Chronic Effects of Dopaminergic Replacement on Cognitive Function in Parkinson’s Disease: A Two-Year Follow-Up Study of Previously Untreated Patients

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Summary

BACKGROUND: The cognitive effects of dopaminergic treatment in Parkinson’s disease (PD) are still controversial.

OBJECTIVE: To evaluate, in previously untreated patients with PD, whether chronic dopaminergic stimulation produces significant cognitive changes; whether they are sustained beyond the period of a few months; and whether the cognitive status of two motor-comparable groups is differently affected by levodopa and pergolide.

DESIGN AND SUBJECTS: Parallel, randomized open study with blind neuropsychologic evaluation of 20 consecutive de novo patients with PD before and 3, 6, 12, 18, and 24 months after monotherapy with levodopa (n = 10) or pergolide (n = 10; 6-month monotherapy; pergolide + levodopa thereafter).

RESULTS: Both treatments were associated with a significant improvement in motor scores and in tests assessing learning and long-term verbal and visual memory, visuospatial abilities, and various frontal tasks. While improvement in motor scores persisted, improvement in activities of daily living and in semantic fluency, Luria’s rhythm and motor and long-term memory tests was not sustained at the 24-month examination. Further, performance on attentional, short-term memory, and the Stroop tests did not change over the course of the study.

CONCLUSIONS: Both treatments were associated with incomplete but long-lasting (18 mos) improvement in many cognitive tasks which declined thereafter, suggesting that dopaminergic replacement is not enough to compensate for all cognitive deficits of PD.

Key Words: Parkinson’s disease—Cognition—Levodopa—Pergolide—Frontal functions.

A wide range of relatively subtle cognitive deficits can be observed in patients with Parkinson’s disease (PD).1 Deficits have been recognized in different cognitive domains such as memory,2,3 visuospatial processing,4 attention,5 concept formation, and executive functions.6 Although cognitive decline is admitted to be an integral feature of the evolution of PD, little is known about the pathophysiological basis, the rate of progression, and the pharmacologic response of this decline. The similarities of some cognitive deficits to those reported following focal lesions of the prefrontal cortex,6 together with dopamine’s role in the modulation of complex circuits linking the basal ganglia with prefrontal cortex, have led to the hypothesis that changes in the levels of dopamine stimulation may modify cognitive performance.6,7 However, in patients with PD levodopa has been reported to improve,5,8–10 impair,7,10,12 or not affect11,12 frontal cognitive performance, and to improve,13–15 impair, or not affect memory functions.12 Differences in experimental design and methodology with conclusions drawn from unselected group studies may partially explain these discrepancies.6,12 For instance, adverse effects of levodopa on frontal cognitive performance have been reported mainly for patients who exhibit a “wearing-off” or fluctuating motor response to oral levodopa7,12,16 while treated patients with stable motor response perform with
similiar dopamine stimulation. Assessing the mental status before and after the initiation of treatment in recently diagnosed patients can be a better approach for examining the cognitive effects of dopaminergic therapy. However, recently diagnosed patients examined in such studies have previously received other antiparkinsonian drugs or have generally been reassessed only once under levodopa treatment and at different stages between studies, ranging from a few months, when motor response is expected to be optimal, to many years after the initiation of treatment. The different timespans covered in these studies might further puzzle the cognitive effects of dopaminergic therapy, because it has not been established whether the putative cognitive changes appear later than the motor ones or decline shortly thereafter. Indeed, experimental data from humans and animals suggests that motor and cognitive deficits may be dissociable. Neuropsychologic examinations repeated at regular intervals after initiation of treatment can provide reliable indications of whether the cognitive status is changing and, if so, how rapidly and in what ways. The present study on previously untreated patients with PD was designed to investigate: (1) whether chronic dopaminergic stimulation produces significant cognitive changes; (2) whether the cognitive changes are sustained beyond the period of a few months; and (3) whether the cognitive status of two motor-comparable groups is differently affected by dopaminergic drugs with a different mode of action (that is, levodopa vs pergolide). Accordingly, we conducted a 2-year parallel and randomized open study with blind neuropsychologic evaluation of 20 consecutive de novo patients with PD who were randomly assigned to 6 months of monotherapy with levodopa (n = 10) or pergolide (n = 10) and periodically given parallel forms of a comprehensive neuropsychologic test battery chosen to tap major aspects of cognitive functions known to be abnormal in PD. After the 6-month assessment, the addition of levodopa in the pergolide group was planned to compensate for the predictable decline of motor function if treatment was maintained with the dopamine agonist alone. This design permitted a further 18-month comparison of the cognitive effects of levodopa alone versus levodopa plus a dopamine agonist, one of the usually recommended treatment strategies for early PD.

**PATIENTS AND METHODS**

**Subjects**

Twenty newly diagnosed patients who fulfilled the London Brain Bank Criteria for idiopathic PD and had never received antiparkinsonian medication (13 women and 7 men; mean age 65.7 ± 8.9 yrs; mean duration of symptoms 14.3 ± 6.2 mos) were consecutively recruited from the outpatient clinic of the Movement Disorder Unit of the Neurology Department at Sant Pau Hospital, Autonomous University of Barcelona, Spain, for inclusion in the study. Informed consent was obtained from all patients. The patients included were direct referrals from the community and were not selected by any predetermined criterion other than those appropriate for diagnosis. Thus, the patient population, although small, is probably a representative sample of PD. Patients with a Mini-Mental State Examination score <24, history of major psychiatric disorders, psychoactive medication, alcoholism, stroke, neurosurgical operation, or any other condition known to impair mental status other than PD were excluded. Subjects with low mood, possibly associated with PD, but without meeting DSM-IV diagnostic criteria for major depression or dysthymia were included. All subjects were self-declared as right-handed. The patients were randomly assigned to two branches of treatment with three daily doses of pergolide (n = 10) or levodopa (n = 10). Table 1 shows the demographic and clinical data of the two groups of patients studied.

