Relation Between Clinical Characteristics of Parkinson’s Disease and Cognitive Decline

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ABSTRACT

This study examined how cognitive impairments in Parkinson’s disease (PD) are related to clinical characteristics such as age at testing, duration of illness, motor impairment, and especially age at disease onset. To address these issues, we administered 14 tests of memory, language, visuospatial, and frontal lobe capacities to 104 PD patients and 60 healthy volunteers of comparable age and education. The participants completed 1–9 test sessions over 1–10 years. Duration of PD was associated with deteriorating performance on most cognitive tests, independent of age-related decline. Severity of motor impairment, indexed by Hoehn and Yahr stages, was positively related to impairment on almost all cognitive tests, holding age and duration constant. For some tests, especially those that were motorically demanding and those that assessed language skills, cognitive deficits appeared earlier in the disease course for late-onset than for early-onset PD patients. These late onset deficits were synergistic effects beyond the additive contributions of disease duration and normal aging. These findings may assist physicians in advising PD patients and their families about the future course of the illness.

Numerous studies have reported cognitive impairment in patients with Parkinson’s disease (PD) relative to healthy volunteers, on measures of declarative memory, working memory, visuospatial skills, language, speed of cognitive processing, frontal lobe capacities, and attentional processes (Aarsland et al., 2001; Allain et al., 1995; Brown & Marsden, 1990; Growdon, Corkin, & Rosen, 1990; Jacobs et al., 1995; Karayanidou, 1989; Levin & Katz, 1995; Levin, Torer, & Rey, 1992; Mohr et al., 1992; Natsopoulos et al., 1993; Ogden, Growdon, & Corkin, 1990; Owen et al., 1992; Palazzini et al., 1995; Pate & Margolin, 1994; Pillon et al., 1996; Postle, Jonides, Smith, Corkin, & Growdon, 1997; Postle, Locascio, Corkin, & Growdon, 1997; Tachibana, Aragane, Miyata, & Sugita, 1997; Tsai, Lu, Hua, Lo, & Lo, 1994; Waterfield & Crowe, 1995; Wermuth, Knudsen, & Boldsen, 1996). Deficits were found even when demented patients were excluded (Goldman, Baty, Buckles, Sahrmann, & Morris, 1998; Growdon et al., 1990).

Of special concern in some studies has been the relation between age at onset of PD and cognitive decline. Some studies have reported that patients with later onset decline more sharply than those with earlier onset (Aarsland et al., 1996; Caparros-Lefebvre, Pecheu, Petit, Duhamme, & Petit, 1995; Errea & Ara, 1999; Graham & Sagor, 1999; Mahieux et al., 1998; Reid, 1992; Reid et al., 1989), whereas other studies have found no relation between age at onset and cognitive impairment (Bayles et al., 1996; Hughes et al., 2000; Strittmatter & Cramer, 1992). In some of these studies, however, age at onset was treated as a categorical variable using arbitrary cutoffs.
COGNITION IN PD

(Caparros-Lefebvre et al., 1995; Mahieux et al., 1998; Reid, 1992; Reid et al., 1989). Further, age at onset, duration of illness, and age at testing were sometimes confounded (Bayles et al., 1996; Caparros-Lefebvre et al., 1995; Mahieux et al., 1998).

The primary objective of the present study was to assess whether and how cognitive decline in PD is related to age at disease onset, with age treated as a continuous variable, and whether any resultant deficit was more than the simple sum of the pernicious effects of aging and disease duration. This matter of “onset effects” is deceptively complex, conceptually and methodologically. Conceptually, we were asking whether those who acquire PD at a relatively early age tend to show a different functional relation between duration of PD and cognitive decline than is found among those for whom onset is later, and whether this difference is more than can be accounted for by a simple superimposing of effects of the normal aging process. Further, we wanted to know whether this phenomenon occurred for some domains of cognition and not others (e.g., across memory, language, visuospatial, and frontal lobe domains).

Aside from the conceptual issue, answering questions about effects related to age at onset of illness is methodologically problematic because age at testing, duration of illness, and age at onset are mathematically interdependent; each is necessarily determined as a function of the other two (Goldbe, 1991; Katzen, Levin, & Llabre, 1998). If one of these variables is held constant, the other two correlate perfectly; if two are held constant, the other also becomes fixed. If PD patients of different onset age are matched to be at the same age at time of testing (or age is equated by statistical covariance), they must of necessity differ in duration of illness also. Conversely, if they are equal in duration, they must be of different ages. Thus, in these cases, any observed relation between onset age and cognitive performance can be attributed to the duration differences or to the age at testing differences, respectively. A seemingly invincible confounding exists. Recognizing these problems, some studies (Dubois, Pillon, Stenicke, Lhermitte, & Agid, 1990; Haeckes-Dewick, 1996) have tried to disentangle the variables by contrasting cognitive differences between groups of early and late onset PD patients, matched for duration, with differences between parallel groups of healthy volunteers who are matched in age to the PD groups. The logic is that a difference between the young and old PD groups that is not mirrored in the control groups, is due to effects of age at onset, beyond the simple effects of aging found in normal people. Analytically, such a finding is an interaction between presence of PD and age. Some of these studies did not find such interactions (Haeckes-Dewick, 1996). In one that did (Dubois et al., 1990), late onset (after age 65) patients showed greater cognitive impairment on frontal-lobe measures than did the early onset patients (before age 45), a finding interpreted as a synergy or compounding of aging and disease process effects.

