Olfactory dysfunction in parkinsonism: A general deficit unrelated to neurologic signs, disease stage, or disease duration

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Article abstract—To explore the nature of the olfactory dysfunction associated with Parkinson's disease (PD), 81 PD patients who scored well on a cognitive screening test were administered the 40-odorant University of Pennsylvania Smell Identification Test; 38 were additionally given a forced-choice phenylethyl alcohol odor detection threshold test. Clinical ratings of 11 neurologic symptoms (three bilateral) were obtained at the time of testing, and odor identification was retested in 24 patients at intervals ranging from 5 to 39 months. Relative to matched controls, the PD patients exhibited consistent and marked decrements on both types of olfactory tests (p < 0.0001). The odor identification deficit was not restricted to any subset of odorants and did not evidence longitudinal change. A factor analysis of the intercorrelations among the variables yielded six easily interpretable factors: general motor, oral motor, olfactory function, cognitive function, tremor, and gender. Olfactory test scores were independent of all other measures, including disease stage and duration. Seventy-two percent of the PD patients were unaware of a smell disorder before testing; those who were aware had significantly lower test scores. A statistical comparison of PD patients' olfactory test scores to those obtained from Alzheimer's disease patients found the olfactory disorders of these diseases to be indistinguishable. The data support the hypothesis that the olfactory deficit of PD is a general and stable one which likely occurs early in the disease process.

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The sense of smell is a major determinant of the flavor and palatability of foods and beverages, and serves as an early warning system for the detection of smoke, dangerous fumes, spoiled food, and polluted environments. It has recently been suggested that disorders of this primary sensory system may have etiologic significance in some dementia-related brain diseases, since (1) olfactory dysfunction is commonly observed in patients with Korsakoff's psychosis (KP), Parkinson's disease (PD), and dementia of the Alzheimer type (DAT). (2) olfactory receptor cells are capable of rapidly transporting a variety of agents, including viruses, from the nasal cavity into the CNS, and (3) major if not maximal neuropathologic changes are observed in the cortical brain regions of DAT patients which receive direct olfactory bulb projections.

To date, the breadth of the olfactory dysfunction present in PD has not been explored, inasmuch as responses to only a few odorants have been evaluated and standardized tests have not been administered. Furthermore, few patients have been tested longitudinally and it is unknown whether the olfactory deficit is correlated with quantitative ratings of specific neurologic symptoms. Several studies suggest that olfactory deficits of parkinsonism are unrelated to factors such as disease stage and duration, although formal exploration of correlations among these indices has not been performed using statistical procedures such as factor analysis or multidimensional scaling. The lack of a relationship between the degree of olfactory dysfunction and such variables as the stage of the disease, the duration of the disease, or the severity of neurologic symptoms would lend support to the hypothesis that the perceptual disorder may be nonprogressive and present early in the disease process.

The present study had several main goals: first, to establish—using well-validated standardized tests of smell function—the nature, frequency, and severity of the olfactory deficits in a large sample of patients with PD; second, to determine if PD-related decrements in odor identification ability occur for a wide range of odorants or for only a limited number; third, to determine if such olfactory dysfunction progresses over test-retest intervals ranging from 5 to 39 months; and fourth, to assess, using factor analysis and multivariate analysis of variance, the relationship between the olfactory test scores of PD patients and such variables as age, gender, the stage of the disease (as measured by the Hoehn and Yahr scale), the duration of the disease, ratings of the degree of neurologic symptoms, previous...
thalamocortical cholinergic output). The number of patients at each of the Hoehn and Yahr stages (see "Assessment of neurologic function," below) was as follows: I = 22, II = 21, III = 25, IV = 38, and V = 67. Two of these patients had previously undergone ventrolateral thalamic surgery for treatment of severe tremor (12 unilateral, 26 patients), other dopamine agonists (eg, Symmetrel; 16 patients), the remaining patient was taking Parlodel alone. Twenty-four patients (14 men and 10 women; respective mean ages ± SD, 65.7 ± 10.1 and 67.2 ± 9.2 years). The number of patients at each of the Hoehn and Yahr stages (see "Assessment of neurologic function," below) was as follows: I = 22, II = 21, III = 25, IV = 38, and V = 67. Two of these patients had previously undergone ventrolateral thalamic surgery for treatment of severe tremor (12 unilateral, 26 patients), other dopamine agonists (eg, Symmetrel; 16 patients), the remaining patient was taking Parlodel alone.