**Design**

Each patient received a depression questionnaire (Beck Inventory) and a comprehensive neuropsychologic study before and 3, 6, 12, 18, and 24 months after the initiation of treatment. At the beginning of treatment, patients were instructed to progressively increase dosage

**TABLE 1. Demographic and basal clinical data of the 20 patients with Parkinson’s disease**

<table>
<thead>
<tr>
<th>Total sample</th>
<th>Pergolide group</th>
<th>Levodopa group</th>
<th>t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 20)</td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>65.7 ± 8.9</td>
<td>63.7 ± 10.5</td>
<td>67.3 ± 7.5</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>13/7</td>
<td>6/4</td>
<td>7/3</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>5.8 ± 5.0</td>
<td>6.7 ± 6.4</td>
<td>5.2 ± 4.1</td>
</tr>
<tr>
<td>Disease duration (mos)†</td>
<td>14.3 ± 6.9</td>
<td>14.1 ± 7.3</td>
<td>14.4 ± 6.2</td>
</tr>
<tr>
<td>Hoehn/Yahr (tremor/akinetic rigid)</td>
<td>1.6 ± 0.6</td>
<td>1.5 ± 0.6</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>Predominant symptom</td>
<td>16/4</td>
<td>8/2</td>
<td>8/2</td>
</tr>
<tr>
<td>Side of maximal involvement (right/left)</td>
<td>9/11</td>
<td>4/6</td>
<td>5/5</td>
</tr>
<tr>
<td>Depression (Beck Inventory)</td>
<td>9.3 ± 6.8</td>
<td>10.1 ± 7.9</td>
<td>8.5 ± 5.9</td>
</tr>
</tbody>
</table>

NS, not significant results.

All data shown as mean ± standard deviation.

* Fisher’s exact test.
† Prior to commencing treatment.
of the study drugs every 3 days until reaching 1.5 mg pergolide per day or 300 mg levodopa per day. Thereafter, doses were titrated individually, always by the same examiner (D.L.V.), blind to the treatment regimen, who suggested to a non-blind examiner (B.P.S.) whether a dosage modification should be made. Titration was made according to standard clinical criteria following each patient self-evaluation of functional ability, side effects, and monthly examination with the Unified Parkinson’s Disease Rating Scale (UPDRS) subscale I (orientation, behavior, and mood; maximum score = 16 points), II (activities of daily living; maximum score = 52 points), and III (motor examination; maximum score = 108 points). Patients randomized to levodopa received this drug as monotherapy during the entire length of the study, whereas patients randomized to pergolide received this drug as monotherapy until the day after the 6-month neuropsychologic evaluation when levodopa was added to the pergolide treatment. Safety assessments, performed at all programmed monthly visits and whenever necessary, included any adverse events or dopaminergic-induced symptoms according to the UPDRS subscale IV (fluctuations, dyskinesias, and other complications). Concomitant medication needed for chronic diseases not excluded by entry criteria were continued. Routine hematologic and biochemical examinations, clinic cardiac evaluation, and electrocardiogram were performed at study entry and at the end of the study.

Neuropsychologic Testing

All patients were examined with a battery of neuropsychologic tests especially selected to cover a wide range of cognitive deficits (memory, motor speed, visuospatial and frontal functions) previously reported among patients with PD. To minimize practice effects, four different parallel forms of various neuropsychologic tests more susceptible to learning effects were used. The order of administering the different tests forms was randomized and balanced across the 20 subjects and the four first assessments (basal to 12-month evaluation) following five different orthogonal Latin square distributions. On the two final assessments, subjects received the parallel forms that corresponded to their first and second evaluations. A board-certified neuropsychologist (C.G.S.) blind to the treatment regimen administered all neuropsychologic tests. Testing followed a fixed sequence and was completed over a period of 1 to 2 days with suitable rest periods.

Attention and Short-Term Memory

Span performance for digits was assessed by the Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS) using alternative lists of digit sequences drawn from a table of random numbers for repeated examinations. Span performance for visual designs was assessed by the multiple-choice version of the Benton’s Visual Retention Test (BVRT) using roughly equivalent figure design forms for repeated examination.

Verbal Learning and Long-Term Verbal Memory (After a 20-Minute Delay)

Verbal learning and long-term verbal memory were evaluated with the Rey Auditory Verbal Learning Test (RAVLT). Parallel lists with appropriate set of words for recognition testing were applied.

Visuospatial and Visuoconstructive Abilities (Through Copy), and Long-Term Visual Memory (After a 20-Minute Delay)

Visuospatial and visuoconstructive abilities, and long-term visual memory were evaluated with the Rey-Osterrieth Complex Figure Test (RCFT). Subjects were informed in advance of the recall session. The original and three alternative figures of the RCFT designed for retesting purposes, were used.

Motor Speed

Motor speed was evaluated using the Trail Making Test (TMA) part A, the finger tapping test, and three versions of simple reaction time, namely, visual, aleatory visual, and auditory. Finger tapping test consisted of recording the number of taps during 25 seconds with right and left hands. The visual reaction time was recorded as the mean of reactions for stimulus (square of 10 × 10 cm) projected in the central horizontal meridian of the video monitor for simple visual reaction time and at any point of the video monitor for simple aleatory visual reaction time. For simple auditory reaction time, the stimulus was a sound randomized between two options: low-frequency (100 cycles/sec) or high-frequency (500 cycles/sec). The stimuli were not preceded by any warning. They appeared after a random interstimuli interval ranging from 2000 to 3000 msec and were repeated 20 times in each test following a set of five trials. Subjects were instructed to press the space bar of a keyboard with their preferred hand, either the dominant or the less affected hand. Four alternate and comparable forms of the TMA were used.

Frontal Tasks

Frontal tasks were assessed using letter and category fluency tests, a computerized version of the Stroop Test, the Luria Rhythm Reproduction and Motor Tests, and the arithmetic subtest of the WAIS. The set FAS and three other alternative sets of letters with Spanish values comparable to FAS were used for
letter-fluency and four alternative sets of semantic categories of comparable difficulty each (that is, animals found on a farm vs animals that live in the jungle) were used for category-fluency. Four different sequences of the Luria Rhythm test were used. Alternative forms of Luria’s motor test consisted on the inversion of the primary fist-palm-side sequence (that is, palm-fist-side, side-fist-palm, and fist-side-palm). The original and three parallel forms of roughly comparable items of the arithmetic subtest of the WAIS were used. The same format of the Stroop test was used on each examination. The Stroop test included two parts. Part one (word) consisted of 20 colored stimuli (blue, green, yellow, or red asterisks) that were displayed randomly on a computer screen with the patient required to press the key of the same color as quickly as possible when the stimulus appeared. Part two (color) consisted of the random display on the screen of the names of the four colors in words, each name appearing in a non-corresponding color (for example, name red; color blue) with the patient required to press the key that corresponded to the color of the letters and not to the color name, thus requiring the patient to inhibit the immediate impulse to answer according to the written word. Performances were scored as reaction time (msec) for correct responses (time window 2000 ms). Performances were scored as reaction time (msec) for correct responses. The “Stroop-effect” was measured by the difference between the interference (color) and control (word) condition.