A recent study (Katzen et al., 1998) analyzed the relation between cognitive dysfunction in PD and age at onset and duration, all treated as continuous variables, and removed normal aging effects with a statistical adjustment based on a regression conducted among control participants. In that study, late onset was associated with greater impairment on measures of visuospatial ability, verbal memory, and executive functions. Though commendable in its methodological inventiveness, the study by Katzen et al. was not longitudinal. Moreover, they assessed only linear, additive effects of onset age on cognition, not possible onset dependent differences in more complex patterns of change over time.

Our study examined the onset issue in cognitive decline in PD in an analytical manner within the framework of a longitudinal design. We included PD patients and healthy volunteers, and used all available information on age at testing, duration of PD, and age at onset, leaving all these variables as naturally continuous, rather than potentially losing information by basing analyses on groups formed by dividing participants at arbitrary cutoffs. Further, we employed data analysis methods that were sensitive to subtle and complex effects over time, and we administered a broad array of cognitive tests. We disentangled the confounded effects of age at testing, duration of illness, and age at onset of
illness by defining onset effects as different curvilinear patterns of change dependent on onset age, the result of interactions between age and duration.

METHODS

Participants

PD Patients
This group included 104 patients (68 men and 36 women) examined in the Movement Disorder Unit of the Neurology Department at the Massachusetts General Hospital (MGH; Tables 1 and 2). They comprised all the patients in the unit who met the inclusion criteria for this study: a diagnosis of typical idiopathic PD (Ward & Gibb, 1990) and participation in at least one cognitive test session. Initial symptoms were unilateral for about 80% of patients (equally left-sided and right-sided). Patients had varying numbers of sessions across the study during which cognitive tests were administered as part of routine followup. About 80% of patients had more than one test session. There was a total of 374 sessions across all PD patients. The mean interval between sessions was approximately 1–1.5 years. The mean length of time in the study for PD patients was 3.6 yrs (SD = 2.7; maximum = 10). Blessed Dementia Scale (BDS; Information, Memory and Concentration section, IMC) assessments were conducted during clinic visits within 90 days of each cognitive testing session (on the same day for approximately 75% of the sessions). Information concerning medications was available for all 104 patients. Most patients (85 out of 104) were taking some kind of anti-Parkinson medication at one or more points in the study. The most common drugs were levodopa (71 patients), deprenyl (45), anticholinergics (37), dopamine agonists (33), and symmetrel (17). Other common medications were antihypertensive (26), and cardiac drugs (20). Antidepressants were taken by 18 patients. Separate analyses of the effects of antidepressant and anti-cholinergic medication on cognitive test performance were conducted. Specifically, we ran the same analyses indicated below but with the inclusion of factors indicating whether drugs were being taken or not and interactions of these factors with other terms. We did not find any significant effects involving the drug terms; we will, therefore, not report these results in detail here.

At first testing, about 70% of the PD patients were at Hoehn and Yahr (HY; 1967) Stage 1 or 2 (unilateral involvement only or bilateral without impairment of balance, respectively). Of the 104 PD patients, 37 showed increases in HY score (i.e., in severity) at one or more points in the study and no decreases; 30 had more than one score but remained at the same HY stage; 17 had only one HY stage recorded (usually because they had only one test session). For 12 patients, a one or two level decrease in HY occurred at one point in time (sometimes preceded or followed by increases), usually coinciding with the introduction of a new medication or an increase in dosage of a current one. Extreme scores of zero (no sign of PD) and five (wheelchair bound or bedridden) occurred for 2 and 4 patients respectively, in each case at one point in the study, except that 1 patient had a zero at two sessions midway through his participation. Of the 104 PD patients, 8 had no HY data.