Methods. Parkinson's disease study group. A total of 93 PD patients were initially evaluated. However, since 12 of these individuals failed to achieve a score of 35 or higher on our cognitive screening test (see "Assessment of cognitive function," below), the final study group consisted of 81 subjects (46 men and 35 women; respective mean ages ± SD, 65.7 ± 10.1 and 67.2 ± 9.8 years). The number of patients at each of the Hoehn and Yahr stages (see "Assessment of neurologic function," below) was as follows: I = 22, II = 21, III = 25, IV = 38, and V = 67. Two of these patients had previously undergone ventrolateral thalamic surgery for treatment of severe tremor (12 unilateral, 26 patients), other dopamine agonists (eg, Symmetrel; 16 patients), the remaining patient was taking Parlodel alone. Twenty-four patients (14 men and 10 women; respective mean ages ± SD, 65.7 ± 10.1 and 67.2 ± 9.8 years). The number of patients at each of the Hoehn and Yahr stages (see "Assessment of neurologic function," below) was as follows: I = 22, II = 21, III = 25, IV = 38, and V = 67. Two of these patients had previously undergone ventrolateral thalamic surgery for treatment of severe tremor (12 unilateral, 26 patients), other dopamine agonists (eg, Symmetrel; 16 patients), the remaining patient was taking Parlodel alone.

Matched control subjects. Control subjects were individually matched to each PD patient on the basis of age, gender, smoking behavior, and ethnic background. Those serving as controls for the odor identification testing were, within the constraints of the matching variables, randomly selected from a computer-based registry of over 5,000 free-living healthy individuals from whom odor identification test data were available. Those serving as controls for the threshold studies were similarly obtained from a parent group of approximately 500 normal subjects to whom the threshold test had been administered. The matches were exact for the variables of gender, smoking behavior, and ethnic background. For age, exact matching occurred in 94% of the cases; the remaining matches were within ±1 year. All controls consisted of persons with no major diseases or illnesses known to be associated with olfactory dysfunction.

Alzheimer's disease patient comparison group. The odor identification testing data from 25 patients with DAT (11 men and 14 women; respective mean ages, 66.36 ± 9.02 and 71.07 ± 7.40) and phenylethyl alcohol threshold data from 15 patients with DAT (6 men and 9 women; respective mean ages, 65.00 ± 11.71 and 71.22 ± 7.01) were compared statistically to the analogous data generated by the PD patients of this study. The DAT patients had scored ≥35 on the cognitive screening test and satisfied the NINCDS-ADRDA criteria for diagnosis of presumptive Alzheimer's disease. Details of the DAT subjects and testing are described elsewhere.

Odor identification testing. The University of Pennsylvania Smell Identification Test (UPSIT; commercially available as the Smell Identification Test™, Sensonics, Inc., Haddonfield, NJ) is a standardized microencapsulated odor test consisting of four booklets containing 10 odors apiece, one odorant per page. The stimuli are embedded in 10- to 50-μm diameter microcapsules fixed and positioned on brown strips at the bottom of each page. A multiple-choice question with four response alternatives for each item is located above each "scratch and sniff" odorized strip. The subject is required to answer one of the four alternatives, even if no smell is perceived (ie, the test is forced-choice). The stimuli, which are described in detail elsewhere, were selected on the basis of a number of criteria: (1) that they span a wide range of qualitative odor classes, and include both pleasant and unpleasant odors; (2) that they comprise both single and multiple component odors (anethole is an example of the former, chocolate extract of the latter), given the possibility that the olfactory system codes information on the basis of a multiple profile-multiple receptor site process; (3) that most be undetectable via intranasal trigeminal afferents; (4) that they be familiar and readily identifiable by many types of people when presented in a forced-choice, multiple-alternative format; and (5) that they produce no untoward reactions or discomfort in the patient, as determined from studies of their perceived irritability, intensity, pleasantness, and other psychological attributes. The UPSIT is highly reliable (short-term test-retest r = 0.95) and sensitive to a variety of olfactory deficits, including those associated with aging, smoking, cystic fibrosis, KP, and Hallmann's syndrome. Interestingly, the scores on this test correlate (r = 0.87) with the lumbar CSP levels of a major metabolite of norepinephrine (3-methoxy-4-hydroxyphenylacetic acid (MHPG)) in CSF.

