAN single-photon emission computed tomography. The study was approved by the Institutional Review Board at the Dresden University of Technology.

Olfactory Testing

Olfactory testing was performed using the ‘Sniffin’ Sticks’ test kit [13, 14] which involves tests for odor threshold (T), odor discrimination (D), and odor identification (I). Odor identification was assessed for 16 common odors (orange, leather, cinnamon, menthol, banana, lemon, licorice, garlic, coffee, apple, pineapple, rose, fish, anise, clove, and turpentine) using a multiple forced-choice design, namely subjects identify odors by selecting the best label from a list of 4 descriptors. Results of the 3 subtests are presented as a composite TDI score (range: 1–48), which is the sum of the results obtained for threshold (range: 1–16), discrimination (range: 0–16), and identification (range: 0–16) measures [14].

Statistical Analyses

We assessed the performance of specific cutoff points for olfaction test measures to detect PD using specificity and sensitivity, positive and negative predictive values (PPV and NPV) according to the Bayes’ theorem, and the likelihood ratio. ROC plots including calculation of the area under the curve (AUC) were used to display sensitivity and specificity of olfactory testing measures for the detection of PD. For the generation of cutoff values from ROC

analysis, we used the Youden index as a measure of the theoretical optimum of test scores. Results are presented as mean $\pm$ SD and range, as mean with 95% confidence interval (95% CI) in parentheses, or as number with percentage in parentheses. Variables were compared by one-way ANOVA/ANCOVA with Bonferroni-adjusted post hoc t tests or the χ^2 test as appropriate. Statistical significance was defined for all analyses as $p < 0.05$. Statistical tests were performed using SPSS 19.0 (SPSS, Chicago, Ill., USA).

Results

Study Cohort

The characteristics of the study cohort are shown in table 1. Of a total of 302 tremor subjects, 299 subjects were included in the analysis (3 subjects were excluded due to incomplete olfactory testing). 167 (55.9%) subjects were diagnosed with PD, 85 (28.4%) with ET and 47 (15.7%) with other tremor disorders [enhanced physiological tremor in 5 (1.7%), neuropathic tremor in 5 (1.7%), multiple system atrophy (MSA) in 5 (1.7%), cerebellar tremor in 2 (0.7%), psychogenic tremor in 2 (0.7%), dystonic tremor in 2 (0.7%), various tremor syndromes in 3 (1.0%), and unclassified tremor in 23 (7.7%) subjects].

Olfactory Testing

All subscores and items of the olfactory testing were completed by 299 out of 302 subjects (99%). There were no adverse events during olfactory testing. Table 1 summarizes the data of the olfactory testing. The mean TDI score in the PD group was significantly reduced compared to those in the ET and the other tremor disorder groups, but no differences in TDI scores were observed between the ET group and the other tremor disorder groups. For the subgroup of patients with MSA as a synucleinopathy such as PD, the mean $\pm$ SD TDI score of 20.5 ± 10.5 (range: 7.0–32.5) was similar to that of PD ($p = 0.644$) but significantly lower compared to that of ET subjects ($p < 0.001$). Similar results were obtained for the subscores of threshold, discrimination, and identification. The TDI scores correlated with age in the PD and ET groups with no differences between all subject groups [linear TDI decline per year of age was -0.160 ($p < 0.001$; 95% CI: -0.234 to -0.086) in PD, -0.185 ($p < 0.001$; 95% CI: -0.282 to -0.089) in ET, and -0.197 ($p = 0.101$; 95% CI: -0.434 to 0.040) in other tremor disorders]. One-way ANCOVA with age as covariate confirmed that the mean TDI scores were significantly different between the subject groups ($p < 0.001$; F value: 103.4). Similar results were observed for the subscores. The TDI score and its subscores did not correlate with sex in all subject groups.