Table 1. Characteristics of Participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>At first testing Mean ± SD</th>
<th>Across all testing sessions Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Parkinson's disease (N=104; 68 men, 36 women)</td>
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</tr>
<tr>
<td>Age</td>
<td>64.7 ± 11.4</td>
<td></td>
<td>31.4</td>
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<tr>
<td>Education (years)</td>
<td>14.9 ± 2.9</td>
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<td>8.0</td>
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<tr>
<td>BDS IMC</td>
<td>2.4 ± 4.0</td>
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<td>0</td>
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<tr>
<td>Age at onset of illness</td>
<td>58.8 ± 12.7</td>
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<td>24.5</td>
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<tr>
<td>Duration of illness (years)</td>
<td>5.7 ± 5.2</td>
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<td>0.2</td>
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<tr>
<td>Healthy volunteers (N=60; 25 men, 35 women)</td>
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</tr>
<tr>
<td>Age</td>
<td>69.8 ± 11.2</td>
<td></td>
<td>48.2</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.1 ± 3.1</td>
<td></td>
<td>7.0</td>
</tr>
<tr>
<td>BDS IMC</td>
<td>0.89 ± 1.29</td>
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<td>0</td>
</tr>
</tbody>
</table>

Note. *Blessed Dementia Scale: Information, Memory, and Concentration Subtest. bThe maximum score was obtained from 80-year-old man; two volunteers had a 4, and five a 3.
Table 2. Cognitive Testing Session/Hoehn and Yahr Stage.

<table>
<thead>
<tr>
<th>Patients with Parkinson's disease (Total = 374)</th>
<th>Healthy Volunteers (Total = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of testing sessions</td>
<td>Frequency</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
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<td>3</td>
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<td>8</td>
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<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Healthy Volunteers

This group included 60 participants, 25 men and 35 women (Tables 1 and 2). They were either spouses or caregivers of patients being seen in the Neurology Service at MGH, or were volunteers from the Harvard Division on Aging. They had no history of dementia or other neurologic or psychiatric disease and signed consent forms. Control participants were significantly (p = .006) older than PD patients at first testing, but the mean difference was only 3 years, and, if anything, the disparity would be expected to produce a conservative error in assessing cognitive impairments in PD. Further, we included age as a covariate in the analyses as needed. PD patients and control participants did not differ significantly in years of education. For healthy volunteers, there was an average of 2.5 years between the first two testing sessions. They were followed for a mean of 0.7 years (SD = 1.5; for those with more than one testing, the range was 0.5–6.3 years).

Cognitive Tests and Other Measures

Age at onset of PD (and duration of illness, derived from it) was obtained from patients and family members. The BDS is a brief mental status examination that measures the presence and severity of dementia (Blessed, Tomlinson, & Roth, 1968). The IMC section tests a participant’s memory and knowledge of personal information and public events. A score of 0–2 is considered normal (for ages up to 65; Growdon & Corkin, 1986), and an increasing number of errors indicates greater impairment up to a maximum of 37.

We used 12 additional cognitive tests assessing declarative memory, language, visuospatial abilities, frontal lobe functions, and abstract reasoning (Table 3). (NYU Stories and Geometric Figures each have two variations giving a total of 14 tests). The tests were selected to sample a broad array of cognitive functions. Not all participants at all sessions had complete data across the tests. Sometimes, one or more tests could not be administered because of time constraints or, more rarely, because of incapacity. Any selection bias due to the latter would have produced a conservative error in excluding data from some sessions when PD patients were most impaired. Disregarding the IMC and Pairs-Left test (both based on incomplete data), 51% of records for PD patients had complete scores on all tests; 43% for control participants. An analysis for a given cognitive test used all available scores for that test, and across groups and tests, 75%–98% of sessions had scores for each cognitive test.

Practice effects for cognitive tests were not a significant confound in this study because (a) four of the tests had alternate forms that were rotated across sessions for a participant (six forms for Delayed Story Recall, and two for Figure Recall, Boston Naming, and
Table 3. Cognitive Tests.