The UPSIT was individually administered to each patient by a trained technician, who released the microencapsulated stimuli, placed them under the patient's nares, and filled in the answer form following the patient's response. In addition to making a forced-choice response to the presentation of each odorant, 41 of the patients were asked to report whether or not an odor sensation was present immediately after smelling the stimulus, and a yes or no was recorded. This additional information was obtained because a number of the initial PD patients indicated that some unidentifiable smell was present on most items.

Odor detection threshold testing. A single staircase, forced-choice odor detection threshold test was used to estimate basal detection sensitivity to phenylethyl alcohol (PEA) (Gold label grade, Aldrich Chemical Co., Milwaukee, WI), an odorant with comparatively little intranasal trigeminal activity. The stimuli consisted of a half-log step concentration series of PEA (−7.50 to −1.00 log vol/vol) dissolved in propylene glycol (Fisher Scientific, P-355). A trial consisted of the random presentation of two 120-ml sniff bottles in rapid succession. One bottle contained 20 ml of a given concentration of the odorant dissolved in the diluent, whereas the other
bottle contained 20 ml of the diluent alone. The bottles were opened and immediately placed over the subject’s nose in a standardized manner described and illustrated elsewhere.30,31 The subject’s task was to report which of the two stimuli evoked the stronger sensation. If no sensations were perceived or if no difference was apparent between the bottles, the subject was still required to choose one or the other bottle. No feedback was given as to the correctness of the responses. The staircase was begun at the −6.00 log concentration step and was moved upward in full log steps until correct detection occurred on four consecutive trials at a given concentration. If a miss occurred on any trial before this time, the concentration was increased by one log unit. When four correct trials occurred at a given concentration, the staircase was reversed and subsequently moved in 0.5 log steps, with either one or two trials at each step (ie, if the first trial missed, the second one was not given, and the staircase was moved to the next higher concentration). The geometric mean of the last four staircase reversal points of a total of seven was used as the measure of sensitivity. Since PEA detection thresholds correlate well with those of many other odors (including acetic acid, diallyl sulfide, camphor, phenol, cyclopentadecanolide, skatole, and isovaleric acid),32 lack of sensitivity to this compound likely reflects general olfactory insensitivity.

Assessment of cognitive function. The Picture Identification Test (PIT), a 40-item forced-choice test of cognitive function, was administered to the PD patients.33 Although designed specifically to control for nonolfactory aspects of the UPSIT, this test correlates with a number of neuropsychological measures (eg, in a study of 58 parkinsonians,34 r = 0.58 with WAIS-R verbal subtest total35 and r = 0.70 with the General Information subtest of the RANIT Memory Test36; both p values < 0.001) and is clearly sensitive to dementia-related cognitive deficits. The PIT is identical in content and format to the UPSIT except that, instead of odorants, line drawings representing each of the 40 odorants used on the UPSIT serve as stimulus items. The pictures of this test (which was always administered after the olfactory test) are located on 2-× 2-inch cardboard squares. Each square is attached to the underlying page on its left side, so that it can be turned to reveal a multiple choice question on the backside of the cardboard square analogous to one of the multiple choice questions of the UPSIT (eg, one item of the test reads, “This picture looks most like: [a] gasoline, [b] pizza, [c] peanuts, or [d] lilac.” The picture for this item is of a pizza pie). The test items and choices are arranged in the same order as those in the UPSIT. This format ensures that an amount of time similar to that occurring between smelling an odorant and generating a response on the UPSIT intervenes between the exposure to the picture and the generation of a response. Subjects who score less than 35 out of 40 on the PIT are assumed to have some type of cognitive or linguistic problem which may confound interpretation of the olfactory test scores. As in the case of the UPSIT, this test was administered by a trained technician and the subject was not required to perform any manual test-related tasks.

Assessment of neurologic function. Neurologic function at the time of testing was assessed using five-category clinical rating scales of the following behaviors (scores range from 0 to 4): tremor (left and right), rigidity (left and right), alternating movements (left and right), bradykinesia, masking, posture, voice, speech, swallowing, and autonomic signs. A nine-category rating scale (ranging from 0 to 8) was used to assess balance, gait, and turning.37 Additionally, each patient was scored on general functional status using the Hoehn and Yahr scale37 whose stages are defined as follows: stage I—unilateral involvement with typically minimal or no functional impairment; stage II—bilateral involvement without impairment of balance; stage III—first signs of impaired righting reflexes, mild to moderate disability; stage IV—severe incapacitation, unassisted walking and standing possible but marked difficulties with balance; stage V—confined to bed or wheelchair unless aided. The time since symptom onset (ie, duration of the disease) in months was also determined.