Table 1. Demographic and clinical data

	Total	PD	ET	Others	p value
Patients, n	299	167	85	47	
Females, n (%)	110 (36.4)	51 (30.5)	41 (48.2)	18 (38.3)	0.022 ^a
Age, years	64.0±10.9 (18–87)	63.9±10.2 (36–85)	63.4±13.0 (18–87)	65.6±8.6 (43–81)	0.526 ^b
Olfactory testing					
TDI, points	–	19.0±6.7 (1.0–34.5)	30.5±4.9 (15.5–42.0)	24.2±7.0 (3.0–34.0)	<0.001 ^b
Threshold, points	–	3.3±2.2 (1.0–10.5)	5.7±2.2 (1.0–12.0)	3.9±2.4 (1.0–11.3)	<0.001 ^b
Discrimination, points	–	8.1±2.9 (0–15)	11.7±2.2 (6–16)	9.4±3.2 (0–15)	<0.001 ^b
Identification, points	–	7.7±3.3 (0–16)	13.1±2.0 (7–16)	10.9±3.1 (2–15)	<0.001 ^b

Values for age and olfactory testing are given as means ± SD with the range in parentheses.

^a Pearson's χ^2 test: subsequent Pearson's χ^2 tests for individual group comparisons revealed significant differences only between ET and PD ($p = 0.006$).

^b One-way ANOVA: post hoc t test with Bonferroni adjustment revealed statistical differences with $p < 0.05$ between all groups, except for the comparison of thresholds between PD and other tremor disorders ($p = 0.231$).

Table 2. Comparison of the utility of TDI, threshold, discrimination, and identification for the detection of PD in tremor syndromes

	TDI (cutoff: normative data from healthy controls) ^a	TDI (cutoff from ROC analysis: 25) ^b	Threshold (cutoff from ROC analysis: 4) ^b	Discrimination (cutoff from ROC analysis: 10) ^b	Identification (cutoff from ROC analysis: 11) ^b
Sensitivity (95% CI)	62.3% (54.4–69.6)	76.0% (69.5–82.5)	68.3% (61.2–75.4)	65.3% (58.1–72.5)	79.0% (72.8–85.2)
Specificity (95% CI)	88.6% (83.2–94.0)	78.8% (71.8–85.8)	65.9% (57.8–74.0)	72.0% (64.5–79.7)	80.3% (73.5–87.1)
PPV ^c (95% CI)	87.4% (80.0–92.5)	81.9% (74.8–87.5)	71.7% (63.9–78.4)	74.7% (66.7–81.3)	83.5% (76.6–88.8)
NPV ^c (95% CI)	65.0% (57.5–71.9)	77.2% (68.0–82.6)	62.1% (53.5–70.1)	62.1% (53.9–69.8)	75.2% (67.1–81.9)
Likelihood ratio	5.5	3.6	2.0	2.3	4.0

^a The age-related cutoff values from age-adjusted normative data by Hummel et al. [14] were 24.9 (<15 years of age), 30.3 (16–35 years of age), 27.3 (36–55 years of age), and 19.6 (>55 years of age).

^b The cutoff values from ROC analysis at the highest Youden index were used for calculations.

^c Calculated using the Bayes' theorem.

ROC analyses revealing sensitivities and specificities of any particular cutoff value of the TDI score and all three subscores to detect PD in tremor disorders are shown in figure 1. The intervals between cutoff values for the TDI score were between 7 (90th percentile specificity) and 28 (90th percentile sensitivity). The same intervals for the threshold subscore were between 2 and 7, for the discrimination subscore between 7 and 12, and for the identification subscore between 9 and 12. The highest Youden index was observed for the TDI score <25 (Youden index: 0.58), for the threshold subscore <4 (0.34), for the discrimination subscore <10 (0.40), and for the identification subscore <11 (0.60). The sensitivity/specificity values obtained at the maximal Youden index were slightly higher for the TDI score (by using both the cutoffs from normative data from healthy controls and

the cutoffs generated by the ROC analysis) and for the identification subscore than for the threshold and the discrimination subscores (table 2). Hence, cutoff points of 24 for the TDI score (meaning that a score of 24 or less indicates PD, whereas 25 or more indicates non-PD tremor) and 3 for the threshold score, 9 for the discrimination score, and 10 for the identification score were used to compare the utility of the tests for the diagnosis of PD in tremor subjects.

