Identifying the Pattern of Olfactory Deficits in Parkinson Disease Using the Brief Smell Identification Test

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Background: Selective olfactory deficits occur in 70% to 90% of patients with Parkinson disease, independent of disease severity and duration. Olfactory testing may be a useful diagnostic aid for Parkinson disease, but the types of odors most commonly affected need to be identified.

Objective: To determine the pattern and types of odors affected in Parkinson disease by means of the University of Pennsylvania 12-item Brief Smell Identification Test (B-SIT; Sensonics, Inc, Haddon Heights, NJ).

Design: Testing patients with Parkinson disease and control subjects in 5 movement disorder clinics.

Participants: Forty-nine nondemented patients with Parkinson disease and 52 age- and sex-matched controls.

Main Outcome Measures: Normal or abnormal olfactory function was determined in each subject according to predetermined age and sex norms. Predictive statistics and discriminant function analyses were performed to determine the pattern and types of odors best discriminating patients from controls.

Results: Abnormal olfactory function was present in 40 (82%) of patients compared with 12 (23%) of controls. The B-SIT score was unaffected by smoking behavior, disease duration, or severity. The sensitivity of the B-SIT for Parkinson disease was 0.82, with a specificity and predictive value of 0.82 and 0.77, respectively. Only 5 of the 12 B-SIT odors (gasoline, banana, pineapple, smoke, and cinnamon) were required to adequately discriminate patients with Parkinson disease from controls.

Conclusions: With the use of the B-SIT, 5 specific odors appear primarily affected in patients with Parkinson disease. Significantly, the ability of patients to detect some odors was unimpaired compared with that of controls. Better diagnostic aids could be developed on the basis of the selective pattern of hyposmia observed in Parkinson disease.

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Seventy percent to 90% of patients with Parkinson disease (PD) have olfactory deficits independent of disease severity and duration. Olfactory dysfunction is thus the second most common feature of this disorder, following rigidity and akinesia, and is equal to the occurrence of tremor. The identification of a common and early hyposmia in PD has led to an interest in olfactory testing as a diagnostic aid. Hyposmia in PD is generally bilateral, even in early hemiparkinsonism, and remains unaffected by parkinsonian medication. Tests of olfaction are commonly based on total olfactory performance after exposure to multiple odors. Although patients with PD perform significantly more poorly with the use of this criterion, more detailed analyses have shown that the olfactory deficit in PD is not general for all odors. Thus, the ability to detect some odors remains unchanged, while the ability to identify other odors is significantly impaired in patients with PD compared with control subjects. For example, the ability to identify the odors of orange and clove is reportedly preserved in PD; in contrast, the ability to identify the odors of wintergreen, pizza, pineapple, anise seed, and licorice is highly compromised. The selectivity of odor detection demonstrated by different olfactory tests suggests a distinct and identifiable pattern of hyposmia in PD. Characterization of this pattern may allow the development of more accurate diagnostic olfactory tests, compared with the assessment of general olfactory function.

The English-language version of the 40-item University of Pennsylvania Smell Identification Test (UPSIT) is used in some clinics to investigate olfactory dys-

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function in PD, although a few of its items or responses are unfamiliar to non–North Americans (eg, root beer). The 12-item Brief Smell Identification Test (B-SIT or Cross-Cultural Smell Identification Test; Sensonics, Inc, Haddon Heights, NJ) was developed by the same group as an abridged test of olfaction that is valid in most cross-cultural settings. We used the B-SIT to identify a selective pattern of olfactory deficits discriminating patients with PD from controls.

### METHODS

#### RECRUITMENT

Patients were recruited into a multisite study called “Diagnosing Early Dopamine Cell Loss” in Sydney, Australia. Informed consent for participation was obtained from each subject, and the study was approved by the human research ethics committees at each site. The diagnosis of PD becomes easier over time, and thus potential diagnostic aids are less important in advanced disease. Therefore, recruitment concentrated on patients with early disease, people presenting for initial neurologic consultation, or people with a family history of PD. Patients with PD were recruited either within specialist movement disorders clinics or via advertising in patient support group publications. Age-matched control subjects were recruited via advertising in the general press.