Statistical Analysis

Statistical analysis consisted of two-way and repeated measures analysis of variance (ANOVA), including the between-subjects factor “treatment” (patients treated with pergolide or levodopa) and the within-subjects factor “time” (basal, time point in relation to treatment initiation), of all variables derived from the UPDRS and the neuropsychologic analysis obtained at +3, +6, +12, +18, and +24 months. In addition, a comparison between the 6- and 12-month and the 18- and 24-month evaluations was performed.

RESULTS

All 20 patients included in the study completed the planned motor and neuropsychologic assessments for the first 12 months of the study. One patient was lost to follow up at the 18-month examination. All patients included continued to fulfill the diagnostic criteria for idiopathic PD.

Drug Dose and Adverse Events

At the end of the sixth month of the study, with both study drugs given in monotherapy, the mean final daily dose was 2.8 mg (range, 1.5–3 mg) in the pergolide group and 435 mg (range, 200–600 mg) in the levodopa group. At the end of the 24 months of the study with levodopa added to pergolide in the pergolide group (from the day after the 6-month examination) and levodopa still in monotherapy in the levodopa group, the mean final daily dose was 2.8 mg pergolide (range, 1.5–3 mg) plus 380 mg levodopa (range, 200–600 mg) in the pergolide group, and 540 mg levodopa (range, 300–600 mg) in the levodopa group. Adverse effects were mild, transient, and presented mainly during the monotherapy phase of the study: nausea, resolved in all cases with the use of domperidone (pergolide, n = 4; levodopa, n = 3); visual hallucinations (levodopa, n = 1); drowsiness (pergolide, n = 1); and anxiety (pergolide, n = 1). Visual hallucinations in the patient taking levodopa lasted only 1 day and disappeared spontaneously, whereas anxiety in the patient with pergolide subsided following 2 mg lorazepam per day for 3 days.

UPDRS Data (Motor Status)

Results of the longitudinal evolution of the mean rating scores of the UPDRS (subscales I, II, and III) corresponding to the time of the neuropsychologic assessments are reported below and summarized in Table 2. At the end of the second year of follow up, one patient developed mild dyskinesias and another patient presented with dyskinesias and mild wearing-off phenomenon. Motor and neuropsychologic examination of this patient was conducted while in the “on” state. There were no significant basal differences between groups on the total UPDRS score (subscales I + II + III) or in the score of each UPDRS subscale. Considering the total UPDRS score (subscale I + II + III), a significant time effect was observed (p = 0.001), without treatment or treatment-by-time differences, with patients improving in all subsequent evaluations (3, 6, 12, 18, 24 mos). However, when separately considered, UPDRS part II (activities of daily living, an index of quality of life) lost significance at the 24-month examination. The addition of levodopa in the pergolide group after the 6-month examination was not associated with a group-by-time effect (that is, both groups obtained a comparable symptomatic benefit).

Neuropsychologic Findings

Results of the neuropsychologic tests are shown in Tables 3, 4, and 5.

Motor Speed (Simple Reaction Time and Finger Tapping)

No significant between-group differences were observed in basal conditions on the TMA, simple visual,
aleatory visual, and simple auditory reaction times, or in the finger-tapping test (Table 3). Except for the TMA test, there were no significant time, treatment or treatment-by-time differences in motor speed tests following the introduction of dopaminergic therapy during the entire length of the study. The addition of levodopa in the pergolide group after the 6-month evaluation produced no significant changes. During the first year of the study, both groups improved their performance in the TMA, but this improvement only reached statistical significance at the 12-month evaluation. Thereafter, this improvement lost significance and, numerically, both groups worsened with respect to baseline at the 18- and 24-month evaluations.

Attention and Short-Term Memory (Span Performance)

No significant differences between groups were observed in basal conditions on the patient’s span performance for digits (Digit-Span) or visual designs (BVRT) (Table 4). There were no significant time, treatment or treatment-by-time differences following the introduction of therapy during the entire length of the study. The addition of levodopa in the pergolide group after the 6-month evaluation produced no significant changes.

Verbal Learning (RAVLT)

There were no significant differences between groups in basal conditions (Table 4). No changes were seen at the 3-month evaluation, but a significant time effect showing a global improvement on the different measures of the test (learning of trials 1 to 5, total trials and long-term recall) was observed in both groups at the 6-month evaluation. This persisted significantly with respect to the unmedicated condition at the 12-month evaluation. However, the long-term recall (trial 6) lost significance at the 18- and 24-month evaluations. No treatment or treatment-by-time differences were observed. The addition of levodopa in the pergolide group was not associated with any additional effect.

Visuospatial and Visuoconstructive Abilities, and Long-Term Visual Memory (RCFT)

There were no significant differences between groups in basal conditions (Table 4). Both groups improved significantly after the introduction of treatment and this im-

TABLE 2. Comparison between patients following treatment with levodopa (LD) and pergolide (PGL) at basal examination and 3-, 6-, 12-, 18-, and 24-month follow up*

