Cognitive and Motor Functioning in Parkinson Disease

Subjects With and Without Questionable Dementia

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Background: The nature of cognitive performance in subjects with Parkinson disease (PD) without dementia is controversial, perhaps because of failure to exclude subjects with unrecognized very mild dementia.

Objective: To compare cognitive and motor functioning in well-characterized subjects with PD without overt dementia with healthy elderly control subjects.

Design: Subjects’ conditions were evaluated clinically and psychometrically at entry into a longitudinal study of cognitive and motor performance in elderly subjects. Measures included a global dementia staging scale, the Washington University Clinical Dementia Rating; psychometric tests, including Logical Memory, Digit Span, Associate Learning, Information, Block Design, Digit Symbol, Trailmaking A, Crossing-off, Boston Naming Test, and Word Fluency; and motor measures, including finger tapping, gait velocity, reaction time, and movement time.

Setting: A university-based research facility.

Subjects: There were 3 groups of subjects: healthy elderly control subjects (n = 43), subjects with PD without dementia (n = 58), and subjects with PD with questionable dementia (n = 22), each evaluated at time of entry.

Results: As expected, both PD groups were impaired on motor measures (gait velocity, finger tapping, and movement time) compared with the healthy elderly control group. Neither PD group showed slowing in reaction time. The subjects with PD with questionable dementia were more impaired on Logical Memory, Block Design, Digit Symbol, and Trailmaking A compared with the subjects with PD without dementia. Although free of clinically evident cognitive dysfunction (Clinical Dementia Rating score, 0), the PD group without dementia was impaired with respect to the healthy elderly control group on all measures from the psychometric assessment except Digit Span, Associate Learning, and Word Fluency.

Conclusions: The PD group without dementia showed global cognitive impairments in comparison with the healthy elderly control group, possibly because the healthy elderly control subjects represented idealized aging. Although the deficits were of small magnitude, this finding suggests that PD may predispose to subclinical cognitive impairment. Longitudinal follow-up is required to determine whether subjects with PD destined to develop overt dementia can be distinguished from those who do not.

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Although it is recognized that many individuals with Parkinson disease (PD) eventually develop overt dementia, the nature of cognitive performance in individuals with PD without dementia is less well characterized. For example, both impaired and preserved function have been reported on a variety of cognitive tasks for subjects with PD without dementia. These different findings must be viewed in the context of the methods for subject selection. Differences in diagnostic accuracy, staging of dementia, and presence of extrapyramidal signs (EPSs) may importantly influence the results and interpretation of data. Whether subjects with PD without dementia exhibit cognitive impairments and, if present, whether these impairments are global or selective is important for the treatment of individuals with PD without dementia and for the determination of which cognitive measures predict the development of overt dementia.

To explore the nature of cognitive abilities in subjects with PD without dementia, we carefully characterized 3 groups of subjects using the Washington University Clinical Dementia Rating (CDR)10: healthy elderly control subjects, subjects with PD without dementia, and subjects with PD with questionable dementia. The CDR was used to minimize the possibility of subjects with unrecognized questionable dementia contaminating the groups without dementia. Although more than one third of otherwise healthy...
SUBJECTS AND METHODS

CLINICAL ASSESSMENT

Subjects were recruited from a variety of sources in the St Louis, Mo, area: patients in the Movement Disorders Clinic in the Department of Neurology, Washington University Medical Center, and at other physicians’ offices, responses to brochures placed at the Parkinson’s Disease Center at Barnes Jewish Hospital, and media appeals. The following recruitment guidelines were observed: a clinical diagnosis of PD, age 65 through 85 years, independently ambulatory, and noninstitutionalized. There were no sex or race restrictions. Healthy elderly control subjects were volunteer participants in longitudinal studies of the Memory and Aging Project (MAP) of the Washington University Alzheimer’s Disease Research Center and agreed to participate in an additional assessment of motor functioning. Exclusionary criteria for all subjects included other neurologic, medical (including overmedication), and psychiatric (including major affective disorders) conditions that could influence cognitive functioning. In addition, subjects who displayed clinical impairment in hearing, visual acuity, or language were excluded from enrollment. From 1989 to 1993, 47 healthy elderly control subjects and 84 subjects with PD who met these criteria were enrolled. These subjects’ conditions were evaluated by MAP physicians (6 neurologists, 4 psychiatrists, and 2 geriatricians). All MAP physicians underwent extensive training in the MAP clinical assessment method and were certified by the MAP director before evaluating subjects’ conditions.