#### CLINICAL TESTING AND SCREENING

All subjects were assessed by a neurologist specializing in movement disorders. For all subjects, the presence and severity of parkinsonian symptoms were determined and quantified by means of the motor section (part III) of the Unified Parkinson’s Disease Rating Scale (UPDRS). In addition, all subjects were categorized according to Hoehn and Yahr criteria. For patients with a clinical diagnosis of PD, all motor testing was performed with the patient taking medication. Cognitive function was assessed by means of a neuropsychological tool that identifies dementia in patients with PD.

### SUBJECT DETAILS

One hundred one white subjects participated, 49 with PD and 52 controls (demographic information is shown in Table 1). Seven patients received their diagnosis of PD at study entry (levodopa naive); 4 had only mild unilateral limb signs (mean ± SD UPDRS score, 6.8 ± 1.5), while the other 3 had some additional facial masking (mean UPDRS score, 8.9 ± 1.1). On questioning, these patients had noticed unilateral PD signs on average for 1 year before assessment (mean, 1.2 ± 0.8 years). Thirty-six of the remaining 42 patients with PD were taking dopaminergic medication at the time of assessment (Table 1). The most common were levodopa-carbidopa or benserazide (14 patients) or levodopa-carbidopa or benserazide plus dopamine agonist(s) (16 patients). The remaining patients were taking levodopa plus agonist plus trihexyphenidyl hydrochloride (2 patients), levodopa plus amantadine hydrochloride (2 patients), levodopa plus agonist plus amantadine (1 patient), or levodopa plus agonist plus selegeline hydrochloride (1 patient). In all subjects, the most common other supplement taken was vitamin E and/or ascorbic acid, or other compounds suggested to have an antioxidant effect (eg, folic acid, ginkgo). These supplements were taken by 17% (n=9) and 16% (n=8) of the control and PD groups, respectively. Disease severity ranged from UPDRS scores of 2 to 45 and time from initial diagnosis ranged from 3 months to 20 years in the 42 patients who had been diagnosed before study entry. Of the 49 patients with PD, 23 (47%) reported being current smokers or having smoked heavily in the past, and a similar proportion of the controls (22/52 [44%]) reported identical smoking behavior (see Table 1).

### OLFACTORY TESTING AND ANALYSIS

Olfactory function was tested by means of the B-SIT according to the manufacturer’s instructions. This test is an abridged, validated version of the UPSIT, incorporating the 12 “scratch-and-smell” odors given in Table 2. Subjects were presented
Abnormal olfactory function was present in 40 (82%) of nondemented subjects with PD compared with 12 (23%) of controls (Table 1). The B-SIT demonstrated high sensitivity, specificity, and predictive value for the diagnosis of PD (Table 2). There was no interaction between total B-SIT score and a history of smoking, PD duration, or PD severity (motor UPDRS and Hoehn and Yahr scores). All control subjects and 20 (40%) of the subjects with PD were unaware of an olfactory deficit before testing. Of the 7 patients diagnosed at assessment, 1 had normal olfactory function, while the remaining 6 exhibited abnormal function. This suggests an early deficit and is consistent with the data for the other cases of stage I PD examined (Table 1). All 8 patients with PD at stage III of disease had abnormal olfactory function (Table 1).