<table>
<thead>
<tr>
<th></th>
<th>UPDRS-I</th>
<th>UPDRS-II</th>
<th>UPDRS-III</th>
<th>BDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD basal</td>
<td>1.9 (2.6)</td>
<td>11.8 (6.8)</td>
<td>24.8 (15.1)</td>
<td>10.1 (7.9)</td>
</tr>
<tr>
<td>PGL basal</td>
<td>2.2 (2.1)</td>
<td>8.7 (4.9)</td>
<td>22.9 (13.6)</td>
<td>8.5 (5.5)</td>
</tr>
<tr>
<td>LD vs PGL basal</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LD 3-month</td>
<td>0.5 (0.9)</td>
<td>5.3 (3.1)</td>
<td>13.6 (9.8)</td>
<td>9.2 (6.3)</td>
</tr>
<tr>
<td>PGL 3-month</td>
<td>0.6 (0.8)</td>
<td>4.7 (3.5)</td>
<td>13.7 (13.4)</td>
<td>8.1 (5.7)</td>
</tr>
<tr>
<td>3-month vs basal</td>
<td>‡</td>
<td>‡</td>
<td>‡</td>
<td>NS</td>
</tr>
<tr>
<td>LD 6-month</td>
<td>0.6 (1.0)</td>
<td>5.8 (3.6)</td>
<td>14.0 (7.2)</td>
<td>9.6 (7.5)</td>
</tr>
<tr>
<td>PGL 6-month</td>
<td>0.9 (1.4)</td>
<td>6.1 (4.4)</td>
<td>15.7 (15.0)</td>
<td>8.8 (6.4)</td>
</tr>
<tr>
<td>6-month vs basal</td>
<td>‡</td>
<td>‡</td>
<td>‡</td>
<td>NS</td>
</tr>
<tr>
<td>LD 12-month</td>
<td>0.9 (1.3)</td>
<td>5.8 (4.3)</td>
<td>15.9 (8.1)</td>
<td>10.0 (6.7)</td>
</tr>
<tr>
<td>PGL + LD 12-month</td>
<td>0.5 (0.5)</td>
<td>6.9 (5.5)</td>
<td>16.1 (15.9)</td>
<td>8.9 (5.8)</td>
</tr>
<tr>
<td>12-month vs basal</td>
<td>‡</td>
<td>‡</td>
<td>‡</td>
<td>NS</td>
</tr>
<tr>
<td>LD 18-month</td>
<td>0.9 (1.3)</td>
<td>6.3 (3.6)</td>
<td>16.0 (9.3)</td>
<td>10.2 (7.3)</td>
</tr>
<tr>
<td>PGL + LD 18-month</td>
<td>0.9 (1.4)</td>
<td>7.1 (4.5)</td>
<td>16.3 (12.4)</td>
<td>9.0 (5.4)</td>
</tr>
<tr>
<td>18-month vs basal</td>
<td>NS</td>
<td>NS</td>
<td>‡</td>
<td>NS</td>
</tr>
<tr>
<td>LD 24-month</td>
<td>0.9 (1.3)</td>
<td>7.4 (4.4)</td>
<td>16.8 (11.0)</td>
<td>9.8 (5.0)</td>
</tr>
<tr>
<td>PGL + LD 24-month</td>
<td>0.9 (1.4)</td>
<td>7.8 (5.5)</td>
<td>15.8 (14.7)</td>
<td>9.6 (6.3)</td>
</tr>
<tr>
<td>24-month vs basal</td>
<td>NS</td>
<td>NS</td>
<td>‡</td>
<td>NS</td>
</tr>
</tbody>
</table>

BDI, Beck Depression Inventory; UPDRS, Unified Parkinson’s Disease Rating Scale; NS, not significant results.

* Data are indicated as mean (standard deviation).
† p <0.05.
‡ p <0.01.
§ p <0.001 (time).
Comparisons 3-, 6-, 12-, 18-, 24-month versus basal and 12-versus 6- and 24-versus 18-month refer to both groups (total sample).
improvement, in comparison with the unmedicated condition, was maintained until the 12-month evaluation. However, all measures of the RCFT tended to decay at the 18- and 24-month evaluations with improvement on visuospatial and visuoconstructive abilities (copy) losing significance with respect to baseline. There were differences in the improvement time course. Long-term visual memory (delayed recall) significantly improved at the 3-month evaluation and visuospatial and visuoconstructive abilities (copy) at the 6-month evaluation. A significant added improvement was observed in both groups on delayed recall when comparing the 12- versus 6-month evaluations. The visuoconstructive ability test also showed a significant treatment-by-time effect: when comparing the 12- versus 6-month evaluation, performance of patients in the levodopa group was poorer whereas the introduction of levodopa in the pergolide group was associated with an added improvement.

**Frontal Tasks**

There were no significant differences between groups in basal conditions in any tests aimed at evaluating frontal functions (Table 5). During the first year of the study, both groups improved their performance in letter and category fluencies. This improvement reached statistical significance at 6 month but did not persist beyond the 12-month evaluation. In addition, a significant treatment-by-time effect on letter fluency was obtained when comparing 6- versus 12-month results because of a decrement of the total number of words of the levodopa group patients at the 12-month evaluation, although their performance was still significantly better than at basal evaluation. Both letter and category fluency improvement lost their significance at the 24-month evaluation, an effect already evident at the 18-month evaluation. Both letter and category fluency improvement lost their significance at the 24-month evaluation, an effect already evident at the 18-month evaluation. No significant time, treatment or treatment-by-time effects were evidenced on Stroop's paradigm following the introduction of therapy during the entire length of the study. A significant time effect without significant treatment or treatment-by-time effects were observed on premotor functions (Luria Rhythm and Motor Tests), as well as on arithmetic abilities, at the 3-, 6-, and 12-month evaluations. When com-

<table>
<thead>
<tr>
<th>Trail making A</th>
<th>Visual RT</th>
<th>Aleatory visual RT</th>
<th>Auditory RT</th>
<th>Tapping Right hand</th>
<th>Tapping Left hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD basal</td>
<td>70.4 (31.2)</td>
<td>415 (176)</td>
<td>364 (138)</td>
<td>353 (75)</td>
<td>121.3 (23.7)</td>
</tr>
<tr>
<td>PGL basal</td>
<td>71.7 (53.1)</td>
<td>375 (216)</td>
<td>364 (178)</td>
<td>329 (108)</td>
<td>94.8 (28.4)</td>
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<tr>
<td>LD vs PGL basal</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LD 3-month</td>
<td>61.1 (31.1)</td>
<td>344 (95)</td>
<td>355 (151)</td>
<td>324 (729)</td>
<td>113.3 (21.7)</td>
</tr>
<tr>
<td>PGL 3-month</td>
<td>71.0 (41.0)</td>
<td>340 (139)</td>
<td>336 (132)</td>
<td>330 (160)</td>
<td>109.1 (30.0)</td>
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<tr>
<td>3-month vs basal</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LD 6-month</td>
<td>59.0 (45.2)</td>
<td>308 (43)</td>
<td>324 (70)</td>
<td>304 (64)</td>
<td>118.6 (24.7)</td>
</tr>
<tr>
<td>PGL 6-month</td>
<td>55.7 (25.7)</td>
<td>337 (145)</td>
<td>350 (150)</td>
<td>298 (135)</td>
<td>116.5 (34.9)</td>
</tr>
<tr>
<td>6-month vs basal</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LD 12-month</td>
<td>52.7 (21.1)</td>
<td>327 (56)</td>
<td>330 (114)</td>
<td>330 (73)</td>
<td>125.4 (30.4)</td>
</tr>
<tr>
<td>PGL + LD 12-month</td>
<td>64.1 (33.0)</td>
<td>355 (147)</td>
<td>391 (153)</td>
<td>347 (118)</td>
<td>116.2 (35.5)</td>
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<td>12-month vs basal †</td>
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<td>12- vs 6-month</td>
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<td>NS</td>
</tr>
<tr>
<td>LD 18-month</td>
<td>84.8 (75.4)</td>
<td>314 (105)</td>
<td>321 (77)</td>
<td>317 (101)</td>
<td>121.1 (16.2)</td>
</tr>
<tr>
<td>PGL + LD 18-month</td>
<td>68.0 (25.4)</td>
<td>335 (80)</td>
<td>320 (63)</td>
<td>328 (76)</td>
<td>105.2 (45.6)</td>
</tr>
<tr>
<td>18-month vs basal ‡</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LD 24-month</td>
<td>75.7 (67.3)</td>
<td>415 (213)</td>
<td>412 (191)</td>
<td>318 (96)</td>
<td>125.0 (17.1)</td>
</tr>
<tr>
<td>PGL + LD 24-month</td>
<td>73.3 (54.9)</td>
<td>335 (62)</td>
<td>319 (41)</td>
<td>320 (64)</td>
<td>117.5 (33.6)</td>
</tr>
<tr>
<td>24-month vs basal ‡</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>24- vs 18-month</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Data are indicated as mean (standard deviation). RTs (reaction times) are indicated in milliseconds. Tapping test is indicated in number of taps in 25 seconds.
† p <0.05.
‡ p <0.01.
§ p <0.001 (time).
NS, not significant results.
Comparisons 3-, 6-, 12-, 18-, 24-month versus basal and 12- versus 6- and 24-versus 18-month refer to both groups (total sample).