Dementia and other neurologic conditions were evaluated by MAP physicians during clinical interviews of the subject and a collateral source and during a standardized neurologic examination of the subject. The clinical diagnostic criteria used for dementia have been validated by neuropathologic examination in a sample of individuals with dementia of the Alzheimer type. The clinical diagnosis of PD was confirmed during the MAP assessment when 2 or more EPSs (bradykinesia, cogwheel rigidity, or resting tremor) were present on examination in the absence in the previous 6 months of medication use with potential extrapyramidal adverse effects. Gait and postural reflex abnormalities were not included as criteria for the diagnosis of PD because these symptoms are common in normal elderly populations. Severity of PD was assessed with the Hoehn and Yahr scale and the Northwestern University Disability Scale. Healthy elderly control subjects with EPSs noted during a standardized neurologic examination or with a Hoehn and Yahr stage of 1 or higher were excluded from our study.

Severity of dementia was staged according to the CDR. The CDR assesses cognitive functioning in 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobby, and personal care. Based on these 6 scores and without reference to psychometric performance, a global CDR score is assigned in which a CDR score of 0 indicates no dementia and a CDR score of 0.5, 1, 2, or 3 indicates questionable, mild, moderate, or severe dementia, respectively. The reliability of the CDR has been established. Subjects with PD with a CDR score of 1 or higher (ie, overt dementia) were excluded. Three subject groups were thus assessed: healthy elderly control subjects (CDR score, 0), subjects with PD without dementia (CDR score, 0), and subjects with PD with questionable dementia (CDR score, 0.5). The entry characteristics of these subject groups are shown in Table 1. Analysis of variance indicated a main effect of group for age (F[2, 120] = 3.13; P<.05) but not for education (F[2, 120] = 0.92; P>.10). A χ² test indicated a significant difference between groups in sex (χ²[2, n = 123] = 10.85; P<.01). The clinical assessment included the brief dementia rating scale developed by Blessed et al. This scale includes a 17-item behavioral checklist, the Blessed Dementia Scale–Cognitive, recorded by the collateral source as to the subject’s cognitive ability to perform instrumental and basic activities of daily living. Data from this checklist are presented in Table 1. The analysis of covariance revealed a significant main effect of group (F[2, 114] = 19.02; P<.001). Tukey-Kramer tests indicated that the PD group with questionable dementia was impaired compared with the healthy elderly control group and the PD group without dementia. There was no difference on the Blessed Dementia Scale–Cognitive between the healthy elderly control group and the PD group without dementia. The clinical assessment also included a 9-item depression inventory. The subject and the collateral source each were asked about the following symptoms in the subject: depressed mood, diminished interest, change in weight or appetite, insomnia or hypersomnia, fatigue or loss of energy, psychomotor agitation or retardation, feelings of worthlessness or excessive or inappropriate guilt, indecisiveness, and recurrent thoughts of death or suicidal ideation. Data from the depression inventory are presented in Table 1.

PSYCHOMETRIC ASSESSMENT

A neuropsychological battery was administered to assess multiple cognitive domains, including memory, attention, language, visuospatial ability, and psychomotor speed. The psychometric assessment was conducted within 1 month of the clinical assessment; each was administered and scored independently of the other. Tests were administered to subjects and scored according to conventional procedures outlined in the test manuals unless otherwise specified. Individual tests included the following:

- Wechsler Memory Scale (WMS) Logical Memory—subjects provide immediate recall of stories read to them.
- WMS Digit Span—subjects recall a series of digits in the same order and in the reverse order.
- WMS Associate Learning—subjects learn a list of paired word associates and immediately recall the second word of the word pair when provided with the first word of the word pair.
- Wechsler Adult Intelligence Scale (WAIS) Information—subjects answer general knowledge questions.
- WAIS Block Design—subjects arrange blocks to match designs.
- WAIS Digit Symbol—subjects transcribe numbers and symbols.
- Trailmaking A—subjects connect a series of numbers with lines.
- Crossing-off—subjects make a slash mark through a set of 96 horizontal lines on a piece of paper. There are 8 lines per row, and subjects cross out the lines from left to right. This test is scored as the number of lines crossed out per second × 100.

Continued on next page
• Boston Naming Test—subjects name pictured items. The administration was modified so that all items were administered and no phonemic cues were given.
• Word Fluency—subjects produce words beginning with the letter S and words beginning with the letter P. Sixty seconds are allowed for each letter. The total number of words provided are scored.

