The Olfactory and Cognitive Deficits of Parkinson's Disease: Evidence for Independence

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In the present study we sought to determine whether the olfactory deficits of parkinsonism are related to the cognitive and perceptual-motor manifestations of the disease. Pearson correlation coefficients were computed among a number of olfactory, neurological, and neuropsychological measures obtained from 58 Parkinson's disease patients, including the University of Pennsylvania Smell Identification Test, a modified Randt memory test, a reaction time test, a finger-tapping test, ratings of motor and neurological function, and selected verbal and performance subtests of the Wechsler Adult Intelligence Scale—Revised. Data from 38 patients with Parkinson's disease who received odor detection threshold testing were also evaluated. The intercorrelation matrix was subjected to a principal components factor analysis which yielded six clear-cut factors: cognitive/memory, gross motor, oral motor, fine motor, olfactory, and tremor. The olfactory factor received strong and nearly exclusive loadings from the olfactory measures (which did not evidence meaningful loadings on any of the other factors). A ten-trial jackknife procedure revealed the factor structure to be stable. Further support of the independence of the olfactory variables from the other measures was provided by multiple regression and canonical correlation analyses. Overall, these findings lend support to the hypothesis that the olfactory disorder of parkinsonism is independent of the cognitive, perceptual-motor, and memory manifestations of the disease.


Significant olfactory dysfunction has been demonstrated in patients who have such degenerative neurological disorders as Alzheimer's disease [1-4], Parkinson's disease (PD) [5-8], Huntington's chorea [9], and Korsakoff's psychosis [10,11]. We recently showed that the olfactory deficits of Parkinson's disease occur for a wide range of odorants; are stable over time; and appear to be unrelated to gender, stage of the disease, ratings of neurological function, and the type(s) of antiparkinsonian medication being used [6]. Although there was no correlation between the olfactory test scores and scores on a simple picture identification test (designed to control for nonolfactory components of our smell identification test) [12], it was not established whether the olfactory measures were similarly unrelated to more demanding indices of perceptual and cognitive function, particularly ones involving memory and fine-motor coordination. Thus, the purpose of the present study was to determine, using factor analysis and other statistical procedures, whether the olfactory deficit of parkinsonism is related to general cognitive, perceptual-motor, and/or memory alterations associated with the disease.

Materials and Methods

Subjects

Fifty-eight patients with idiopathic PD were evaluated. The mean ages (± SD) of the 33 men and 25 women were 65.8 years (± 9.0 years) and 69.2 years (± 8.7 years), respectively. At the time of testing, 57 patients were taking carbidopa-levodopa MSD, either alone (4 patients) or in combination with anticholinergic medication (e.g., benztrazep mesylate; 24 patients), other dopamine agonists (e.g., amantadine hydrochloride; 13 patients), or medications not directly related to dopaminergic or cholinergic activation (e.g., diltiazem hydrochloride; 16 patients). The remaining patient was taking bromocriptine mesylate alone. Seventeen patients had previously undergone ventrolateral thalamic surgery for treatment of severe tremor (10 unilateral, 7 bilateral). All were outpatients of the Department of Neurosurgery, St. Barnabas Medical Center, Livingston, New Jersey, and had provided informed consent before participation. The duration of the parkinsonian symptoms ranged from 3

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months to 55.6 years. The number of patients at each of the Hoehn and Yahr stages (13) were as follows: 16 at stage I, 14 at stage II, 17 at stage III, 9 at stage IV, and 2 at stage V.

Assessment of Cognitive, Perceptual-Motor, and Memory Function

SUBTESTS OF THE WECHELER ADULT INTELLIGENCE SCALE—REVISED. The following subtests of the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (14) were administered to all 58 subjects: Verbal—Information, Digit Span, Vocabulary, and Similarities; Performance—Picture Completion, Block Design, and Digit Symbol. The Arithmetic, Comprehension, Picture Arrangement, and Object Assembly subtests were not administered because of the relatively high correlations of their results with those of the other subtests. Also, we wanted to minimize fatigue, boredom, and other problems associated with test periods of longer than 90 minutes.