Results. Odor identification. The average UPSIT test scores of the 81 PD patients differed markedly and consistently from those of their matched normal controls (figure 1A), as indicated by a significant main effect of subject group in a subject group X gender two-way analysis of variance (ANOVA) (F = 174.28, df = 1/79, p < 0.0001). Neither the gender main effect nor the subject group X gender interaction was significant (respective F values = 0.02 and 0.11, df = 1/79, p > 0.70). The deficit was consistent: 73 of the 81 PD patients had UPSIT scores falling below those of their matched normal controls (90.1%), two (2.5%) had UPSIT scores equal to their controls, and only six (7.4%) had UPSIT scores greater than their controls. The latter subjects were among the oldest in the group and were in an age range where the olfactory function of a significant proportion of the normal population is poor27 (mean age, 77.2 ± 7.36 years). Thirty-one of the PD patients (38.3%) appeared to have major olfactory deficits (based upon the proportion of persons correctly answering an item) across the 40 items of the test was similar to that of the matched controls. For example, a Spearman
rank order correlation computed across odor items yielded an $r = 0.75$ (a $p$ value was not established, since the items over which the correlation was computed are not independent).

To determine statistically within the PD group whether the factors of medication type, disease stage, or thalamic surgery influenced the UPSIT scores, the data (excluding those from the patient taking only Parlodol) were subjected to a medication type (Sinemet alone, Sinemet + anticholinergic agents, Sinemet + other dopamine agonists) by disease stage (I to V) by surgical group (no surgery, surgery) analysis of covariance (ANCOVA) using age as the covariate. Neither the covariate, the main factors, nor the interactions proved significant: $F$ (age) = 0.28, $df = 1/54$, $p = 0.60$; $F$ (medication $[m]$) = 0.08, $df = 3/54$, $p = 0.97$; $F$ (disease stage $[ds]$) = 0.90, $df = 4/54$, $p = 0.47$; $F$ (surgical group $[sg]$) = 0.10, $df = 1/54$, $p = 0.75$; $F$ ($m \times ds$) = 0.72, $df = 9/54$, $p = 0.69$; $F$ ($m \times sg$) = 1.30, $df = 3/54$, $p = 0.28$; $F$ ($ds \times sg$) = 0.78, $df = 3/54$, $p = 0.51$; $F$ ($m \times ds \times sg$) = 1.31, $df = 1/54$, $p = 0.26$.

To establish whether disease duration influenced the UPSIT scores, a partial correlation between disease duration and UPSIT scores was computed which controlled out the effects of patient age at the time of testing. No significant relationship was observed ($r = 0.08$, $df = 78$, $p = 0.47$), as graphically depicted by the flat regression line relating disease duration to UPSIT scores (figure 2). The finding of no association between the olfactory test scores and the disease duration or progression is also supported by the longitudinal testing, which revealed no significant average change from the first to the second test (mean UPSIT scores $\pm SD$ for first and second test administrations, $21.58 \pm 7.30$ and $19.42 \pm 7.48$, respectively; $t = 1.63$, $df = 23$, $p = 0.12$), and (2) no significant correlation between the length of the intertest intervals and the differences between the test scores on the two test occasions (Pearson $r = 0.15$, $df = 22$, $p > 0.20$). As would be expected, a positive correlation was present between the UPSIT scores on the two test administrations, indicating that the position of a given patient's test score was reasonably stable relative to those of the group (Pearson $r = 0.61$, $df = 22$, $p < 0.001$).

It is interesting that all but one of the 41 patients who were asked whether or not an odor was present on each UPSIT item answered affirmatively on most items, even when identification could not be made. Indeed, of these 40 patients, 29 (72.5%) reported that they perceived some type of an odor on all 40 items, seven (17.5%) reported perceiving an odor on 39 of the items, and four (10.0%) reported perceiving an odor on 35 to 38 of the items. The sole person who indicated that most items produced no odor had reported to us before testing that he suffered from a smell problem. His UPSIT score proved to be 14, a value suggestive of total or near-total anosmia.