MOTOR ASSESSMENT

All subjects in this study were administered the following motor assessment battery within 6 months of the clinical and psychometric assessment. Subjects with PD fasted overnight and withheld use of initial morning antiparkinsonian medications until the completion of the motor assessment. A single trained technician rated severity of PD with the Hoehn and Yahr scale and the Northwestern University Disability Scale. The Hoehn and Yahr scale ranges from stage I (mild, unilateral involvement) to stage V (confinement to a bed or wheelchair unless aided). The distribution of Hoehn and Yahr staging for the groups is shown in Table 2. Hoehn and Yahr data for 2 subjects from the PD group with questionable dementia were missing. A χ² test indicated that there was no significant difference in Hoehn and Yahr staging between the 2 PD groups (P>.10). The Northwestern University Disability Scale scores are also presented in Table 2. This scale has 5 items, and overall scores range from 0 to 50. We coded the items such that higher scores indicate greater impairment. There was no difference in the Northwestern University Disability Scale scores between the 2 PD groups as indicated by a t test (P>.10).

Finger Tapping

The number of finger taps with the index finger was measured in 6 10-second trials. This was recorded electronically in 3 positions for each hand: wrist and elbow restrained, elbow restrained, and no restraint. The task was presented in blocks by restraint position. Subjects began finger tapping with the dominant hand.

Psychometric Assessment

There was a significant main effect of group for all psychometric tests (except Digit Span and Word Fluency), indicating differences in group performance (Table 3). These group differences were examined with Tukey-Kramer tests (Table 4). Both PD groups generally performed significantly more poorly than the healthy elderly control group. The PD group with questionable dementia was impaired with respect to the PD group without dementia on Logical Memory, Block Design, Digit Symbol, and Trailmaking A.

Gait Velocity

Gait velocity was assessed by attaching footpads with electrical contacts and pressure-activated foot switches to the shoes worn by subjects. Gait velocity measured how long it took subjects to walk 10 meters.

Reaction Time and Movement Time

A Fitts task was used to measure reaction time and movement time. Subjects held a stylus in the dominant hand and rested the stylus on a target area. On receiving a verbal "ready" signal immediately followed by an auditory tone, subjects moved the stylus as quickly as possible from the start position to a designated target. There were 4 different targets 60 cm from the start position with diameters of 3.8 cm, 2.5 cm, 1.9 cm, and 1.2 cm. The task was presented in blocks by target size from the largest to the smallest target. There were 10 trials for each target. Reaction time was the duration between the auditory tone and removal of the stylus from the start position. Movement time was the duration to move the stylus to the target once the stylus was removed from the start position. All assessment procedures and means for obtaining informed consent were approved by the Institutional Review Board of Washington University School of Medicine.

Statistical Analyses

All analyses were conducted using computerized statistical software (SAS 6.11, SAS Institute Inc, Cary, NC). Between-group differences were examined using analysis of covariance except as noted. Age and sex were used as covariates because the groups were not matched on these measures. In addition, antidepressant medication, depressive symptoms from the subject, and depressive symptoms from the collateral source were used as covariates to control for the effects of medications used and depression on performance. Post hoc pairwise comparisons were conducted using the Tukey-Kramer test. The level of significance was set at 2-tailed .05.

Results of the motor assessment at entry are presented in Table 5. There was a main effect of group for gait velocity (F[2, 109] = 7.58; P<.001) such that both PD groups were slower than the healthy elderly control group as indicated by Tukey-Kramer tests. The 2 PD groups did not differ significantly (P>.10). Because the finger-tapping variables were not counterbalanced, the finger-tapping scores were analyzed as number of taps averaged across side and position. There was a main effect of group (F[2, 103] = 9.53; P<.001). Tukey-Kramer tests indicated that both PD groups were slower in finger tap-
The PD group with a CDR score of 0.5 performed more poorly than the PD group with a CDR score of 0 on 4 tasks from the psychometric assessment: Logical Memory, Block Design, Digit Symbol, and Trailmaking A. Three of these tasks have both cognitive and motor components and are timed, suggesting that speed is important. Speeded performance (cognitive and motor) is sensitive to the psychometric deficits associated with questionable dementia in subjects with PD.