Differences in odor identification between PD and control groups were found for 8 of the 12 odors tested (odors gasoline through rose, Table 2). Soap and chocolate were rarely misidentified (high negative predictive value), whereas turpentine was poorly identified (Table 2). Sensitivity of discrimination for most odors was consistently poor (Table 2). Loss of ability to identify gasoline had the highest predictive value (Table 2), but only 17 (35%) of patients with PD exhibited this deficit. The greatest sensitivity, specificity, and statistical power for detecting PD was associated with the odor of paint thinner (Table 2), although approximately 30% of controls could not identify this odor (Table 2). These data show different deficits in different patients, consistent with variable but selective hyposmia in PD.\(^1,^3\)

The use of 12 odors correctly classified 81% of cases (44 controls [85%] and 38 patients with PD [76%]). Removal of the odors with the lowest comparative ratios (turpentine, lemon, chocolate, soap, and rose) correctly classified 82% of cases (\(\chi^2=19.6, P<.001\); 46 controls [88%] and 36 patients with PD [73%]). Subsequent removal of onion and paint thinner still correctly classified 82% of cases (\(\chi^2=3.4, P<.008\), with more controls correctly classified (n=50 [96%]) but fewer patients with PD (n=33 [67%]). Removal of additional odors from the test abolished its discriminatory power. The data thus indicated that 5 of the 12 B-SIT odors (gasoline, banana, pineapple, smoke, and cinnamon) are required to adequately discriminate patients with PD from controls, with low probability of false-positive diagnoses.

### RESULTS

Abnormal olfactory function was present in 40 (82%) of nondemented subjects with PD compared with 12 (23%) of controls (Table 1). The B-SIT demonstrated high sensitivity, specificity, and predictive value for the diagnosis of PD (Table 2). There was no interaction between total B-SIT score and a history of smoking, PD duration, or PD severity (motor UPDRS and Hoehn and Yahr scores). All control subjects and 20 (40%) of the subjects with PD were unaware of an olfactory deficit before testing. Of the 7 patients diagnosed at assessment, 1 had normal olfactory function, while the remaining 6 exhibited abnormal function. This suggests an early deficit and is consistent with the data for the other cases of stage I PD examined (Table 1). All 8 patients with PD at stage III of disease had abnormal olfactory function (Table 1).

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### Comment

We confirm previous reports of an olfactory dysfunction in 70% to 90% of nondemented patients with PD,\(^1,^3\) which is unrelated to disease duration, severity, or par-

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**Abbreviations:** NPV, negative predictive value; PPV, positive predictive value.

<table>
<thead>
<tr>
<th>Odor</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Ratio†</th>
<th>P Value†</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.82</td>
<td>0.82</td>
<td>0.77</td>
<td>0.77</td>
<td>15×</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gasoline</td>
<td>0.35</td>
<td>0.61</td>
<td>0.94</td>
<td>0.98</td>
<td>27×</td>
<td>.005</td>
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<tr>
<td>Banana</td>
<td>0.35</td>
<td>0.60</td>
<td>0.85</td>
<td>0.88</td>
<td>7×</td>
<td>.002</td>
</tr>
<tr>
<td>Pineapple</td>
<td>0.47</td>
<td>0.64</td>
<td>0.79</td>
<td>0.90</td>
<td>6×</td>
<td>.002</td>
</tr>
<tr>
<td>Smoke</td>
<td>0.50</td>
<td>0.65</td>
<td>0.77</td>
<td>0.90</td>
<td>5×</td>
<td>.003</td>
</tr>
<tr>
<td>Cinnamon</td>
<td>0.35</td>
<td>0.59</td>
<td>0.77</td>
<td>0.87</td>
<td>4×</td>
<td>.004</td>
</tr>
<tr>
<td>Paint thinner</td>
<td>0.65</td>
<td>0.69</td>
<td>0.70</td>
<td>0.73</td>
<td>4×</td>
<td>.003</td>
</tr>
<tr>
<td>Onion</td>
<td>0.35</td>
<td>0.66</td>
<td>0.70</td>
<td>0.77</td>
<td>4×</td>
<td>.003</td>
</tr>
<tr>
<td>Rose</td>
<td>0.57</td>
<td>0.59</td>
<td>0.78</td>
<td>0.94</td>
<td>5×</td>
<td>.15</td>
</tr>
<tr>
<td>Soap</td>
<td>0.22</td>
<td>0.56</td>
<td>0.67</td>
<td>0.94</td>
<td>2×</td>
<td>.05</td>
</tr>
<tr>
<td>Chocolate</td>
<td>0.13</td>
<td>0.54</td>
<td>0.60</td>
<td>0.73</td>
<td>2×</td>
<td>.17</td>
</tr>
<tr>
<td>Lemon</td>
<td>0.43</td>
<td>0.58</td>
<td>0.51</td>
<td>0.33</td>
<td>1×</td>
<td>.59</td>
</tr>
</tbody>
</table>
kinsonian medication. Olfactory dysfunction was not significantly affected by smoking behavior in either the PD or control group. The B-SIT effectively discriminated between patients with PD and control subjects (82% sensitivity and specificity), with 5 of the 12 odors primarily contributing to this power. Each patient with PD had difficulty identifying at least 2 of these 5 core odors, with few patients having difficulty with all odors. This shows a highly selective but variable pattern of olfactory dysfunction in PD.