**TABLE 3.** Motor speed: neuropsychologic performance of patients with Parkinson’s disease following treatment with levodopa (LD) and pergolide (PGL) at basal examination and 3-, 6-, 12-, 18-, and 24-month follow up*
paring results of the 6- versus 12-month evaluations, a significant added improvement of the Luria Motor Test was obtained in both groups, as well as a significant treatment-by-time effect on arithmetic abilities, with patients on the levodopa group worsening while patients on the pergolide group showing added improvement after the addition of levodopa. While Luria Motor and Arith- metic tests maintained significant differences with respect to baseline, significant improvement in the Luria Rhythm Test was lost at 18- and 24-month evaluations. Comparison between these two last evaluations revealed a significant worsening in the Luria Motor Test at the 24-month evaluation.

DISCUSSION

In this study we used a parallel design to examine the longitudinal effects of chronic dopaminergic replacement with levodopa and the direct-acting dopamine agonist pergolide in a range of cognitive domains in previously untreated patients with PD. We observed that: (1) chronic dopaminergic replacement with levodopa or pergolide was associated with significant motor (UPDRS parts II and III) and cognitive improvement evidenced in tests assessing learning and long-term verbal and visual memory, visuospatial abilities, and various executive tests indicative of frontal lobe functioning; (2) the beneficial motor and neuropsychologic changes maintained long-term (1-year) significant differences with respect to the unmedicated condition; however, activities of daily living (UPDRS part II) and performance in some frontal (semantic fluency, Luria’s Rhythm, and Motor tests) and long-term memory tasks declined thereafter and no longer showed drug-related improvement at the 24-month examination; and (3) much of the significant improvement in neuropsychologic testing (long-term memory, Luria rhythm, and motor and arithmetic-WAIS tests) paralleled the significant changes in motor function, whereas others appeared long after the beneficial motor changes had taken place, ranging from the 6-month evaluation (learning and long-term verbal memory, copy of the RCFT, letter and category fluency tests) to the 12-month evaluation (TMA test). No signif-

TABLE 4. Attention and memory: neuropsychologic performance of patients with Parkinson’s disease following treatment with levodopa (LD) and pergolide (PGL) at basal examination and 3-, 6-, 12-, 18-, and 24-month follow up*

<table>
<thead>
<tr>
<th>Test</th>
<th>Basal (mean ± SD)</th>
<th>3-month (mean ± SD)</th>
<th>6-month (mean ± SD)</th>
<th>12-month (mean ± SD)</th>
<th>18-month (mean ± SD)</th>
<th>24-month (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit span (errors)</td>
<td>7.4 ± 1.4</td>
<td>7.3 ± 1.4</td>
<td>7.5 ± 1.6</td>
<td>8.2 ± 2.4</td>
<td>8.2 ± 2.4</td>
<td>6.4 ± 1.6</td>
</tr>
<tr>
<td>BVVRT (errors)</td>
<td>5.1 ± 2.2</td>
<td>4.5 ± 2.0</td>
<td>4.8 ± 3.0</td>
<td>4.7 ± 4.3</td>
<td>4.8 ± 2.2</td>
<td>4.1 ± 2.1</td>
</tr>
<tr>
<td>RAVLT Trials 1 to 5</td>
<td>33.2 ± 6.4</td>
<td>35.4 ± 7.2</td>
<td>38.4 ± 7.0</td>
<td>41.7 ± 13.1</td>
<td>40.0 ± 13.1</td>
<td>42.2 ± 9.9</td>
</tr>
<tr>
<td>RAVLT Trial 6</td>
<td>5.1 ± 3.7</td>
<td>6.3 ± 3.2</td>
<td>6.4 ± 3.0</td>
<td>7.4 ± 3.4</td>
<td>6.2 ± 3.8</td>
<td>6.3 ± 4.2</td>
</tr>
<tr>
<td>Copy Delayed recall</td>
<td>19.0 ± 8.0</td>
<td>22.1 ± 8.1</td>
<td>23.0 ± 6.1</td>
<td>21.2 ± 4.8</td>
<td>18.1 ± 7.1</td>
<td>19.2 ± 8.7</td>
</tr>
<tr>
<td>RCFT</td>
<td>6.7 ± 4.4</td>
<td>10.5 ± 4.7</td>
<td>11.8 ± 4.3</td>
<td>14.2 ± 6.5</td>
<td>11.7 ± 7.2</td>
<td>12.7 ± 6.2</td>
</tr>
</tbody>
</table>