Odor detection. Overall, the PD patients evidenced higher average odor detection threshold values (ie, exhibited lower sensitivity) than did their matched controls (figure 1B; group factor $F$ in subject group by gender ANOVA = 26.19, $df = 1/36$, $p < 0.0001$). As in the case of the odor identification task, no differences were observed between the olfactory measures of the male and female subjects: $F$ (gender) = 1.39, $df = 1/36$, $p = 0.25$; $F$ (gender $\times$ group) = 3.63, $df = 1/36$, $p = 0.065$. Relative to their controls, 29 (76%) of the 38 PD patients evidenced higher detection threshold values (ie, lower sensitivity) and one evidenced an equivalent value (2.6%). All but two (aged 57 and 58 years) of the eight subjects who performed better than their matched controls were within the age range where the detection threshold of the control is expected to be high (ages = 64, 69, 73, 73, 77, and 88 years).24

In a manner analogous to what was observed for the odor identification test scores, an ANCOVA (age = covariate) found no influence of the factors of medication type, disease stage, or thalamic surgery upon the threshold measure: $F$ (age) = 0.02, $df = 1/21$, $p = 0.89$; $F$ (medication $[m]$) = 0.56, $df = 3/21$, $p = 0.65$; $F$ (disease stage $[ds]$) = 0.84, $df = 4/21$, $p = 0.52$; $F$ (surgical group $[sg]$) = 1.16, $df = 1/21$, $p = 0.29$; $F$ ($m \times ds$) = 0.43, $df = 4/21$, $p = 0.79$; $F$ ($m \times sg$) = 0.30, $df = 1/21$, $p = 0.59$; $F$ ($ds \times sg$) = 0.31, $df = 2/21$, $p = 0.74$.

To determine whether detection threshold values were related to disease duration, we computed a partial correlation coefficient between these variables which removed the effects of patient age from the relationship. As was the case with UPSIT scores, no significant relationship was observed ($r = -0.16$, $df = 35$, $p = 0.34$; figure 3).

Relationship between UPSIT and threshold values. A Pearson correlation coefficient was computed between the UPSIT scores and the PEA detection threshold values for the 38 subjects who had taken both types of tests. This coefficient was of moderate size ($r = -0.52$, $p < 0.001$) and of similar magnitude to that observed between these variables in an earlier study of 25 patients with Alzheimer's disease (Spearman $r = -0.45$).11

Relationships among sensory measures and ratings
of neurologic function. To determine the nature of the relationships among the olfactory, cognitive, and neurologic measures of this study, we subjected the matrix of their intercorrelations to a principal components factor analysis with varimax rotation.38 Six factors were extracted (eigenvalues [EVs] > 1.00) which accounted for 73.4% of the total variance. As can be seen in the table, this analysis strongly supports the notion that the olfactory measures are independent of the neurologic ratings, as both the UPSIT and detection threshold measures loaded heavily on a single factor (Factor III) which received no strong loadings from any of the other variables. The factors of this analysis were easily interpretable. Factor I (EV = 6.39) is clearly a general motor function factor, being loaded most heavily with the measures of rigidity (left and right), alternating movements (left and right), masking, bradykinesia, Hoehn and Yahr disease stage, and balance, gait, and turning. Factor II (EV = 2.93) had its strongest loadings from the orally-related measures of voice, speech, and swallowing, as well as from the measures of disease duration, thalamic surgery, and Hoehn and Yahr disease stage. Factor III (EV = 2.01) is an olfactory function factor, whereas Factor IV (EV = 1.70) appears to reflect cognitive function, being loaded almost exclusively by the PIT. Factor V (EV = 1.26) is a tremor factor, receiving no meaningful loadings from any other variable. This factor is of particular theoretical interest, since it suggests that tremor is independent of the other neurologic measures. Factor VI (EV = 1.12) is a gender factor, having this variable as its only main loading.

Patient's awareness of the olfactory dysfunction. Each PD patient was asked the following question before formal testing: "Do you suffer from any smell or taste problems?" Twenty-three of the 81 subjects (28%; 11 men and 12 women) answered this question affirmatively. In order to ascertain whether individuals reporting a smell problem had lower UPSIT scores than those who did not, we subjected the UPSIT data to a two-way ANOVA, with the factors of problem report (yes, no) and gender. Those who reported a problem had significantly lower UPSIT scores than those who did not: respective mean UPSIT values ± SD, 17.56 ± 6.56 versus 21.55 ± 7.27; F (problem report) = 5.35, df = 1/77, p = 0.023; F (gender) = 0.60, df = 1/77, p = 0.44; F (problem report × gender) = 2.90, df = 1/77, p = 0.09. A similar analysis of the PIT scores did not reveal any differences between these two groups: respective mean PIT values, 39.39 ± 1.03 and 39.31 ± 1.05; F (problem report) = 0.22, df = 1/77, p = 0.64; F (gender) = 0.06, df = 1/77, p = 0.80; F (problem report × gender) = 3.36, df = 1/77, p = 0.07.