<table>
<thead>
<tr>
<th>Test</th>
<th>Cognitive function purported to measure</th>
<th>Description of test</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York University (NYU) Stories</td>
<td>Verbal memory</td>
<td>Read a one-paragraph story (one of six similar variations); repeat the story after a 10-min delay. Verbatim Score is the number of words recalled (max score = 20) and Gist Score is the number of essential elements of the story, even if the details are wrong (max = 10).</td>
</tr>
<tr>
<td>10-min Recall (Verbatim and Gist)</td>
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<tr>
<td>and Gist Brown, &amp; Osborne, 1980</td>
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<tr>
<td>Geometric Figure</td>
<td>Visual memory/ constructional praxis</td>
<td>Draw an “easy” and “hard” geometric figure (rectangles, diamonds, circles, etc.; one of two variations each) at own pace while viewing the original (Copy condition) and draw the figure from memory after a 10-min delay (Recall condition). Various portions of the subject’s drawing are scored for correct reproduction. (Max score = 10).</td>
</tr>
<tr>
<td>Copy and 10-min Recall conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>for “Easy”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and “Hard” figures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benton Visual Retention (Benton, 1974)</td>
<td>Visual memory (immediate recognition)</td>
<td>View 14 complex designs, each for 10 sec; each followed immediately by 4-choice recognition test. (Max score = 14).</td>
</tr>
<tr>
<td>Boston Naming (Kaplan, Goodglass, &amp; Weintraub, 1983)</td>
<td>Confrontation naming</td>
<td>Name 42 line drawings of common objects shown sequentially (one of two different forms), each within 20 sec. (Max score = 42).</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>Verbal fluency (Semantic)</td>
<td>Name as many four-footed animals as possible in 1 min.; same for vegetables (mean of two taken)</td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>Verbal fluency (Symbolic)</td>
<td>Name as many words beginning with the letter “S” as possible in 1 min.; same for “F” (mean of two taken)</td>
</tr>
<tr>
<td>Stroop Color Naming Test (Stroop, 1935)</td>
<td>Selective attention/ frontal-lobe function</td>
<td>Name the ink color in which incongruent color names are written (45 sec.).</td>
</tr>
<tr>
<td>Raven’s Coloured Progressive Matrices (Raven, 1965)</td>
<td>Abstract reasoning</td>
<td>Choose, from 6 alternatives, the missing section from each of 36 patterned figures presented sequentially (no time limit). (Max score = 36).</td>
</tr>
<tr>
<td>Luria Mental Rotation Test (Golden, Hammeke, &amp; Purisch, 1980)</td>
<td>Visuospatial function</td>
<td>Choose which square in a 4-choice array matches a sample square when rotated; 10 figures with a 10-sec time limit for each. (Untimed score also recorded). (Max score = 10).</td>
</tr>
<tr>
<td>Money Road Map (Money, 1976)</td>
<td>Visuospatial function</td>
<td>Follow a dotted line on a street map and indicate at 32 locations whether turn is left or right. (Max score = 32).</td>
</tr>
<tr>
<td>Picture Arrangement (WAIS–R subset; Wechsler, 1981)</td>
<td>Logical reasoning</td>
<td>Arrange several cartoon pictures serially to create a logical storyline; 10 trials; 1–2 min each; 2 points correct, 1 partial. (Untimed score also recorded). (Max score = 20).</td>
</tr>
</tbody>
</table>
Table 3. (continued)

<table>
<thead>
<tr>
<th>Test</th>
<th>Cognitive function purported to measure</th>
<th>Description of test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picture Arrangement</td>
<td>Frontal-lobe function</td>
<td>Number of pairs of pictures incorrectly left in originally presented positions on the Picture Arrangement Test (above).</td>
</tr>
<tr>
<td>Pairs Left (McFie &amp; Thompson, 1972)</td>
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</tbody>
</table>

Note. High scores on the cognitive tests indicate proficiency and low denote impairment, except for the Pairs Left (and IMC) where number of errors is indexed. Estimates of “alternate form” reliability were possible for some tests by correlating variations. Story Recall evaluated for verbatim reproduction and for recall of the “gist” of the story correlated >.8 for NCS and for PD patients. Because of these high correlations, only results for the verbatim measure were analyzed further. Copying and recall of geometric figures were evaluated for a simple (“easy”) and for a complex (“hard”) figure. Although ceiling effects attenuated correlations for Geometric Figure tests, for the PD patients the r was >.6 for the simple versus complex figure for copying and recall. Scores for copying the easy and hard figures were averaged to produce a single score, and similarly for figure recall. Category and Letter Fluency correlated r = .64 for NCS and for PD patients. An estimate of test-retest reliability was obtained for each cognitive test (including the IMC, but not Geometric Figure tests because of ceilings or the Pairs Left measure because of floor effects) by correlating the first and second scores for each subject; length of time between test sessions was used as a covariate. For PD patients, the r ranged from .64 to .89 across cognitive tests; for NCS, r = .49-.92.

Mental Rotation), (b) inter-session intervals were long (usually 1 year or more), and (c) any practice effects would have operated as a conservative error in attenuating the longitudinal decline we looked for in PD patients.

We employed the HY Scale (Hoehn & Yahr, 1967) as an ordinal measure of the severity of disability in PD (the integers 0-5 denote increasing severity). HY stages are relatively stable, and for purposes of our analyses, HY is preferable to other commonly used measures of specific motor impairments (e.g., the Unified Parkinson’s Disease Rating Scale), which fluctuate considerably over time and are sensitive to transient medication effects.