RANDT MEMORY TEST. A modified Randt memory test was used to evaluate memory functions (15). This test is designed to emphasize individual differences in immediate and short-term memory and is sensitive to memory losses due to diffuse dysfunction of the brain. Various aspects of episodic memory, including rote, associative, discursive, incidental learning, and visual recognition, were measured. Five modules were used: (1) General Information—a mental status questionnaire including orientation for time, place, and person; (2) Five Items—a verbal learning task of five simple unrelated words performed to criterion over three trials, with 10-second distraction periods; (3) Paired Words—a list of six paired associates, varying from closely related to unrelated, learned to criterion with 10-second distraction periods and restricted reminding; (4) Short Story—immediate recall of a brief, meaningful paragraph; and (5) Picture Recognition—immediate recall of a series of simple line drawings of everyday objects, recognized from a larger set of drawings.

NUMBER CANCELLATION TEST. In this paper and pencil task the subject was required to cancel a given number each time it appeared in a list of numbers on a test page. The list consists of 12 lines of single digit numbers with 26 numbers on each line. This task necessitates visual selectivity at a rapid speed using repetitive motor responses. The patient's score is the number of 3s cancelled in 2 minutes. If a patient finishes in less than 2 minutes, the score is prorated for a full 2 minutes.

REACTION TIME TO VISUAL STIMULUS TEST. This test was administered to both the left and right hands in two sessions, with hand order alternated beginning with the right hand. It requires the subject to press a telegraph key as quickly as possible after the presentation of a red light. The response time is recorded and the average of three trials served as the measure.

TAPPING TEST. In this test the number of times that the telegraph key could be tapped during a 10-second time period was recorded. As with the visual reaction time test, left and right hands were tested alternately. The average of three trials served as the dependent measure.

THE PICTURE IDENTIFICATION TEST. The Picture Identification Test (PIT) is designed specifically to control for nonolfactory aspects of the University of Pennsylvania Smell Identification Test (UPSIT), which is described in the next section (12). The PIT is identical to the UPSIT in content, format, and order of item presentation except that line drawings, instead of odors, represent each of the 40 odors used on the UPSIT and serve as stimuli. The pictures used for this test (which was always administered after the UPSIT) appear on 2 x 2-inch cardboard squares. Each square is attached to a booklet page on one side only, allowing it to be turned to reveal a multiple choice question on its backside analogous to one of the questions on 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. This test was administered by a trained technician and the subject was not required to perform any manual test-related tasks.

Assessment of Neurological Function

Neurological function was assessed using 5-point clinical rating scales of the following manifestations (scores range from 0 to 4 points, with 0 = minimal or no symptom/disability and 4 = maximal symptom/disability): tremor (left and right), rigidity (left and right), alternating movements (left and right), bradykinesia, masking, posture, voice, speech, swallowing, and autonomic signs. A 9-point rating scale (ranging from 0 to 8 points) was used to assess balance, gait, and turning, and each patient was scored on general functional status using the Hoehn and Yahr scale (13). The time since onset of symptoms (i.e., duration of the disease) in months was also determined.

Assessment of Olfactory Function

UNIVERSITY OF PENNSYLVANIA SMELL IDENTIFICATION TEST. The UPSIT (commercially available as the Smell Identification Test, Sensonics, Inc, Haddonfield, NJ), is a standardized test comprised of four booklets containing 10 odors each, 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 odorant strip. The subject is required to answer one of the four alternatives, even if no smell is perceived (i.e., the test is forced-choice). The stimuli and the basis for their selection are described elsewhere (17). This test is highly reliable (short-term test-retest r = 0.95) (18) and sensitive to a variety of olfactory deficits, including those associated with aging (19), smoking (19), cystic fibrosis (20), Alzheimer's disease (2), Korakoff's psychosis (11), and Kallmann's syndrome (17).

