

Olfactory function in Parkinson's disease subtypes

M.B. Stern, MD; R.L. Doty, PhD; M. Dotti, MD; P. Corcoran, MSW; D. Crawford, MA; D.A. McKeown, BA; C. Adler, MD; S. Gollomp, MD; and H. Hurtig, MD

Article abstract—Decreased olfactory function commonly occurs in idiopathic Parkinson's disease (PD), regardless of stage, treatment, or duration of disease. In the present study, we sought to determine whether different subtypes of PD, categorized according to well-defined clinical criteria, evidence different degrees of olfactory dysfunction. Significantly different scores on the University of Pennsylvania Smell Identification Test (UPSIT) were present between patients with benign PD and malignant PD (respective means [SD] = 22.51 [8.50] and 17.38 [6.29]) and between tremor-predominant PD and postural instability-gait disorder (PIGD)-predominant PD (23.43 [8.18] versus 17.35 [6.00]). No statistically significant differences in UPSIT scores were observed between young-onset and older-onset PD patients. Women outperformed men in most subtypes examined.

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Decreased olfactory function is common in idiopathic Parkinson's disease (PD)¹ and occurs in many PD patients regardless of severity or duration of the disease symptoms.^{1,2} While olfactory dysfunction is a feature of other neurodegenerative diseases such as Alzheimer's disease,³ the sense of smell is spared to a large degree in essential tremor,⁴ 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism,⁵ and progressive supranuclear palsy (PSP).⁶ Of the parkinsonisms, loss of odor identification ability appears to be relatively specific to PD. However, PD is itself a heterogeneous disorder in both clinical expression and long-term prognosis, and some groups have recognized specific PD subtypes.⁷ We explored the possibility that olfactory function differed among PD subtypes and determined whether the female superiority in odor identification ability noted in other PD studies¹ persists within the PD subtypes.

Methods. One hundred eighteen nondemented PD patients were assigned to PD subtypes based on specific clinical criteria. *Young-onset PD* patients had the onset of clinical symptoms before age 40 years. For the purposes of comparison in this study, all other patients were considered *older-onset*. Patients with *benign PD* evidenced Hoehn and Yahr stage II disease or less for 4 or

more years, while *malignant PD* patients had Hoehn and Yahr stage III or greater. *Tremor-predominant PD* patients had a ratio of mean tremor score to postural instability-gait disorder (PIGD) score of 1.5 or more on the Unified PD Rating Scale, while *PIGD-predominant PD* patients were those in whom the ratio was 1.0 or less.⁷ Patients with *chronic hemiparkinsonism* had unilateral signs for 4 or more years (table 1).

Olfactory testing was performed bilaterally using the University of Pennsylvania Smell Identification Test (UPSIT; commercially available as the Smell Identification Test, Seasonics, Inc, Haddon Heights, NJ). The UPSIT consists of 40 odorants presented with four multiple choice options for each item. UPSIT scores range from 0 to 40 according to the number of correctly identified odorants. Extensive population studies have previously defined normal age-related UPSIT scores^{8,9}; a score of 34 or more is within the range of normal for adults.

Intergroup comparisons were made between young-versus older-onset patients, benign versus malignant PD patients, tremor-predominant versus PIGD-predominant PD patients, and chronic hemiparkinsonism versus all other patients with PD. Since our study was designed to detect differences among PD subtypes and UPSIT scores for normal subjects are well established,⁹ normal subjects were not evaluated. Statistical comparisons among groups employed analysis of covariance (ANCOVA) using age as a covariate and disease group and gender as independent variables. Gender was not used as a factor in the young-onset PD versus older-onset PD comparison because there was only one female with young-onset PD.

From the Movement Disorders Center, Department of Neurology (P. Corcoran and Drs. Adler, Dotti, Gollomp, Hurtig, and Stern), Graduate Hospital, Philadelphia, PA; the Department of Neurology (Drs. Hurtig and Stern), University of Pennsylvania School of Medicine, Philadelphia, PA; and the Smell and Taste Center, Department of Otorhinolaryngology: Head and Neck Surgery (Dr. Doty and D. Crawford and D.A. McKeown), Hospital of the University of Pennsylvania, Philadelphia, PA.