Data Analysis
Conventional statistical methods (analysis of variance, t tests, etc.) were applied where appropriate. With respect to change over time in performance on cognitive tests, however, our data were too complex to permit a detailed analysis using common statistical methods (different numbers of sessions across participants at varying intervals). For these analyses, mixed random and fixed effects linear models were estimated with maximum likelihood methods using the Mixed Procedure in SAS software (SAS Technical Report P-229, 1992). This method builds models on the basis of between- and within-person data, even using data from persons with only one cognitive testing session (e.g., even for one session, a patient’s age and estimated duration of illness contribute to between-person information on effects of aging and disease progression, respectively). Independent (predictor) variables were age, duration of PD, and group membership (PD or control); cognitive test scores were the dependent variables. Quadratic curvilinear predictors for age and duration, and a covariate, years of education, were initially included to test for their effects, and to reduce extraneous variability in cognitive test scores, thereby increasing power to detect other effects of interest. Statistically nonsignificant terms were then removed so that the estimated change model contained only significant predictors. Age and duration of illness were held constant statistically with respect to each other (partial regression coefficients) to ascertain their separate and independent effects on change in cognitive test performance in PD patients. Data from healthy volunteers were included for the additional information they would provide on aging effects, and so that group performance differences could be ascertained (duration of illness for the control participants was set at zero). Terms involving sex were tested in the case of those cognitive tests showing significant sex differences in preliminary analyses. To estimate these complex models, we assumed a homogeneous correlation structure across time (compound symmetry) and random intercepts.

The primary focus of our study was the relation between age at onset of PD and cognitive change. Our statistical methods disentangled the inherently confounded effects of onset age, duration of PD, and age at testing. We did so by defining effects related to onset age as different curvilinear, longitudinal patterns of
change over time dependent on the age at onset. Such complex variation cannot be accounted for by the combined effects of duration and age, at least not in any additive, linear manner. In terms of data analysis, such differences in patterns are equivalent to interactions between age at testing and duration of illness (in their linear and/or curvilinear terms). An interaction is synonymous with nonadditivity; its absence in this case would mean the nature of cognitive decline was independent of when the disease began. Thus, in analyzing change for each cognitive measure, we always tested initially for interactions between age at testing and duration of illness, in both their linear and quadratic terms, in the mixed coefficient models noted above.

RESULTS

Age, Duration, Group, and Sex Effects, and the Relation Between Motor and Cognitive Dysfunction

As a preliminary assessment of sex effects, an analysis of covariance (ANCOVA) was run with the earliest test score for each participant as the dependent variable, separately for each cognitive test (including the IMC), where Group (PD vs. control) and Sex were crossed factors, and age and education were covariates. Main effects for sex were found for two tests: the Money Road Map test \( (p = .0001) \) and Letter Fluency \( (p = .0017) \). In each group, men surpassed women on the Road Map Test \( (p = .001) \), and women were superior to men on Letter Fluency \( (p < .05) \). Pursuant to these findings, sex was included as a factor in all analyses for the Map and Fluency tests.

Assessment of change in cognitive test performance was conducted with the method of mixed random and fixed coefficient modeling. Figure 1 illustrates the estimated model of change for each cognitive test (except those with sex effects) resulting from these analyses by showing maximum likelihood estimated scores across age for control participants and PD patients with different ages at onset of illness. For these analyses, years of education were significantly \( (p < .05) \) and positively predictive of performance for PD and control groups combined, for all cognitive tests, except for nonsignificant relations for the Mental Rotation, Geometric Figure Copying/Recall tests, and the IMC. For all cognitive tests, and across both groups, there was a significant linear or curvilinear decline in performance associated with increasing age (all curvilinear effects are quadratic monotonic, unless otherwise stated).

Within the PD group, for all tests except Delayed Story Recall and Pairs Left, an additional component of decline in performance, independent of effects of aging, was due to linear or curvilinear effects of disease duration. Although the duration effect was absent for Story Recall and Pairs Left, there was a significant main effect of group on level of performance for these measures, with control participants doing better than the PD patients (Fig. 1A). The same group difference occurred for the Picture Arrangement test, superimposed on the duration effect. This effect is reflected in Figure 1B, where the curves for PD patients for Picture Arrangement are not only generally steeper in slope than that for the controls, but, unlike the patterns for other cognitive tests in that figure, they start at a poorer level of performance relative to control participants. There were no group level differences for any other cognitive tests except marginally \( (p = .1) \) for the IMC (PD patients worse than control participants).

Effects of duration of illness were sex specific for the Money Road Map test and for tests of Category and Letter Fluency. For the Map test, women performed at a significantly worse level than men overall (across PD and control groups, and age). Male PD patients, however, showed significantly faster decline across duration than female patients. In the case of the Fluency tests, women performed significantly better than men overall on Fluency for Letters (across groups), and male PD patients declined significantly sooner and faster than the female patients on the Letter and Category Fluency tests.