The UPSIT was administered individually to each patient by a trained technician, who released the microencapsulated stimuli, placed them under each patient's nose, and recorded the answer following the patient's response.

ODOR DETECTION THRESHOLD. Thirty-eight patients received a single staircase, forced-choice odor detection threshold test (21) to estimate basal detection sensitivity to
the odorant phenyl ethyl alcohol (PEA; Gold label grade; Aldrich Chemical Co, Milwaukee, WI), a compound with relatively low intranasal trigeminal stimulatory properties [22, 23]. This 30-minute test, which is described in detail elsewhere [21, 24], uses the geometric mean of the last four staircase reversal points of a total of seven as the measure of sensitivity. Since PEA threshold measures correlate reasonably well with those of a number of other odorants, including acetic acid, dialyl sulfide, camphor, phenyl, cyclopentadecanolide, scatol, and iso-valeric acid [25], lack of sensitivity to this compound may reflect general olfactory insensitivity.

It should be noted that, in the case of 51 subjects, the UPSIT and PEA test data used in this project were from our earlier study [6]. Since our previous data indicated that no significant changes occur in the olfactory function of patients with Parkinson's disease over a time period ranging from 5 to 39 months, we did not readminister the olfactory tests at the time of the collection of the neuropsychological and perceptual-motor data.

Results

Pearson correlations among the sensory, cognitive, perceptual-motor, and neurological measures were computed. Those between the olfactory and the cognitive and perceptual-motor measures were small and not statistically significant. The entire matrix was subjected to a principal components factor analysis with varimax rotation [26]. Factor analysis is a statistical technique that uses the total pattern of relationships among a set of variables to produce a small number of independent underlying dimensions or "factors" that account for these relationships. In essence, this procedure extracts independent clusters of variables that have relationships in common (i.e., correlate with one another) and that differ from clusters of other variables (i.e., do not correlate with them). By examining those variables that have strong relationships ("loadings") with a given factor, the experimenter can often assign the factor a name that reflects the composite of the associated variables. The mathematical details of this procedure are described elsewhere [27, 28].

Because of a widely held assumption that the number of variables in a factor analysis needs to be limited relative to the number of patients evaluated (see, however, the work of Guadagnoli and Velicer [29]), we combined the scores from the WAIS-R Information, Digit Span, Vocabulary, and Similarities subtests into a single verbal score (WAIS-Verbal), and those from the Picture Completion, Block Design, and Digit Symbol subtests into a single performance score (WAIS-Performance). Similarly, we combined the Randt General Information, Five Items, Paired Words, Short Story, and Picture Recognition modules into a Randt Memory Score. Even though the total number of variables was still high following these procedures, the factor structure was found to be stable using a ten-trial jackknife iterative validation procedure.

As can be seen in the Table, six easily interpretable factors were extracted that accounted for a total of 73.6% of the variance. In accord with standard statistical procedures, only factors with eigenvalues (EV) of greater than 1.00 were extracted (an EV is a measure of the amount of the total variability accounted for by a factor). Factor I (EV = 8.69) is clearly a cognitive/memory factor, loading most heavily (i.e., loadings > 0.50) with the Randt memory, PIT, Letter Cancellation, and WAIS-R Verbal and Performance measures. Interestingly, this factor also had factor loadings of greater than 0.50 from the neurological measures of bradykinesia and masking. Factor II (EV = 3.26) is a gross-motor factor, having factor loadings greater than 0.50 for the neurological ratings of rigidity and alternating movements. Factor III (EV = 2.19) appears to be an oral-motor factor, with loadings of greater than 0.50 on the speech, voice, and swallow neurological ratings. Interestingly, this factor also received strong loadings from the variables of disease duration; balance, gait, and turning; and thalamic surgery. Factor IV (EV = 2.06) is a fine-motor factor, having strong factor loadings from the finger-tapping and reaction time tests of the left and right hand. Factor V (EV = 1.79) is clearly an olfactory function factor, having the only loadings greater than 0.50 from the UPSIT and the PEA odor detection threshold test. Factor VI (EV = 1.15) is a tremor factor, having the neurological ratings of left and right tremor as its primary loadings.