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Address correspondence and reprint requests to Dr. Matthew B. Stern, Department of Neurology, Graduate Hospital, 18th and Lombard Street, Philadelphia, PA 19146.

Table 1. The definition, distribution, and ages of patients with Parkinson's disease subtypes

Subtypes	Definition	Number			Age (\pm SD)		
		Total	Male	Female	Total	Male	Female
Young-onset PD	Onset \leq 40 years	9	8	1	42.44 (9.34)	42.50 (9.99)	42.00 (10.00)
Older-onset PD	All other patients with onset $>$ 40 years	109	80	49	66.08 (9.34)	66.96 (8.71)	65.02 (10.02)
Benign PD	Stage I or II \leq 4 years	80	44	36	64.53 (11.29)	65.48 (12.02)	63.56 (10.37)
Malignant PD	\geq Stage III	29	19	10	63.55 (12.55)	60.16 (12.12)	70.00 (11.21)
Tremor-predominant PD	On the Unified PD Rating Scale, ratio of mean tremor score/mean PIGD score \geq 1.5	40	19	21	65.20 (9.98)	66.32 (10.44)	64.19 (9.70)
PIGD-predominant PD	On the Unified PD Rating Scale, ratio of mean tremor score/mean PIGD score \leq 1.2	23	13	10	68.30 (7.90)	64.00 (6.48)	73.90 (5.92)
Chronic hemiparkinsonism	Unilateral signs for \geq 4 years	22	10	12	64.05 (12.78)	63.20 (15.33)	64.75 (10.87)
Nonchronic hemiparkinsonism	All patients with bilateral PD	96	58	38	64.33 (10.93)	64.22 (11.30)	64.50 (10.49)

Table 2. UPSIT means and standard deviations for PD subtypes

Patient group	Mean UPSIT score (SD)		
	Whole group	Male	Female
Entire study population	21.15 (8.11)	19.37 (7.00)	23.58 (9.00)
Young-onset PD	22.11 (8.13)	22.63 (8.64)	18 (0)
Older-onset PD	21.07 (8.15)	18.93 (6.74)	23.69 (9.06)
Benign PD	22.51 (8.50)	20.00 (7.60)	25.64 (8.60)
Malignant PD	17.38 (6.29)	18.79 (6.30)	15.10 (4.84)
Tremor-predominant PD	23.43 (8.18)	20.32 (6.68)	26.24 (8.47)
PIGD-predominant PD	17.35 (6.00)	18.23 (6.67)	16.30 (6.53)
Chronic hemiparkinsonism	24.36 (8.48)	22.80 (9.03)	25.67 (8.11)
Nonchronic hemiparkinsonism	20.42 (7.94)	18.78 (6.51)	22.92 (9.27)

Eta was computed to determine the proportion of variance accounted for (ie, the effect size) due to the main factor within each of the statistical comparisons.

Results. The number and average age (\pm SD) of the subjects within each of the PD subtypes are indicated in table 1, and the mean (\pm SD) UPSIT scores are given in table 2. The overall mean UPSIT score for all subjects was 21.5 (SD = 8.15), a value within the range of UPSIT scores noted in PD patients tested in an earlier work.¹ Importantly, however, the mean UPSIT values differed significantly among several of the PD subtypes (table 2). Thus,

while still markedly abnormal, the UPSIT scores were higher in the benign than in the malignant PD patients and higher in the tremor-predominant than in the PIGD-predominant PD patients (respective comparisons: $F[1, 104] = 12.20, p = 0.001$; $F[1, 58] = 8.79, p = 0.004$). Large standard deviations were noted within each of these study groups, and the eta values for these two comparisons were small (respective values = 0.09 and 0.12), reflecting considerable unexplained variance in the test scores. No significant differences in UPSIT scores were found between (1) the young-onset PD and older-onset PD patients and (2) the chronic hemiparkinsonism patients and other PD patients, although the p values did approach significance (respective comparisons: $F[1, 115] = 2.93, p = 0.09$; $F[1, 113] = 3.39, p = 0.07$). In the latter analysis, the women evidenced higher UPSIT scores than did the men ($F[1, 113] = 4.24, p = 0.04$), a phenomenon that appeared to be marginally present, but not statistically significant, in most of the other groups.