Using mixed coefficient models within the PD group, we also sought to establish whether HY was related to age and duration of illness, and then to relate all the three variables to cognitive impairment. With HY as the dependent variable, age and duration at visit (as simultaneous predictors) were each found to have a significant quadratic relation to HY. Although interaction terms were not significant, dual quadratic
relations of opposite sign reflected a pattern of decelerating deterioration to an asymptote of relatively higher functioning for earlier onset patients compared to those with later onset. Although age was a significant ($p = .04$) predictor of HY, duration of illness was significant at a more stringent level ($p = .0002$) and accounted for 22% more variance in HY beyond what age accounted for; age was uniquely associated with only 14% of the variance. Thus, duration of PD was more closely tied to HY than was age, a finding that provided support for the accuracy of our measure of duration and the validity of HY as an index of progression of PD.

The relation between HY and cognitive test performance among PD patients was assessed.
with mixed coefficient models in which the predictors were HY, education, and linear/cubicalinear terms for age and duration of illness. (Only linear effects of HY were examined because HY is ordinal and extreme scores of 0 and 5 were infrequent). By controlling for age (HY and age were correlated $r = .33$ across all PD test sessions), any intimate relation between the progressive motor impairment of PD, as indexed by HY, and cognitive impairment could be assessed apart from spurious associations via age-related cognitive deterioration. Also, by holding duration of illness constant (duration and HY were correlated $r = .37$), the adjusted relation between HY and cognitive test scores indexed any tendency for motor and cognitive dysfunction to be intimately conjoined even as motor dysfunction varied among patients judged to be equivalent in duration. Terms were retained in a model only if they were found to predict the dependent variable (cognitive test) significantly or marginally ($0.05 < p \leq 0.1$).

HY positively predicted extent of impairment on all cognitive tests (including the IMC; nonsignificantly so for only one, the Benton test). Age was at least a marginally ($p < .08$) significant simultaneous positive predictor (linear or curvilinear) of impairment for all tests. As an illustrative example of these effects, Figure 2 displays a three-dimensional (3D) scatterplot of HY and age vs. the IMC. IMC scores went up, that is, worsened, as HY went up within a given strata of age, that is, holding age constant; the same occurred for IMC versus age with HY constant.
Our analyses and this graphic analogue separate out the otherwise confounded effects of HY and age on cognitive test scores. Duration had a significant or marginal ($p < .09$) linear or curvilinear relation to impairment only in the case of the Mental Rotation, Raven's Matrices, Benton Visual Retention, and Fluency tests (impairment increased with duration). Thus, for the other cognitive tests, any significant covariation of impairment with duration of illness was largely accounted for by change in HY once it was introduced into the model, though age still independently accounted for variation in cognition at each strata of HY.

Effects of Age at Onset
Strictly speaking, for some cognitive tests, significant effects for age and duration of illness were linear and curvilinear interactions between the two variables. Duration interacted with age, however, only in the sense of a variation in how sharply the performance of PD patients veered from the path of decline due to normal aging, not whether or not it did (Fig. 1B). An interaction between duration and age indicated a different pattern of change over time in cognitive function dependent on age at onset of PD. Interactions between duration and age, that is, age at onset effects, were significant for Geometric Figure Copying and Recall, Boston Naming, Category and Letter Fluency, Mental Rotation, Picture Arrangement, and the IMC. For cognitive tests with age at onset effects, patterns of change were complex, but in general, patients with early onset differed from other patients in that they did not show a decline in performance that immediately and sharply diverged from the shallower decline characteristic of control participants. Instead, they tended to follow, for a period, a path similar to that of the control participants, and only later veered off from that to markedly poorer performance (Fig. 1B; this pattern also occurred for Letter and Category Fluency). Interestingly, motor impairments in PD showed a pattern of change similar to that of cognitive impairments on those tests with onset effects.

Examples of Change Effects
To demonstrate that the estimated models in Figure 1 reflect actual data patterns, Figure 3
Fig. 3. Examples of cognitive test scores versus age, PD duration and age at onset. 3D scatterplots of cognitive test scores (vertical axis) versus age, duration of illness and/or onset age for PD patients are shown for the Stroop test (top panel) and for the Boston Naming Test (bottom). (Multiple observations per patient. The top figure is truncated on the left where there were no data). In the top panel, duration and age are shown as separate (horizontal) axes so that their respective relations to test scores can be separated visually (as our analyses did computationally). Axes for duration and age at onset are similarly employed in the bottom panel.

displays 3D scatterplots of scores for selected cognitive tests versus age at testing, duration, and/or age at onset for PD patients. The two panels are meant to provide, respectively, examples of cognitive tests with no effect of age at onset (Stroop Test – top panel) and with significant onset effects (Boston Naming – bottom). The top panel shows how duration and age were independently and additively related to cognitive decline for the Stroop test. The scores tended to decline with increasing duration at each strata of age, and conversely with increasing age, holding duration constant. The bottom panel highlights the tendency for scores on the Boston Naming Test to decline with duration, and also shows that this relation is more pronounced as an
increasing function of age at disease onset (consistent with the pattern for Boston Naming in Fig. 1B).