Since the distributions of some of the neurological rating variables were slightly skewed, we also performed analogous factor analyses following both square root and log transformations of the data. In both cases no meaningful changes in the factor structure emerged.

Additional statistical analyses were performed to confirm our observation of apparent independence of the olfactory measures from the other variables. First, canonical correlations [30] were computed between the two olfactory measures and the variables within each of the five factors that had loadings greater than 0.50 (see boxes in the Table). Unlike a standard correlational procedure which provides an estimate of the relationship between two variables, a canonical analysis provides a determination of the relationship between two sets of independent variables. Bartlett's tests of Wilks' lambda [31] revealed no significant relationships for any of the five sets of these analyses (χ² values; cognitive = 10.97, df = 12, p > 0.50; gross motor = 8.62, df = 10, p > 0.50; oral motor = 13.39, df = 14, p > 0.40; fine motor = 6.88, df = 6, p > 0.30; tremor = 2.87, df = 4, p > 0.50). Second, multiple regression analysis [26] was performed between each olfactory variable and the major factor loadings of each factor. None of the resulting F values were significant at the 0.05 alpha probability level.
**Varimax Rotated Factor Matrix for Primary Variables of the Study**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor I (Cognitive/Memory)</th>
<th>Factor II (Oral Motor)</th>
<th>Factor III (Fine Motor)</th>
<th>Factor IV (Olfactory)</th>
<th>Factor VI (Tremor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randt memory</td>
<td>.880</td>
<td>-.077</td>
<td>-.157</td>
<td>.024</td>
<td>-.086</td>
</tr>
<tr>
<td>WAIS-R (Perf)</td>
<td>.810</td>
<td>-.204</td>
<td>-.147</td>
<td>-.088</td>
<td>-.001</td>
</tr>
<tr>
<td>WAIS-R (Verb)</td>
<td>.780</td>
<td>-.165</td>
<td>-.039</td>
<td>-.078</td>
<td>-.052</td>
</tr>
<tr>
<td>PIT</td>
<td>.763</td>
<td>-.191</td>
<td>.158</td>
<td>-.141</td>
<td>.014</td>
</tr>
<tr>
<td>Cancellation</td>
<td>.753</td>
<td>-.045</td>
<td>-.368</td>
<td>-.246</td>
<td>.108</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>-.527</td>
<td>-.433</td>
<td>.355</td>
<td>.400</td>
<td>.309</td>
</tr>
<tr>
<td>Rigidity (L)</td>
<td>.050</td>
<td>.883</td>
<td>-.062</td>
<td>.066</td>
<td>-.018</td>
</tr>
<tr>
<td>Rigidity (R)</td>
<td>-.074</td>
<td>.858</td>
<td>.014</td>
<td>.086</td>
<td>.050</td>
</tr>
<tr>
<td>Alternating move (L)</td>
<td>-.392</td>
<td>.792</td>
<td>.186</td>
<td>.033</td>
<td>-.025</td>
</tr>
<tr>
<td>Alternating move (R)</td>
<td>-.378</td>
<td>.748</td>
<td>.222</td>
<td>-.057</td>
<td>.041</td>
</tr>
<tr>
<td>Masking</td>
<td>-.499</td>
<td>.564</td>
<td>.407</td>
<td>.221</td>
<td>.186</td>
</tr>
<tr>
<td>Reaction time (R)</td>
<td>-.298</td>
<td>.491</td>
<td>-.022</td>
<td>.437</td>
<td>.265</td>
</tr>
<tr>
<td>Speech</td>
<td>-.064</td>
<td>-.021</td>
<td>.839</td>
<td>.059</td>
<td>-.040</td>
</tr>
<tr>
<td>Disease duration</td>
<td>.036</td>
<td>.114</td>
<td>.789</td>
<td>.135</td>
<td>-.097</td>
</tr>
<tr>
<td>Voice</td>
<td>-.313</td>
<td>.035</td>
<td>.786</td>
<td>-.043</td>
<td>-.053</td>
</tr>
<tr>
<td>Thalamic surgery</td>
<td>.022</td>
<td>.012</td>
<td>.682</td>
<td>-.092</td>
<td>.193</td>
</tr>
<tr>
<td>Balance, gait, turning</td>
<td>-.425</td>
<td>.342</td>
<td>.639</td>
<td>.160</td>
<td>.227</td>
</tr>
<tr>
<td>Disease stage</td>
<td>-.426</td>
<td>.458</td>
<td>.601</td>
<td>.201</td>
<td>.233</td>
</tr>
<tr>
<td>Swallow</td>
<td>-.010</td>
<td>.001</td>
<td>.523</td>
<td>.232</td>
<td>-.454</td>
</tr>
<tr>
<td>Tapping (L)</td>
<td>.041</td>
<td>-.068</td>
<td>-.079</td>
<td>-.070</td>
<td>.097</td>
</tr>
<tr>
<td>Tapping (R)</td>
<td>.189</td>
<td>-.101</td>
<td>-.132</td>
<td>-.818</td>
<td>.133</td>
</tr>
<tr>
<td>Reaction time (L)</td>
<td>-.294</td>
<td>.409</td>
<td>-.109</td>
<td>.546</td>
<td>.271</td>
</tr>
<tr>
<td>Smell threshold</td>
<td>.142</td>
<td>.091</td>
<td>.102</td>
<td>.056</td>
<td>.888</td>
</tr>
<tr>
<td>UPSIT</td>
<td>.344</td>
<td>-.028</td>
<td>.024</td>
<td>.205</td>
<td>-.617</td>
</tr>
<tr>
<td>Tremor (L)</td>
<td>.050</td>
<td>-.104</td>
<td>.167</td>
<td>.082</td>
<td>-.042</td>
</tr>
<tr>
<td>Tremor (R)</td>
<td>-.079</td>
<td>.205</td>
<td>-.057</td>
<td>-.050</td>
<td>-.219</td>
</tr>
</tbody>
</table>