* Data are indicated as mean (standard deviation).
† p < 0.05.
‡ p < 0.01.
§ p < 0.001 (time).
∥ p < 0.001 (treatment by time).
NS, not significant results; BVRT, Benton Visual Retention Test; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey-Osterrieth Complex Figure Test.
Comparisons 3-, 6-, 12-, 18-, 24-month versus basal and 12-versus 6- and 24-versus 18-month refer to both groups (total sample).
Cant changes in the course of the study were observed on attentional, short-term memory, and the Stroop tests. Overall, the present study supports the idea that improvement of cognitive deficits with dopaminergic replacement in untreated PD patients is partial and not sustained, although more extensive than previously thought.11,15 Part of the initial cognitive improvement, however, might be attributed to practice effects rather than from pharmacologic treatment.30 A common feature of practice effects in neuropsychologic testing is that they generally occur between the first and second examination with the same test.30 Therefore, the use of parallel versions (like in the present study) multiple baseline testing, or comparison with a control group have been proposed in follow-up studies.23,30 We thought that a comparison with a control group of de novo PD patients maintained during 2 years without dopaminergic treatment was not practical. Thus, delayed improvement or deterioration, as observed with some tests in this 2-year follow-up study, are difficult to explain by practice effects. Nevertheless, no improvement was observed on the Stroop test, which may show some practice effects in healthy control subjects23 and for which we used no alternative forms, and on tests assessing attention and short-term memory (Digit Span and BVRT) for which alternative forms were used. The lack of beneficial effects of dopaminergic replacement on these tests and the deterioration along the study on those tasks showing benefit argue against a general influence of practice along the study. Instead, it could arise as a rather coherent pattern of differential effects of dopaminergic treatment on task performance in patients with PD. In the following sections we discuss the cognitive effects of chronic dopaminergic therapy over time in each test separately and consider some theoretical aspects and clinical implications relevant to dopamine and cognitive function.

### Cognitive Effects of Dopaminergic Therapy

#### Motor Speed

The finger tapping test and simple reaction time tasks were not responsive to the drugs in the present study. This finding is in keeping with the results of several studies that have shown clinical changes in bradykinesia.

### Table 5. Frontal tasks: neuropsychologic performance of patients with Parkinson’s disease following treatment with levodopa (LD) and pergolide (PGL) at basal examination and 3-, 6-, 12-, 18-, and 24-month follow up*

|                | Letter fluency | Category fluency | Word RT | Stroop color RT | Stroop effect | Luria rhythm (errors) | Luria motor (maintenance) | Arithmetic (WAIS) |
|----------------|----------------|------------------|---------|----------------|---------------|----------------------|--------------------------|----------------|-----------------|
| LD basal       | 19.7 (9.0)     | 42.8 (7.9)       | 1051 (100) | 1675 (416)     | 455 (415)     | 4.4 (2.1)            | 21.7 (8.3)              | 6.1 (1.7)       |
| PGL basal      | 19.4 (13.0)    | 46.7 (14.3)      | 1167 (413) | 1468 (515)     | 563 (433)     | 3.9 (2.9)            | 30.3 (14.4)             | 6.9 (2.6)       |
| LD vs PGL basal| NS             | NS               | NS       | NS             | NS            | NS                   | NS                       | NS             |
| LD 3-month     | 21.9 (7.7)     | 44.3 (10.8)      | 1206 (240) | 1830 (512)     | 886.7 (1504)  | 3.0 (2.5)            | 33.0 (8.0)              | 7.2 (2.0)       |
| PGL 3-month    | 21.7 (17.3)    | 49.3 (18.2)      | 1386 (429) | 1958 (1688)    | 687.0 (435)   | 3.7 (2.6)            | 33.3 (14.7)             | 8.9 (4.0)       |
| 3-month vs basal| NS             | NS               | NS       | NS             | NS            | NS                   | NS                       | NS             |
| LD 6-month     | 26.3 (9.7)     | 48.4 (8.3)       | 1282 (439) | 1608 (600)     | 1896.2 (2901) | 3.0 (3.0)            | 36.7 (8.1)              | 7.4 (2.4)       |
| PGL 6-month    | 24.1 (17.0)    | 50.7 (15.1)      | 1311 (368) | 2991 (2206)    | 629.9 (583)   | 3.5 (3.5)            | 36.6 (19.3)             | 8.8 (4.7)       |
| 6-month vs basal| †              | †                | NS       | NS             | NS            | †                    | †                        | †              |
| LD 12-month    | 24.1 (7.9)     | 48.4 (7.8)       | 1281 (292) | 1565 (426)     | 607.1 (795)   | 2.9 (2.5)            | 37.9 (11.1)             | 6.7 (2.1)       |
| PGL + LD 12-month| 23.0 (13.1)   | 50.0 (13.1)      | 1396 (379) | 1718 (912)     | 646.8 (448)   | 2.8 (4.3)            | 39.6 (19.1)             | 9.3 (4.3)       |
| 12-month vs basal| †              | †                | NS       | NS             | NS            | †                    | †                        | †              |
| 12- vs 6-month | NS             | NS               | NS       | NS             | NS            | †                    | †                        | †              |
| LD 18-month    | 25.0 (10.0)    | 45.7 (13.2)      | 1322 (452) | 1347 (477)     | 343.4 (414)   | 3.7 (2.7)            | 41.1 (9.9)              | 8.4 (4.6)       |
| PGL + LD 18-month| 25.8 (5.8)    | 47.5 (7.5)       | 1264 (309) | 1452 (492)     | 349.3 (409)   | 3.8 (1.9)            | 38.0 (7.1)              | 7.4 (2.1)       |
| 18-month vs basal| †              | †                | NS       | NS             | NS            | †                    | †                        | †              |
| LD 24-month    | 21.0 (9.3)     | 42.1 (12.6)      | 1271 (361) | 1632 (1154)    | 486.8 (797)   | 3.9 (3.0)            | 37.2 (10.7)             | 8.2 (3.3)       |
| PGL + LD 24-month| 20.3 (5.8)    | 42.1 (10.0)      | 1279 (250) | 1721 (732)     | 422.5 (612)   | 4.0 (2.8)            | 27.5 (10.3)             | 7.8 (2.2)       |
| 24- vs 18-month| †              | †                | NS       | NS             | NS            | †                    | †                        | †              |

* Data are indicated as mean (standard deviation).
† p <0.05.
‡ p <0.01.
¶ p <0.001 (time).
§ p <0.05.
¶¶ p <0.01.
NS, not significant results; RT, reaction times indicated in milliseconds; WAIS, Wechsler Adult Intelligence Scale.

Comparisons 3-, 6-, 12-, 18-, 24-month versus basal and 12- versus 6- and 24-versus 18-month refer to both groups (total sample).
without changes in reaction time (see reference 12 for a review). The scenario might be different with more complex reaction time tasks. Three studies have shown that dopamine replacement is not essential for simple motor processing but does produce a specific reduction in cognitive information processing time in more complex tasks. Although simple and complex reaction times may be mediated through separate parallel pathways and/or on different neurotransmitter influences, they may still fall along a continuum pathway for response processing. Therefore, we would predict that reaction time in tasks associated with stimulus discrimination with the attendant increase in the time required for motor organization would be highly sensitive to dopamine depletion. The fact that the TMA was the only motor speed task that achieved significant improvement along the study may point in this direction.