In agreement with the apparent selectivity of olfactory dysfunction suggested by our discriminant function analyses, Hawkes and Shephard reported that 2 UPSIT odors (wintergreen and pizza) can discriminate PD with high sensitivity and specificity, although these odors cannot be used in populations outside North America. As UPSIT results are related to ethnicity, an important feature of the B-SIT is its validity in a cross-cultural setting. Of the 12 odors tested, we found that the 5 specific odors, gasoline, banana, pineapple, smoke, and cinnamon, discriminated PD more effectively than the entire B-SIT test. A characteristic pattern of hyposmia in PD has also been reported with the German “sniffin’ sticks” test. Indeed, in agreement with our findings, these authors also reported that banana and pineapple discriminated patients with PD from controls, while orange, clove, rose, and lemon were ineffective. All available data thus argue for a selective, restricted pattern of hyposmia in PD. An advantage of the B-SIT is its simple presentation and administration. The 12 B-SIT odors are presented independent of possible variations in qualities, such as odor intensity and purity. Differences in odor intensity have been shown to affect odor identification in PD; thus, presenting variations in these odor qualities may improve test discrimination, although possibly at the cost of increasing test complexity and administration time.

Our results suggest that, while general tests of olfactory function are routinely used in some clinical settings, more specific olfactory tests for PD for clinical use can be developed. Such tests must be investigated not only in patients with PD but also in a wide range of other disease conditions. Data to date suggest that olfactory dysfunction may be a useful tool for the discriminative diagnosis of PD from other parkinsonian disorders, as olfaction appears to be preserved in progressive supranuclear palsy, benign essential tremor, multiple system atrophy, and corticobasal degeneration. Previous studies in patients with dementia have reported an olfactory dysfunction that has been suggested to be similar to that occurring in PD. More recent evidence, however, indicates that olfactory dysfunction may be associated with the pathological presence of Lewy bodies, rather than changes related to Alzheimer disease. Olfactory testing may therefore prove useful for the discriminant diagnosis of dementia with Lewy bodies, as well as PD. Longitudinal follow-up of patients with postmortem confirmation of disease type will be required to determine the specificity and strength of the reported associations.

To date, pathological changes in PD have been reported in various regions involved in olfactory function, including the anterior olfactory nucleus, the olfactory bulb, the periamygdaloid cortex, and the olfactory mucosa, as well as an impairment in sniffing, although the primary pathological event(s) resulting in olfactory dysfunction is unknown. We study and those of others show that olfactory dysfunction is an early event in PD and may precede the development of motor dysfunction. Indeed, a recent study investigating preclinical signs of PD in relatives of patients demonstrated dopamine dysfunction in asymptomatic subjects with hyposmia, with 2 subjects subsequently developing PD within the study time. The olfactory deficit in PD appears stable and is not an inherited trait. The specific pattern of olfactory dysfunction that we have identified in PD provides the necessary information for the further development of olfactory tests designed specifically to assist in the early, discriminant diagnosis of PD, and possibly even for preclinical disease.

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