Although the differences were less than those seen for the subjects with PD with a CDR score of 0.5, subjects with PD without clinical indication of dementia (CDR score, 0) also performed more poorly than healthy elderly control subjects on a wide range of tasks measuring memory, language, visuospatial, and psychomotor abilities. The results indicate that the subjects with PD without dementia are subtly impaired even on cognitive tasks with no motor involvement. Other investigations of cognitive functioning in subjects with PD without dementia have yielded mixed results. On certain measures, subjects with PD without dementia have been reported to perform without difficulty relative to control subjects: Digit Span, Information, and Boston Naming Test. On Logical Memory and Associate Learning, however, some investigators find the performance of subjects with PD without dementia to be similar to that of control subjects whereas others find worse perfor-
mance for subjects with PD without dementia. Similarly, performance on Word Fluency is reported both as intact and as impaired in subjects with PD without dementia.

It is possible that referral bias or differences in selection criteria may contribute to differences in the results from our study compared with those in the literature. The subjects in our study were older than subjects in other studies; therefore, our subjects may have had PD longer. Duration of disease in subjects with PD without dementia has been shown to relate to cognitive functioning. The sample size in our study was larger than in other studies; thus, we have greater statistical power. The criteria for a diagnosis of PD did not include gait and postural reflex abnormalities. Subjects had to display 2 or more other EPSs to be diagnosed as having PD. While this selection criteria increased the certainty that subjects included in the PD groups actually had PD, it may limit the generalizability of our findings. Our healthy elderly control group excluded subjects with even minor age-related cognitive decline and thus minimized contamination by preclinical dementia that may confound other samples. The CDR is sensitive to very mild cognitive impairments, an advantage over measures such as the Mini-Mental State Examination or similar brief tests that are confounded by effects of age, education, and ethnic status and are insensitive to early-stage dementia in well-educated individuals. Our controls were also free of any EPS. Elderly people with EPSs are impaired on cognitive measures compared with elderly individuals without EPSs. Thus, our controls appear to represent idealized aging, without even subtle cognitive or extrapyramidal impairment. While such strict selection criteria may limit the generalizability of our findings, we believe that using such a control group, rather than one likely to be contaminated by preclinical or unrecognized mild disease, allows differences between truly healthy aging and PD to be revealed.

Another difference between our study findings and those in the literature is that we used the CDR to stage the severity of dementia. The quantitative impairments detected on the psychometric assessment for the PD group with a CDR score of 0 were not reported by the collateral sources and were not detected by the MAP physicians during the clinical assessment. These quantitative deficits were very mild and may have been insufficient to interfere with activities of daily living. It is possible, however, that the CDR score may have been confounded by difficulty separating impairment attributable to motor dysfunc-

### Table 4. Scores on the Psychometric Assessment Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Group</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logical Memory</td>
<td>Healthy Elderly Control Subjects</td>
<td>10.4 (2.8)</td>
<td>3.0-15.0</td>
<td>7.2 (3.2)†</td>
<td>0.5-13.0</td>
<td>5.3 (2.6)†</td>
<td>2.0-12.5</td>
</tr>
<tr>
<td></td>
<td>Subjects With PD Without Dementia</td>
<td>12.7 (2.4)</td>
<td>7.0-15.0</td>
<td>11.7 (2.3)</td>
<td>7.0-15.0</td>
<td>11.4 (1.8)</td>
<td>8.0-14.0</td>
</tr>
<tr>
<td></td>
<td>Subjects With PD With Questionable Dementia</td>
<td>15.0 (3.7)</td>
<td>7.5-21.0</td>
<td>13.2 (3.5)</td>
<td>6.0-20.0</td>
<td>10.6 (3.5)†</td>
<td>6.0-18.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.9 (3.6)</td>
<td>14.0-29.0</td>
<td>20.8 (4.4)†</td>
<td>7.0-27.0</td>
<td>19.2 (4.6)†</td>
<td>11.0-28.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35.3 (7.3)</td>
<td>20.0-48.0</td>
<td>30.1 (9.2)†</td>
<td>4.0-46.0</td>
<td>22.0 (11.3)‡</td>
<td>0.0-45.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49.1 (12.4)</td>
<td>30.0-80.0</td>
<td>39.1 (10.9)†</td>
<td>18.0-68.0</td>
<td>28.0 (15.9)‡</td>
<td>5.0-62.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42.3 (16.7)</td>
<td>18.0-91.0</td>
<td>55.0 (22.0)†</td>
<td>26.0-131.0</td>
<td>75.5 (30.7)‡</td>
<td>37.0-180.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>172.8 (32.1)</td>
<td>72.0-234.0</td>
<td>134.9 (30.4)†</td>
<td>77.0-200.0</td>
<td>126.9 (36.4)†</td>
<td>77.0-192.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>57.4 (3.1)</td>
<td>48.0-60.0</td>
<td>54.6 (4.4)†</td>
<td>38.0-60.0</td>
<td>52.6 (5.9)†</td>
<td>39.0-59.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32.8 (10.9)</td>
<td>13.0-55.0</td>
<td>28.0 (10.9)</td>
<td>10.0-58.0</td>
<td>25.3 (11.1)</td>
<td>6.0-61.0</td>
</tr>
</tbody>
</table>