**Attention and Short-Term Memory**

The lack of significant improvement in attentional and short-term memory tasks assessed in the present study is also in accordance with previous studies showing preserved immediate recall of verbal and visual material in early PD and no significant changes in tasks such as the Digit Span test after the introduction of levodopa. Moreover, the lack of improvement of two classic measures of attention such as the Digit Span and the BVRT strongly argues against the suggestion that the relatively few beneficial cognitive changes observed at early stages of PD in previous studies reflects a nonspecific increase in alertness rather than an improvement in specific cognitive operations. Studies in patients with advanced PD reported attentional deficits or electro-physiological abnormalities suggestive of a disturbed frontal regulation of attentional processes. Thus, we cannot exclude the possibility that meaningful changes in our attention tests were undetected, either as a result of the relatively little effort required of patients to perform the assessed tasks or because the degree of dopamine depletion in our patients with early PD had not yet reached a critical enough severity to reveal the dopamine dependence of these tasks. In fact, the basal scores of our patients in both the Digit Span and the BVRT tests were the only two tests with scores within the normal range of a control group of healthy individuals studied with a similar battery in our department.

**Verbal Learning (RAVLT)**

In the present study, improvement in verbal learning (RAVLT) was not significant at the 3-month evaluation, but a significant global improvement of the test was observed in both groups at the 6- and 12-month evaluations. In a study of de novo patients examined in an untreated state and within 4 months after the introduction of dopaminergic therapy, Cooper et al. observed no significant effects of dopaminergic therapy on all subtests of the Wechsler Memory Scale. Because the most impressive verbal learning gains in the present study did not appear until the 6-month evaluation, verbal learning in PD may have a delayed pattern of improvement instead of a total lack of response to dopaminergic replacement as suggested by Cooper et al. Noteworthy, patients with PD with caudate grafts of fetal dopaminergic tissue showed a numeric improvement in verbal memory at 12 months after surgery that reached statistical significance at 24 months and declined between 24 and 36 months after surgery.

**Visuospatial and Visuoconstructive Abilities, and Long-Term Visual Memory**

In their follow-up study of a group of untreated patients, Cooper et al. observed that the ability to copy complex geometric designs (Rey/Taylor figures) showed a mild but significant improvement from the untreated to the treated state in patients receiving either levodopa or bromocriptine, whereas the performance of patients receiving anticholinergics remained unchanged. In the present study, dopaminergic treatment with either levodopa or pergolide was associated with a significant improvement of visuospatial and visuoconstructive functions as measured by the RCFT. While improvement on delayed recall of the RCFT appeared at the 3-month evaluation and was maintained until the last examination at 24 months, significant improvement on copy did not appear until the 6-month examination and was lost at the 18-month point. Interestingly, the patients of Cooper et al. were reassessed after an interval of approximately 4 months, a point comparable to our 3-month examination when our patients still had not achieved the full pattern of significant changes, including both copy and delayed recall of the RCFT seen at the 6-month and maintained until the 12-month evaluation. In our view, this suggests that visuoconstructive functions may be at least partially sensitive to dopaminergic stimulation with a delayed and short-lasting pattern of improvement and make it unlikely that the primary deficit contributing to poor performance in copying is disordered motor function. Previous data on normal short-term memory with impaired long-term memory in patients with PD, coupled with the dissociation between short- and long-term memory tasks under dopaminergic replacement observed in the present and other studies, may indicate that under dopamine deficiency, registration processes may be
efficient but may have insufficient encoding to achieve normal long-term memory performance.

**Frontal Tasks**

With the only exception being the Stroop test, performance in the frontal tasks assessed in the present study of de novo patients showed significant improvement at some point in the first 6 months of treatment. The lack of improvement in the Stroop test might be attributed to heterogeneous effects of dopaminergic stimulation on frontal tasks or to the manner of testing. Performances in the computerized version of the Stroop test used in the present study were scored as reaction time for correct responses. The lack of improvement of the markedly slow motor response observed both in the word and the color parts of the task might have masked possible cognitive changes making it difficult to discriminate for a significant Stroop effect (perceptual interference) that could have been more obvious by eliminating the reaction time component of the test. On the other hand, differential effects of dopaminergic stimulation could be explained on the basis of distinct processing mechanisms similar to the dissociation between object and spatial processing domains that occurs in primate prefrontal cortex. It could be argued that performance in the Stroop test may depend on a separate brain region less sensitive to dopamine manipulation, unless differences may be caused by the diverse requirements of the frontal tasks used in the present study. In this connection, Brown and Marsden demonstrated a dissociation between standard and complex versions of the Stroop test in patients with PD: the presence of distracters (the words) did not unduly increase task difficulty in patients with PD but the requirement to perform a concurrent task (random number generation) disrupted performance, even when the correct response was cued, an aid that has previously been shown to reduce Stroop interference in patients with PD. Accordingly, we recently observed in patients with advanced PD that a simple version of the Stroop test appeared less sensitive to dopamine challenge than the Wisconsin Card Sorting Test. Whether this depends on factors associated with prolonged treatment or with the progression of the disease, or both is presently unknown.

**Dopamine and Cognitive Function**

Selective depletion of dopamine in the prefrontal cortex of Rhesus monkeys selectively impairs prefrontal cognitive function (a task of delayed alternation performance); this behavioral deficit could be selectively reversed with dopamine agonists such as levodopa and apomorphine. Thus, if abnormal dopamine regulation in the prefrontal cortex plays a role in the cognitive defects of PD, an initial “frontal” cognitive benefit after dopamine replacement should be expected in untreated patients with PD, as it occurred in the present study. The mechanism by which dopamine replacement also improved performance in other tasks such as learning and long-term memory, visuospatial and visuoconstructive
abilities might be more difficult to explain. However, learning and long-term memory deficits might follow prefrontal damage in humans, and tasks like word list recall seems particularly sensitive because it demands planning and organization. Further, experimental data has suggested that learning and memory processes depend on a dopaminergic reward network intimately involving the prefrontal cortex. Conceivable, dopaminergic replacement in our untreated patients with PD might have enhanced memory processes by facilitating accessing or activating the problem-solving component of memory retrieval. On the other hand, the action of dopamine in long-term memory must also be viewed within the wider context of interaction of dopamine with other neurotransmitter systems, particularly the cholinergic neurotransmitters.