Comparison of PD and DAT olfactory function. To compare the UPSIT test scores of the PD patients to those of the DAT patients,11 we first matched each PD patient to a DAT patient on the basis of ethnic background, age, gender, and smoking habits, and subjected the UPSIT data to an ANCOVA with disease type as the factor and PIT scores as the covariate (n = 25 pairs). An equivalent analysis was performed on the odor detection threshold values (n = 15 pairs). The covariate was necessary because many of the PIT scores of DAT patients fell below those of the PD patients within the 35 to 40 PIT score range (eg, whereas 16 of the PD patients scored 40, only six of the DAT patients did so), and therefore it was not possible to match directly a number of the subjects on this important variable.

The ANCOVA revealed no significant difference between the UPSIT test scores of the DAT and PD groups, although the PIT covariate was highly significant, indicating that even within the PIT range from 35 to 40 the DAT patients perform more poorly than the PD patients: F (disease type) = 0.54, df = 1/47, p = 0.47; F (PIT) = 7.48, df = 1/47, p = 0.009. A similar result occurred for the analysis of the detection threshold data, although the covariate did not reach significance at the 0.05 level, likely because of the smaller sample size: F (disease type) = 0.25, df = 1/27, p = 0.77; F (PIT) = 3.12, df = 1/27, p = 0.089.

Discussion. The present study demonstrates that a large majority of patients with parkinsonism have olfactory dysfunction. When detection threshold measures were employed, approximately 75% of the patients evidenced less sensitivity than their matched controls, and when odor identification testing was employed, over 90% of the patients evidenced lower test scores than their matched controls. This degree of dysfunction is greater than that noted in earlier studies, likely due, in part, to the sensitivity of the present measures to olfactory dysfunction and the use of a full complement of individually matched control subjects. Thus, in 1980 Korten and Meulstee40 reported that 40 of 80 PD patients under their care were "unable to smell adequately," although formal sensory testing was not performed. Using quantitative testing, Anasari and Johnson8 found that 10 of 22 (45%) male parkinsonians had elevated detection thresholds for the odor of amyl.
An important observation of the present work is the finding that the olfactory dysfunction of parkinsonism is a general one, not being confined to any particular subset of odorants. The present data suggest, however, that the olfactory deficit is rarely total anosmia, in that only 13% of the 38 patients who received detection threshold testing were unable to detect the highest odorant concentration presented, a figure in close correspondence to a 17% anosmia rate reported earlier.10

Furthermore, all but one of the 41 PD patients who were asked whether or not an odor was present on each threshold test item answered affirmatively to 35 or more of the 41 odorants. The three factors of interest were labeled by those authors as Gross Motor Efficiency, Speech and Facial Motor, and Tremor, which correspond to Factors I, II, and V of the present study, respectively. Their fourth factor, Fine Motor, was probably not observed in the present study because we did not examine analogous measures of fine motor activity. The observation that tremor is independent of other measures of motoric function has additional factor analytic support in the literature,43,44 and provides credence to the contention of Kuypers45 that the motor system may be composed of two major subdivisions.