DISCUSSION

On almost all cognitive tests, duration of PD was associated with deteriorating performance, independent of decline related to aging. Severity of motor impairment due to PD was also related to impairment on almost all cognitive tests, holding age and duration constant. For some tests, decline was more gradual for patients with earlier onset. The pervasiveness, across cognitive tests, of statistical significance associated with all these effects (and the fact that p values were often < .01) precludes their being the result of chance effects due to multiple significance testing. This discussion addresses issues that are central to the interpretation of our results.

Is Intellectual Deterioration in Idiopathic PD Related to Disease Duration, Age at Testing, and Stage of Motor Impairment?

For a few cognitive tests, we found only a difference in mean level of performance between PD patients and healthy volunteers of the same age, with the patients performing worse (Delayed Story Recall and Pairs Left of Picture Arrangement; Fig. 1A). For most cognitive functions we assessed, however, we found evidence that intellectual deterioration in PD is an increasing function of PD duration, independent of and superimposed on the normal deleterious effects of aging that were apparent in both the PD and control group. Cognitive impairments associated with PD are not an uncommon finding, though their pervasiveness across the cognitive functions we assessed was notable. We delineated the longitudinal nature of decline in these functions in some detail (Fig. 1) and separated out components of normal aging effects and disease duration per se.

HY was significantly associated with cognitive impairment for virtually all the cognitive functions we assessed. These findings were obtained when age and duration of illness were held constant statistically. Thus, in PD there appears to be an intimate association between motor impairment specifically and cognitive dysfunction, even among patients of the same age and the same estimated chronological length of the illness.

A methodological issue concerns the extent to which our measures of cognitive deficits in PD are directly affected by motor impairment. Such contamination should not have had an influence on our results. Most of our cognitive tests required no motoric action at all or the actions were performed by the examiner (e.g., the rater traces the path in the Map test). The Geometric Figure Recall and Copying tests were the ones most motorically demanding, but Story Recall, which required no physical movement, correlated well with Figure Recall (r = .50) and to the same degree for both PD patients and control participants. Further, others (Boller, Passafiume, & Keefe, 1984) have reported that cognitive impairments in PD are found whether or not tasks require motor responses.

Is Cognitive Deterioration in PD Related to Age at Disease Onset?

We defined cognitive effects related to age at onset of PD as different patterns of change in cognitive performance over time, dependent on age at onset. For a number of cognitive tests, we found evidence of complex differences in patterns of longitudinal change related to onset age (Fig. 1B). Typically, in these cases, patients who were relatively young at onset of PD showed stability early in the disease before deteriorating more sharply. In contrast, those who were older at point of onset showed more immediate decline upon acquiring the illness. Similar findings have been reported in some cross-sectional studies for frontal lobe tests (Dubois et al., 1990; Katzen et al., 1998) and a variety of other measures of memory and visuospatial function (Katzen et al., 1998), with later onset age predicting poorer performance. For some cognitive tests, we found the pattern of change did not significantly vary with onset age (Fig. 1A). Whether a test did or did not show effects related to onset age was not a function of cognitive domain. Some frontal lobe measures, for example, Letter Fluency, showed an onset age
effect, whereas others, for example, the Stroop Test (Fig. 1A), did not. The inconsistency between this result and that of others who have found onset effects for frontal lobe/executive functions may be partly the result of different measures employed. For example, Dubois et al. (1990) and Katzen et al. (1998) employed the Wisconsin Card Sorting Test (Nelson, 1976) to measure frontal lobe functioning and we did not, while we used the Stroop Test, and they did not. It was notable that all tests of language skill were among those showing the onset effects (Boston Naming and Fluency Tests). Also, onset effects occurred for the most motorically demanding tests, geometric figure copying and recall. Normal aging effects were slight for the copying measure, but PD patients diverged from normal functioning for the copying and recall measure, and more so as a function of later onset age (Fig. 1B). We found that HY stage also showed a more gradual deterioration for early as opposed to late onset patients (as others have reported; Diamond, Markham, Hoehn, McDowell, & Muehler, 1989; Goetz, Tanne, Stebbins, & Buchman, 1988), paralleling onset effects in some cognitive tests, and suggesting an intimate connection between motor and cognitive decline.