The present results do not imply that frontal and memory impairment in untreated PD is exclusively dependent on a dopaminergic deficit or may be totally reversed by dopamine replacement. Their performance in many tests (RAVLT, RCFT, TMA, letter and category fluency, and Luria’s Rhythm and Motor tests) both before and after dopaminergic replacement were under the normal range of control subjects. Moreover, a substantial part of the cognitive improvement associated with dopaminergic treatment seen in the present study was not sustained over time. This could be attributed to at least two associated factors: (1) the progressive loss of dopaminergic innervation, causing further dopamine depletion in the prefrontal-caudate loop together with progressive nondopaminergic cortical or subcortical lesions; and (2) pharmacodynamic alterations of the dopamine receptors related to chronic nonphysiological (pulsatile) dopaminergic stimulation. The progressive loss of presynaptic terminals may result in a diminished capacity of presynaptic vesicular storage and regulated release of the dopamine formed from levodopa and a diminution of the ability of these terminals to buffer fluctuations in plasma levodopa. In this context, levodopa may increase extracellular dopamine concentrations more than in normal or less denervated striata further producing a “presynaptic supersensitivity” with the appearing of motor and “frontal” cognitive fluctuations. This may be partially responsible for the loss of the initial dopamine-sensitive cognitive benefit observed in the present study and for some of the reported, mainly frontal-related, adverse cognitive effects of levodopa observed in patients with advanced PD. In accordance, animal data not only show that levodopa may reverse prefrontal cognitive deficits, poor performance in a delayed alternation task, caused by selective dopamine depletion in the prefrontal cortex, but also indicate that excessive dopamine turnover in the prefrontal cortex is detrimental to the same cognitive task. Moreover, a balance between prefrontal and striatal dopamine with specific behavior interactions has been suggested. Thus, Roberts et al. observed that elevated extracellular dopamine in the caudate nucleus, occurring as long-term striatal adaptive change in 6-hydroxidopamine lesioned monkeys with a marked depletion of dopamine limited to the prefrontal cortex, was associated with a selective improvement on an attentional set shifting task comparable to the WCST (extradimensional shifting) whereas other attentional tasks of intradimensional shifting showed no changes, and a spatial delayed response performance was impaired. This behaviorally specific effect of elevated striatal dopamine is consistent with the impairment in attentional set-shifting ability observed in patients with PD and the improvement observed with medication. It also suggests that a ruptured balance of the interaction between prefrontal and striatal dopamine resulting from excessive extracellular dopaminergic stimulation underlies the impairment of the WCST and other frontal tasks observed in patients with advanced PD in association with high levodopa plasma levels. Taken together, these data indicate that there may be a critical range of dopaminergic activity for optimal prefrontal cortex-dependent cognitive functioning and that exceeding this range can result in dysregulation and further cognitive impairment.

Despite their different mode and site of therapeutic action, levodopa (which is decarboxylated to dopamine in residual dopaminergic terminals) and pergolide (a direct dopamine receptor agonist), both in monotherapy and combined to levodopa, showed a similar profile of motor and cognitive changes along the study. Dopamine itself exerts actions on D1 and D2 receptors and pergolide is a preferential D2 but also a D1 receptor agonist. While it seems clearly established that D2 receptor stimulation is beneficial in relieving parkinsonian motor deficits, the role played by the D1 receptor remains controversial. However, animal data support that the symptomatic motor effect of dopamine agonists might depend on both dopamine D2 and D1 receptor activity. Comparative studies on either the motor or cognitive effects of dopamine agonists in de novo PD patients are lacking. Differences in D1 activity between pergolide and bromocriptine (bromocriptine is a D2 agonist but also a D1 antagonist) has been postulated to explain the greater motor potency of pergolide in comparative studies of these drugs in combination with levodopa in patients with advanced PD. In contrast to the comparable motor effects of pergolide and levodopa in

Movement Disorders, Vol. 15, No. 4, 2000
monotherapy during the first 6 months of the present study, in the short-term study of Cooper et al., the motor benefit was significantly lower in the bromocriptine-treated group. Nevertheless, no cognitive differences between bromocriptine and levodopa were observed in the Cooper et al. study: both groups of previously untreated patients examined with a comprehensive neuropsychologic battery only showed cognitive benefit in a working memory and a cognitive sequencing task. Both, a short-term follow up (no more than 4 months) and a suboptimal motor improvement with bromocriptine might have influenced their results. Experimental evidence indicates that D2 mechanisms may influence cognitive functions in monkeys and humans. However, a preferential role of prefrontal D1 versus D2 receptors for prefrontal tasks modulation has been shown in monkeys indicating a D1 direct gating of selective excitatory synaptic inputs to prefrontal neurons during cognition. Further, in human volunteers, at comparable doses pergolide but not bromocriptine facilitated visuospatial working memory performance. The design of our study does not allow for conclusions about the particular role of D1 and D2 receptors on the cognitive response to dopaminergic modulation in patients with PD. However, with the reserves resulting from the relatively small sample size of each group, the lack of remarkable cognitive differences between treatments in our study might indicate that both direct (pergolide) and indirect (levodopa) combined stimulation of D1 and D2 receptors are likely to produce similar cognitive benefit in untreated patients with PD. Studies with dopaminergic agonists with preferential action on different subtypes of the D1 and D2 receptor families are needed to further explore the selective vulnerability of cognitive processing to dopaminergic dysfunction and the response to different forms of dopaminergic replacement.

In conclusion, our results show that dopaminergic replacement, either with levodopa or pergolide, is associated with a better performance in a range of cognitive measures that is maintained at least during the first year of treatment. Nevertheless, the enhancement of cognitive function may be incomplete, implicating mainly frontal tasks but also tasks tapping other cognitive domains such as memory or visuoconstructive abilities, suggesting that dopaminergic replacement does not compensate for all of the cognitive deficits of patients with PD and that other factors intervene. Further assessment of this cognitive dissociation can be useful in refining the definition of the cognitive deficit and the effects of dopaminergic treatment for PD. Although PD may begin as a pure dopaminergic pathology, abnormalities of several other neuronal systems have also been found and their contribution to the pathophysiology of cognitive deterioration could be important. Early-appearing cognitive deficits might actually antedate the detection of parkinsonian motor deficits both in animal models and in humans with PD. Thus, in the absence of specific pharmacologic therapy for the cognitive deficits of PD, there might be no compelling reason to avoid prescribing dopaminergic agents in de novo patients who could benefit from a reduction in cognitive dysfunction.

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