The ROC analyses indicated that the identification subscore had a similar discriminatory power (AUC of ROC) compared to the TDI compound score, but a higher discriminative power (higher AUC of ROC) compared to the other subscores (fig. 1). ROC analyses for the subsample of subjects with PD or ET only excluding the other tremor disorder subjects revealed similar results and

Fig. 1. ROC curves displaying the sensitivity and specificity of TDI (a), threshold (b), discrimination (c) and identification (d) for diagnosis of PD within the overall tremor population.

the same cutoffs for the TDI score and all subscores for discriminating PD from ET (data not shown).

Reducing the combination of identification scores from 16 odors in the original test battery down to the 8 (cinnamon, menthol, banana, licorice, apple, pineapple, anise, and fish) or 4 (banana, licorice, pineapple, and anise), odor identification scores using the odors with the best performance (highest AUC in ROC) led to similar discriminatory power as the full 16-odor identification score (AUC for the 8-odor score: 0.86 (95% CI: 0.82–0.91), $p < 0.0001$; AUC for the 4-odor score: 0.84 (95% CI: 0.79–0.88), $p < 0.0001$).

Utility of Olfactory Testing to Discriminate PD from Other Tremor Syndromes

Table 2 compares the utility of the TDI score and its subscores to detect PD in subjects with tremor by applying the cutoff scores from ROC analyses using the Youden

index and for TDI scores using the cutoffs generated from age-adjusted normative data of a healthy control sample [14]. Using these cutoff scores, the TDI score and the identification subscore provided high sensitivity (NPV) and specificity (PPV) of approximately 80% for detecting PD in a cohort of consecutive tremor subjects. Similar results were obtained for the detection of PD in the sub-cohort of subjects with ET excluding the other tremor disorders (data not shown).

Discussion

The present study shows sufficient diagnostic validity for psychophysical olfactory testing to diagnose PD in tremor disorder subjects with high PPV and NPV of approximately 80% independently of tremor subtype, age, or gender. In agreement with previous reports [1, 2, 8],

we observed significantly lower olfactory function in subjects with PD compared to those with ET and other tremor disorders [2, 8], but we did not detect any differences in age dependency between PD, ET, and other tremor disorders. As in a previous report [15], olfactory function in MSA as a synucleinopathy sometimes resembling PD in the first disease stages was similar to that in PD. Our data clearly support the view that inexpensive olfactory testing may constitute a suitable diagnostic instrument for detecting PD in subjects with tremor syndromes independently of age, gender and tremor subtype.

External validity measured by ROC analysis using the available diagnostic criteria combined with functional brain imaging in unclear cases as the external validation criterion indicated that both the composite TDI score and the identification subscore have sufficient discriminatory power as a diagnostic tool for detecting PD in tremor disorders. Applying the standard age-related cutoff values for the TDI score generated from normative data of a healthy cohort [14], the TDI score had high specificity (PPV) but only modest sensitivity (NPV) for the detection of PD. The optimal cutoff for the TDI score as assessed by ROC analysis using the Youden index in our study was 24, leading to high values for specificity (PPV) and sensitivity (NPV). Interestingly, using a single odor identification test with 16 or even less odors also seems to have sufficient discriminatory validity for detecting PD in tremor subjects.

The comparison between the diagnostic accuracy of olfactory testing and previously reported data on DAT-SCAN single-photon emission computed tomography imaging [16] suggests that functional brain imaging is associated with higher diagnostic validity for the detection of PD in tremor disorders (sensitivity for the clinical diagnosis of parkinsonism of 97% and specificity for ET of 100%). However, olfactory testing is an easy and inexpensive technique which might be available at each Movement Disorder Center. In contrast to functional brain imaging, no adverse events are expected and no administration of radioactive compounds is required [16].