Some (Dubois et al., 1990) have speculated that onset effects on cognition in PD are due to the fact that younger patients have reserves in some cognitive functions that they can call upon to compensate for impairments in other functions, whereas older patients do not. Evidence from functional neuroimaging studies of age-related changes in performance of cognitive tasks may be relevant here. Cabeza's (2001) review of functional neuroimaging studies in healthy young and older participants indicates that it is the older people who have more bilateral activation. Two possible theories are cited to explain this finding: dedifferentiation of activation or compensatory activation in the older people. The dedifferentiation theory posits that older persons have difficulty recruiting specialized neural mechanisms, whereas the compensatory hypothesis asserts that older persons employ homologous lateral structures to bolster impaired processing. Future imaging studies may show whether PD patients with early versus late onset show differences in activation during cognitive tasks analogous to those found in younger versus older healthy persons. These findings would be theoretically important.

Relation Between Behavioral Deficits and the Pathophysiology of PD

PD is generally considered a disease of motor impairment, with prominent tremor, muscular stiffness, slowed movements, and postural instability. These symptoms occur because of neuronal degeneration in the pars compacta of the substantia nigra, with a resultant decrease in dopaminergic neurotransmission to the putamen and caudate nuclei (collectively known as the striatum) of the basal ganglia. These nuclei project to the globus pallidus and thalamus, ultimately influencing neuronal firing patterns in the motor cortex. PD is a progressive disease and the severity of motor impairment reflects the extent and severity of ongoing neuronal dysfunction and loss. Because of the pervasive motor abnormalities, cognitive impairments in PD are often overlooked; indeed, in his original description James Parkinson (1817) specifically noted “... the senses and intellect being uninjured.” It is now widely appreciated, however, that cognitive impairments are common in PD, and appear linked to the severity of motor impairments (Growdon & Corkin, 1986; Growdon et al., 1990; Hayashi, Hanyu, Kurashima, Tokutake, & Yanagisawa, 1996; Mortimer, Pirozzolo, Hansch, & Webster, 1982; Van Spandonck, Berger, Horstink, Buytenhuijs, & Cools, 1996). Further, a recent study (Levy et al., 2002) found that the incidence of dementia was related to the severity of extrapyramidal symptoms in PD. Explanations for the close association between cognitive and motor deficits, although incomplete, have centered on anatomic and biochemical observations. Alexander, DeLong, and Strick (1986) described five basal ganglia-thalamocortical circuits that work in parallel and influence restricted portions of the frontal lobe. One of these circuits, the “dorsolateral prefrontal” circuit, likely supports cognitive functions, including encoding and retrieval processes as well as executive or control functions. The cognitive deficits in PD may be explained by dysfunction within this circuit (Taylor et al., 1986). Similarly, disruption of the “motor” circuit may account for the motor
impairments in PD. Biochemical observations support the importance of these anatomical connections. The functional integrity of the striatum depends upon receiving dopaminergic projections from the substantia nigra. Replacing the dopamine deficiency by administering levodopa suppresses many of the motor abnormalities of PD; even in PD patients with mild motor impairments, increasing brain levels of dopamine significantly with levodopa improved cognitive test performance, especially on tests that reflect frontal lobe function (Growdon et al., 1998).

CONCLUSIONS

This longitudinal study of 104 PD patients demonstrated that PD is associated with impairments in a wide array of cognitive capacities: long-term memory, language, visuospatial, and frontal lobe functions. PD leads to greater deterioration in these capacities over time than would be expected to occur as the result of normal aging. Further, there seemed to be an intimate connection between severity of motor impairment and cognitive dysfunction among patients of the same age and time since onset of the illness. We also found evidence of age at onset effects on cognitive decline, apart from the additive influences of duration of illness and aging. For some cognitive functions, especially language skills, deficits were subtle at an early onset age, and decline occurred sharply only for patients with later onset. Although the cognitive deficits associated with PD are generally more subtle than those caused by other neurological conditions (e.g., Alzheimer’s disease, stroke, tumor etc.), they still could affect daily functioning adversely, and therefore should be addressed clinically. At a single point in time, and especially in patients with recent, young onset, cognitive dysfunction may not be obvious. In late-onset PD, however, cognitive deficits are of sufficient severity that they may warrant pharmacologic intervention. This need underscores the value of developing compounds that enhance cognition in age-related degenerative disease. Further, our findings may be helpful to physicians in advising PD patients and their families about the future course of their illness.

Using multiple measures of cognition, we developed a model of cognitive decline in early-versus late-onset PD. What is needed now is a neural model that incorporates anatomical and neurochemical alterations in early- versus late-onset PD and links the cognitive model to specific neural abnormalities.

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