*Based on data from 58 patients (except for PEA threshold measures, which are based on data from 38 patients). Loadings of greater than 0.50 are boxed for emphasis.

PEA = phenyl ethyl alcohol, R = right, L = left, WAIS-R = Wechsler Adult Intelligence Scale—Revised, PIT = Picture Identification Test, UPSIT = University of Pennsylvania Smell Identification Test.

**Discussion**

The results of the present study lend support to the hypothesis that the olfactory deficits of PD are independent of the other cognitive, memory, perceptual-motor, and neurological manifestations of the disease. In addition, the findings suggest that cognitive and memory dysfunctions of PD are interrelated, as indicated by loadings on a common factor in the factor analysis (factor I). It is noteworthy that the number of cancellations, which involves both cognitive and motor skills, loaded almost exclusively on this factor, suggesting that this test is sensitive to the cognitive deficits of PD. The fact that the Hoehn and Yahr scale loaded on the oral-motor, gross-motor, and cognitive/memory factors suggests that this scale taps all three of these general dimensions of the disease.

The factors derived from a factor analysis, such as the one performed in this study, depend on the number and type of variables entered into the analysis, the nature of the factor rotations, as well as a host of other variables, including the sample size and the types of patients evaluated. Despite the variance arising from such parameters, however, the few published factor analytic studies of parkinsonian neurological symptoms provide data strikingly similar to the data of this study, even though the previous emphasis has been on motor function. For example, Petrinovich and Hardyck [32] extracted four factors from 9-point ratings of a number of parkinsonian behavioral symptoms of 40 PD patients before and after thalamic surgery. Before surgery, the four extracted factors were a gross-motor efficiency factor, a speech and facial motor factor, a right-side function factor, and a left-side function factor. The first two of these factors clearly correspond to factors II and III, respectively, of the present study. After surgery, the four extracted factors were a gross-motor efficiency factor, a speech and facial motor factor, a fine-motor skills factor, and a tremor factor—factors that appear identical to factors II, III, IV, and VI of the present work. When we omitted the data from the 18 subjects.
of our study who have undergone thalamic surgery, and subjected the remaining data to factor analysis, we did not appreciably change the factor structure (i.e., it remained analogous to that observed in the postoperative data of Petrinovich and Hardyck). Thus, the fact that we did not extract factors reflecting left and right body sides does not appear to be related, in our patient group, to thalamic surgery.