Table. Varimax rotated factor matrix for primary variables of the study*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor I</th>
<th>Factor II</th>
<th>Factor III</th>
<th>Factor IV</th>
<th>Factor V</th>
<th>Factor VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternating movements (L)</td>
<td>0.848</td>
<td>0.019</td>
<td>-0.212</td>
<td>0.175</td>
<td>-0.075</td>
<td>-0.120</td>
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<tr>
<td>Alternating movements (R)</td>
<td>0.860</td>
<td>-0.036</td>
<td>0.293</td>
<td>-0.300</td>
<td>0.013</td>
<td>-0.036</td>
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<tr>
<td>Rigidity (L)</td>
<td>0.768</td>
<td>-0.113</td>
<td>0.198</td>
<td>-0.166</td>
<td>0.054</td>
<td>-0.183</td>
</tr>
<tr>
<td>Rigidity (R)</td>
<td>0.540</td>
<td>0.502</td>
<td>-0.018</td>
<td>0.381</td>
<td>0.110</td>
<td>0.308</td>
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<tr>
<td>Masking</td>
<td>0.701</td>
<td>0.410</td>
<td>0.029</td>
<td>0.342</td>
<td>0.065</td>
<td>0.141</td>
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<tr>
<td>Bradykinesia</td>
<td>0.640</td>
<td>0.334</td>
<td>0.029</td>
<td>0.381</td>
<td>0.185</td>
<td>0.336</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>0.635</td>
<td>0.556</td>
<td>0.109</td>
<td>0.252</td>
<td>0.254</td>
<td>0.153</td>
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<tr>
<td>Balance, gait &amp; turning</td>
<td>0.494</td>
<td>0.277</td>
<td>0.183</td>
<td>0.223</td>
<td>0.015</td>
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<td>Voice</td>
<td>0.137</td>
<td>0.865</td>
<td>0.075</td>
<td>0.040</td>
<td>0.002</td>
<td>0.016</td>
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<tr>
<td>Speech</td>
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<td>0.837</td>
<td>-0.034</td>
<td>0.042</td>
<td>-0.138</td>
<td>-0.041</td>
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<tr>
<td>Time since onset</td>
<td>0.131</td>
<td>0.785</td>
<td>-0.143</td>
<td>-0.065</td>
<td>0.065</td>
<td>0.048</td>
</tr>
<tr>
<td>Thalamic operation</td>
<td>0.043</td>
<td>0.703</td>
<td>0.147</td>
<td>0.150</td>
<td>0.038</td>
<td>-0.265</td>
</tr>
<tr>
<td>Swallow</td>
<td>0.069</td>
<td>0.566</td>
<td>-0.386</td>
<td>-0.148</td>
<td>0.020</td>
<td>0.317</td>
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<tr>
<td>Autonomic signs</td>
<td>0.055</td>
<td>0.469</td>
<td>0.399</td>
<td>0.433</td>
<td>0.153</td>
<td>0.040</td>
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<tr>
<td>Olfactory threshold</td>
<td>0.076</td>
<td>-0.086</td>
<td>0.857</td>
<td>-0.157</td>
<td>0.026</td>
<td>0.322</td>
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<tr>
<td>UPSIT</td>
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<td>-0.211</td>
<td>0.304</td>
<td>0.043</td>
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<td>PIT</td>
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<td>0.017</td>
<td>-0.033</td>
<td>-0.322</td>
<td>-0.058</td>
<td>0.146</td>
</tr>
<tr>
<td>Tremor (L)</td>
<td>-0.031</td>
<td>0.041</td>
<td>-0.086</td>
<td>-0.030</td>
<td>0.854</td>
<td>0.146</td>
</tr>
<tr>
<td>Tremor (R)</td>
<td>0.066</td>
<td>-0.036</td>
<td>-0.055</td>
<td>0.004</td>
<td>0.811</td>
<td>-0.059</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.097</td>
<td>-0.101</td>
<td>0.137</td>
<td>0.060</td>
<td>0.071</td>
<td>0.821</td>
</tr>
</tbody>
</table>

* Based on 81 patients (except for PEA threshold measures, which are based on 38 patients).
R Right.
L Left.

Loadings > 0.50 are boxed for emphasis.

acetate relative to controls, and Ward et al10 reported that 49% of 72 parkinsonians were unable to identify the odor of fresh ground coffee, and 35% the odor of cinnamon Lifesaver candy, even though written response alternatives were presented.