*For all measures except Trailmaking A, lower scores indicate poorer performance; PD, Parkinson disease.
†Significantly less than the healthy elderly control subjects (P < .05).
‡Significantly less than the subjects with PD without dementia (P < .05).

### Table 5. Scores on the Motor Assessment Measures

<table>
<thead>
<tr>
<th>Measure†</th>
<th>Group</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait velocity</td>
<td>Healthy Elderly Control Subjects</td>
<td>1.1 (0.2)</td>
<td>0.7-1.7</td>
<td>1.0 (0.2)†</td>
<td>0.4-1.5</td>
<td>0.9 (0.2)†</td>
<td>0.6-1.3</td>
</tr>
<tr>
<td>Finger tapping</td>
<td>Subjects With PD Without Dementia</td>
<td>52.9 (8.2)</td>
<td>35.0-71.0</td>
<td>46.7 (10.3)†</td>
<td>19.3-62.5</td>
<td>44.5 (12.4)†</td>
<td>5.8-62.3</td>
</tr>
<tr>
<td>Reaction time</td>
<td>Subjects With PD With Questionable Dementia</td>
<td>3.2 (0.2)</td>
<td>2.8-3.9</td>
<td>3.2 (0.2)</td>
<td>2.7-3.6</td>
<td>3.2 (0.2)</td>
<td>2.8-3.6</td>
</tr>
<tr>
<td>Movement time</td>
<td></td>
<td>4.1 (0.3)</td>
<td>3.6-4.9</td>
<td>4.3 (0.2)†</td>
<td>3.8-5.1</td>
<td>4.3 (0.2)†</td>
<td>3.9-4.8</td>
</tr>
</tbody>
</table>

*For all measures except finger tapping, higher scores indicate poorer performance; PD, Parkinson disease. Reaction time and movement time data are presented as log-transformed median latencies.
†Significantly less than the healthy elderly control subjects (P < .05).
tion from impairment due to cognitive decline. That is, minor functional impairment may have been mistakenly attributed to PD rather than to very mild cognitive involvement.

There are also a number of alternative explanations for our findings that do not involve study design that need to be addressed. The PD group without dementia may have included subjects who later will develop overt dementia. These subjects could be considered as having preclinical dementia because no dementia was detected on clinical examination. However, subtle cognitive decline may have been evident on formal psychometric testing of these subjects. Inclusion of such preclinical cases may have lowered the group means. The possibility of preclinical dementia in subjects with PD is not unreasonable given estimates of dementia prevalence in subjects with PD ranging from 11% to 25%.

Longitudinal assessment of the present PD group without dementia will allow determination of whether the cognitive impairment is static and inherent in all subjects with PD or whether the cognitive impairment may indicate the development of overt dementia in a subset of subjects with PD. Although the influence of the use of antiparkinsonian medications on cognition is controversial, effects of medication potentially could contribute to the performance differences between subjects with PD and controls in this study because drugs were not withheld at the time of psychometric assessment. Although unlikely because the groups were matched on years of education, it is also possible that the control group had a higher premorbid intelligence than the PD group without dementia and that this difference could influence our findings. It is also unlikely that group differences in depression can account for our findings because antidepressant medication and depressive symptoms were controlled in the analyses.

In terms of motor functioning, both PD groups were significantly impaired in comparison with healthy elderly control subjects as measured by gait velocity, finger tapping, and movement time. Reaction time was not slowed in either PD group in comparison with healthy elderly control subjects. Although some investigators have found that subjects with PD without dementia respond as quickly as healthy elderly control subjects in reaction time tasks, others have found that both subjects with PD without dementia and with dementia are slower than healthy elderly control subjects in these tasks. Our results may be attributable to task demands, as Malapani et al showed that the degree of slowing is related to task complexity. A more complex and cognitively demanding reaction time task than the simple Fitts paradigm used in our study possibly would reveal subtle slow-

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