To more closely explore the possibility of sex differences within the other test groups, we increased statistical power by performing, within each study group, one-way ANCOVA with gender as the sole group factor and age as the covariate. Women significantly outperformed the men in all cases, with the exception of the groups containing the smallest sample sizes (ie, the young-onset group [$n = 9$], the PIGD-predominant PD group [$n = 23$], and the

chronic hemiparkinsonism group ($n = 22$). The gender main effects were as follows: for older-onset PD, $F(1, 106) = 8.59, p = 0.004$; for benign PD, $F(1, 77) = 8.95, p = 0.004$; for tremor-predominant PD, $F(1, 37) = 5.48, p = 0.03$; and for nonchronic hemiparkinsonism, $F(1, 93) = 7.37, p = 0.008$. With the exception of the tremor-predominant PD versus the PIGD-predominant PD comparison, age proved to be a significant covariate in all of the analyses (all $ps < 0.001$).

Discussion. Previous studies of olfactory function in PD have demonstrated that olfactory impairment is present not only early in the disease process, but is bilateral² and independent of (1) the use of anti-PD medication,^{1,2} (2) a number of neurologic and neuropsychological measures influenced by PD, and (3) disease stage.³ The present study adds to these observations by showing that there are subtle differences in the ability to identify odors among recognizable PD subtypes, with forms associated with milder disability seeming to evidence slightly better UPSIT performance. These PD subtypes are based on clinical criteria related to, but distinct from, the Hoehn and Yahr scale, and may therefore account for the difference between the present study and earlier observations by Doty et al.,¹ in which there was no correlation between olfactory loss and Hoehn and Yahr stage or duration of PD. Several subtypes in our study (benign PD and chronic hemiparkinsonism), for example, are defined both by degree and duration of clinical signs while tremor-predominant PD patients included patients with Hoehn and Yahr stages I to III. In addition to enabling us to detect small differences in olfactory function between several groups, we feel that analyzing PD according to these subtypes is more consistent with the clinical heterogeneity of PD and variable rate of disease progression.

Of the nine study groups, the PIGD-predominant PD and malignant PD patients evidenced the lowest average UPSIT scores, scores which, in some cases, were four to seven points lower than those of other PD subtype study groups. While some of these individuals were represented in both of these subtypes, a number of the malignant PD patients had sufficient tremor to prevent them from being included in the PIGD PD group. Nevertheless, olfactory function was similarly impaired in these patients, who manifested a greater degree of functional disability than the tremor-predominant or benign PD patients.¹

The present data indicated that female PD patients tend to outperform male PD patients within each patient subgroup, although these effects were not large and, in a few instances, were not present (eg, the malignant PD and PIGD-predominant PD groups). Since the latter groups comprised relatively small samples, they might be present in

larger samples. Overall, these data imply that the gender difference noted in normal subjects⁴ is present in most PD patients—regardless of the subtype of disease.

The cause of olfactory loss in PD is unknown. The olfactory vector hypothesis implies that olfactory receptor cells are vulnerable to external agents (neurotoxins) that damage the olfactory system as they enter the brain (see reference 2). An alternative hypothesis suggests that olfactory dysfunction occurs as part of the degenerative process in PD, with degeneration of the olfactory bulb or other region occurring early in the course of PD. Circumstantial support for this concept includes recent findings of olfactory sparing in MPTP-induced parkinsonism⁵ and PSP⁶ in which dopaminergic neurons in the mesocorticolimbic system are not as affected as in PD. The present findings suggest that there are subtle differences in olfactory function among PD subtypes and support previous attempts to distinguish between the variable PD patient groups. However, additional clinicopathologic correlation will be necessary to determine whether or not distinctive pathophysiologic substrates underlie the different clinical expressions of PD.

Understanding the heterogeneity of PD is becoming increasingly important in an era when novel therapeutic interventions are designed to not only treat symptoms, but also to alter the natural history of PD. Future studies need to determine if tests of olfactory function are of value in helping to predict the course of PD.

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