The results of the factor analysis unequivocally indicate that the olfactory dysfunction of PD is independent of gender, disease stage, medication type, thalamic surgery, and ratings of neurologic function. Thus, the UPSIT and olfactory threshold measures loaded on only one factor of the analysis—a factor which received no strong loadings from any of the other variables. It is interesting that the neurologic symptom factors extracted in the analysis are strikingly similar to three of the four interpretable factors extracted by Petrinovich and Hardyck42 in a study of 40 parkinsonians who had undergone ventrolateral thalamic nucleus and globus pallidus surgery. The three factors of interest were labeled by those authors as Gross Motor Efficiency, Speech and Facial Motor, and Tremor, which correspond to Factors I, II, and V of the present study, respectively. Their fourth factor, Fine Motor, was probably not observed in the present study because we did not examine analogous measures of fine motor activity. The observation that tremor is independent of other measures of motoric function has additional factor analytic support in the literature,43,44 and provides credence to the contention of Kuypers45 that the motor system may be composed of two major subdivisions.
Our finding of equivalent degrees of odor identification and detection dysfunction in patients with Alzheimer's disease and parkinsonism is of particular significance, in that it suggests the possibility that the underlying physiologic mechanism may be the same. It is noteworthy that the well-established neuropathologic indicators of DAT (ie, neuritic plaques and neurofibrillary tangles) are estimated to be present in 20 to 40% of PD patients, although in most instances the presence of high levels of neuritic plaques and neurofibrillary tangles occur only in PD patients who evidence marked dementia. Recent work by our group demonstrates that olfactory dysfunction is found in both demented and nondemented PD patients, suggesting that dementia (and by inference the presence of high numbers of plaques and tangles) is probably not the primary basis of the olfactory problem.

The basis of the olfactory dysfunction of parkinsonism is unknown. As with other features of this disease, the olfactory deficit appears to have a low concordance rate in monozygotic twins, suggesting that it is not an inherited trait. Assuming this to be the case, several hypotheses can be entertained to explain the olfactory dysfunction of PD. First, the olfactory pathways (including the receptors) could be impaired directly by environmental agents etiologically related to PD. It is well established that olfactory receptor cells evidence atypically active transport mechanisms and serve as a primary means of entry for viruses and certain environmental agents into the CNS. Second, it is conceivable that the underlying disease process decreases the resistance of the olfactory system to viral or environmental agents which cause destruction of the olfactory pathways, but are otherwise unrelated to the PD etiology (of course, such a decrease in resistance could also accompany etiologic agents). It is noteworthy in this context that the most common cause of permanent smell loss in patients evaluated at our Center is influenza or upper respiratory infections, and that the average age for such loss is in the early 50s. Third, it is conceivable that sectors of the olfactory system are predisposed to destruction from degenerative or neuropathologic processes, including ischemia, which relate to an underlying disease process associated with PD. Finally, it is possible that decrements or alterations in CNS transmitter levels or receptors account for the olfactory dysfunction. Several lines of evidence suggest, however, that a simple relationship between brain levels of catecholamines and the olfactory dysfunction is unlikely. First, Ward et al. have noted clear-cut olfactory dysfunction in both medicated and unmedicated parkinsonians. Second, we and others have uniformly failed to find an association between the type or combination of drug therapy and the degree of olfactory dysfunction. Third, only PD patients who evidence dementia have lowered norepinephrine or MHPG levels in the locus ceruleus, even though nondemented PD patients also evidence olfactory dysfunction. Fourth, elimination or major reduction of the olfactory bulb norepinephrine in rats by localized injection of 6-hydroxydopamine does not alter basal olfactory sensitivity, although some other aspects of olfactory function (eg, preferences) may be affected. Interestingly, however, the olfactory function of rats who have not sustained damage to central catecholaminergic systems can be altered in a dose-related fashion by d-amphetamine, a drug known to have a major influence on D-2 dopaminergic receptors.

Although the present data indicate that olfactory dysfunction is markedly altered in PD, it should be noted that alterations in other sensory systems have been described. Thus, it is now generally recognized that some parkinsonians exhibit visual impairments, including problems in judging the visual vertical, the postural vertical, and the visual horizontal. PD patients also exhibit abnormalities in the electro-oculogram and in both auditory and visual evoked potentials. Recently, Bulens et al. reported that over one-half of the 39 patients they evaluated for contrast sensitivity had loss in one or both eyes. The degree to which these various sensory phenomena represent common underlying pathologies requires further study.

Whatever the basis of the olfactory anomalies associated with PD or their association with other perceptual disorders, the present data indicate that the olfactory deficits are present in most PD patients, reflect severe decrements in the ability to both detect and identify odorants, are distributed across a wide range of odorant types, evidence no progression with time, are unrelated to current medications or prior thalamic surgical intervention, and are independent of such factors as patient age, patient gender, disease stage, disease duration, and measures of numerous symptoms associated with PD. Furthermore, this research suggests that the olfactory disorder of PD may be equivalent to that observed in DAT, and therefore dependent upon a common neuropathologic substrate.

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References

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