Our study has some limitations. We performed a retrospective study in tremor subjects who were seen consecutively. Hence, only a limited clinical dataset was available (e.g. no data on disease onset or duration were available), and the diagnosis in the majority of cases was made using standard clinical diagnostic criteria with limited diagnostic accuracy [11, 12]. The diagnosis was confirmed with functional imaging in only 29% of subjects. Another point of criticism could be the fact that data were only obtained in a single university-based study

center with a potential bias in patient referral. On the other hand, since we calculated our data in a consecutive tremor subject cohort, the presented diagnostic accuracy data apply for tremor patients independently of demographic characteristics and tremor subtype and thus apply for tremor patients at their first diagnostic consultation.

In conclusion, this study demonstrates that olfactory testing is a valid and useful instrument in detecting PD in tremor disorders. It has sufficient sensitivity and specificity with an age-independent cutoff point for the TDI score of <25, which is independent of demographic parameters. The external validity ranked highly as indicated by the ROC analysis. TDI and odor identification scores were related to the absence or presence of PD in tremor subjects. In comparison to most other tools for this diagnostic problem, olfactory testing has the advantages of being very brief, inexpensive, and easy. In a stepwise diagnostic approach, olfactory testing should thus be used as a first diagnostic test prior to more laborious and expensive tests such as functional brain imaging.

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References

- 1 Haehner A, Boesveldt S, Berendse HW, et al: Prevalence of smell loss in Parkinson's disease – a multicenter study. *Parkinsonism Relat Disord* 2009;15:490–494.
- 2 Doty RL: Olfactory dysfunction in Parkinson disease. *Nat Rev Neurol* 2012;8:329–339.
- 3 Stern MB, Doty RL, Dotti M, et al: Olfactory function in Parkinson's disease subtypes. *Neurology* 1994;44:266–268.
- 4 Doty RL, Stern MB, Pfeiffer C, Gollomp SM, Hurtig HI: Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1992;55:138–142.
- 5 Heckmann JG, Höcherl C, Lang CJG, Platsch G, Hummel T: Hemihyposmia in case of hemiparkinsonism. *Eur J Gen Med* 2004;1:72–73.
- 6 Busse K, Heilmann R, Kleinschmidt S, et al: Value of combined midbrain sonography, olfactory and motor function assessment in the differential diagnosis of early Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2012;83:441–447.
- 7 McKinnon J, Evidente V, Driver-Dunckley E, et al: Olfaction in the elderly: a cross-sectional analysis comparing Parkinson's disease with controls and other disorders. *Int J Neurol* 2010;120:36–39.
- 8 Shah M, Muhammed N, Findley LJ, Hawkes CH: Olfactory tests in the diagnosis of essential tremor. *Parkinsonism Relat Disord* 2008;14:563–568.
- 9 Busenbark KL, Huber SJ, Greer G, Pahwa R, Koller WC: Olfactory function in essential tremor. *Neurology* 1992;42:1631–1632.
- 10 Louis ED, Jurewicz EC: Olfaction in essential tremor patients with and without isolated rest tremor. *Mov Disord* 2003;18:1387–1389.
- 11 Hughes AJ, Daniel SE, Kilford L, Lees AJ: Accuracy of clinical diagnosis of idiopathic parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–184.
- 12 Deuschl G, Bain P, Brin M: Consensus statement of the Movement Disorder Society on Tremor. *Ad Hoc Scientific Committee. Mov Disord* 1998;13(suppl 3):2–23.
- 13 Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G: 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem Senses* 1997;22:39–52.
- 14 Hummel T, Kobal G, Gudziol H, Mackay-Sim A: Normative data for the 'Sniffin' Sticks' including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *Eur Arch Otorhinolaryngol* 2007;264:237–243.
- 15 Muller A, Mungersdorf M, Reichmann H, Strehle G, Hummel T: Olfactory function in parkinsonian syndromes. *J Clin Neurosci* 2002;9:521–524.
- 16 Benamer TS, Patterson J, Grosset DG, et al: Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group. *Mov Disord* 2000;15:503–510.