More recently, Reynolds and Montgomery [33] used videotapes to assess the behaviors of 84 PD patients who performed a sequence of nine common tasks of daily living in a standardized format. Of three general factors that were extracted, one reflected problems with walking and balance (having components similar to factor II of this study); one reflected problems with tremor (identical to factor VI); and one reflected masked facies, stooped posture, and a deficiency of overflow movements during conversation (having components in common with factor III).

Even though a number of new variables were included in this study, the general factor structure appears congruent with our earlier work [5], with the exception of the extraction of a fine-motor factor (which could not be observed previously because no such measures were made) and a greater number of loadings on the cognitive factor, which we now call a cognitive/memory factor. As before, discrete factors of olfactory function, tremor, general motor function, and speech and voice were extracted. Gender, posture, and autonomic signs were not included as variables in the present analysis, because there was a statistical need to limit the number of variables subjected to analysis relative to the sample size, because gender fell out in the previous analysis as a separate factor and did not contribute significant loadings to the other factors, and because posture and autonomic signs did not contribute significantly to any of the factors in our previous analysis.

The neurological rating of bradykinesia loaded heavily on the cognitive/memory factor. This finding is in agreement with findings of several previous reports [34–36] which indicate that bradykinesia, more so than tremor and rigidity, relates to deficits in recent memory and cognition. It also suggests that bradykinesia may be a marker for a subtype of PD in which cognitive and memory deficits predominate.

Currently, the physiological basis of the olfactory dysfunction of parkinsonism is unknown. Assuming, as suggested by twin studies, that the problem is not an inherited trait [8], several explanations for the anomaly should be considered (for a more detailed discussion, see [6]). First, given their relatively direct exposure to the outside environment, the olfactory receptor cells themselves could be impaired by environmental agents etiologically related to Parkinson's disease, which make their way from the nasal cavity to the brain [37, 38]. Second, it is conceivable that the resistance of the olfactory system to viral or environmental agents, otherwise etiologically unrelated to the disease process, is decreased by the disease. Third, it is possible that decrements or alterations in central nervous system transmitter levels or receptors may be involved. However, if the olfactory dysfunction is due to either a catecholaminergic or a cholinergic neurotransmitter system anomaly, it is not reversed by drug treatment [6–8]. Furthermore, no association has been shown between dopaminergic or anticholinergic therapy and the degree of olfactory dysfunction [7, 8], and clear-cut olfactory dysfunction in both treated and untreated patients with PD has been reported [5, 8]. Fourth, it is possible that sectors of the olfactory system may be predisposed to degenerative or neuropathological processes nonspecifically associated with PD.

The apparent ubiquity of olfactory dysfunction in a number of dementia-related diseases would appear to lend circumstantial support to this notion. Fifth, it is possible that the olfactory disorder is part of a larger sensory/perceptual dysfunction complex analogous to that recently described for Korsakoff's psychosis, and that several sensory problems may exist in the same individual [11]. It has now been demonstrated that impairments in vision and audition accompany PD, including abnormalities in the electrooculogram and in both auditory and visual evoked potentials [39–44]. Obviously, more research is needed to determine which, if any, of these hypotheses is correct.

Regardless of the basis of the olfactory disorder associated with PD, the present data suggest that it is largely independent of the PD-related cognitive, perceptual-motor, and memory deficits, in addition to disease stage, disease duration, and clinical ratings of motor symptoms.

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