The differential effect of PD and normal aging on early explicit sequence learning

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Abstract—*Background:* Motor sequence learning is abnormal in PD. However, it is not known whether this defect is present during the earliest stages of the illness or whether it reflects specific limitations in dividing attention between cognitive and motor requirements. *Methods:* Fifteen patients with early stage PD and 10 age-matched and 9 younger normal controls moved the right dominant hand on a digitizing tablet to eight targets presented on a screen in synchrony with a tone at 1-second intervals. The tasks were as follows: 1) CCW—a timed-response task where targets appeared in a predictable counterclockwise order; 2) RAN—a reaction time task where targets were random and unpredictable; 3) SEQ—a task with multiple demands emphasizing explicit learning and target anticipation in which subjects learned a sequence while reaching for targets; and 4) VSEQ—subjects learned a visual sequence without moving. *Results:* CCW and RAN yielded similar results in all groups. In patients with PD, sequence learning was the same in SEQ and VSEQ and was slower compared to both control groups. In older controls, learning was faster in VSEQ than in SEQ, whereas younger controls learned equally fast in both tasks. *Conclusions:* Despite normal motor execution, the initial phases of sequence learning are impaired in early PD independent of task requirements, possibly reflecting reduced working memory. Learning was slower in older than younger controls only in tasks with multiple demands, presumably due to reduced attentional resources.

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Although the motor symptoms of tremor, bradykinesia, rigidity, and postural instability are the hallmark of PD, subtle signs of cognitive impairment may be demonstrated with neuropsychological tests in the earliest stages of the disease.[1-5] Cognitive deficits have been reported in nondemented patients with PD in multiple domains,[6] including working memory and attention.[3,5,7] Patients with PD are also slower in the acquisition of sequenced behaviors.[8-19] For example, although they are capable of learning motor sequences, they require longer time to do so.

To further characterize the impairment of sequence learning in PD, three issues need to be addressed. First, it is not known whether sequence learning is already affected in early PD. Second, it is not known whether PD is associated with an impairment of explicit sequence learning, where working memory and attention play a major role. The previously reported deficits concerned implicit learning, as assessed by serial reaction time paradigms.[20] Such paradigms pose minimal demands on working memory, as shown also by the lack of dorsolateral prefrontal cortex (DLPFC) activation.[21] Third, it has not been ruled out that slower learning in PD is simply a consequence of bradykinesia. This is important because, in patients at advanced clinical stages (Hoehn & Yahr III and IV[22]), defective sequence learning appears to be correlated with the severity of motor signs.[19]

We therefore compared the performance of unmedicated patients with PD in early stages (I and II) of the disease with a group of age-matched normal controls. To assess the effects of aging, we also studied a group of normal younger subjects. The time course of sequence learning was studied on a movement-by-movement basis in each individual subject. We used a novel set of tasks, involving early detection and target anticipation, which have a prominent explicit component. These tasks engage working memory and are associated with the activation of DLPFC.[23] The effects of different attentional and working memory demands were also examined. Finally, to correct for the potential confound of bradykinesia, we compared learning tasks with motor ones requiring kinematically equivalent performance.

Subjects. We studied one group of patients with PD and two groups of normal controls. All patients and normal subjects were right-handed and scored more than 27 on Mini-Mental State Examination[24]; they underwent MRI to exclude potential structural brain lesions (e.g., stroke, mass lesion, or hydrocephalus/atrophy). Written informed consent was obtained from all participants under a protocol approved by the institutional review board of North Shore University Hospital and Columbia University.

The patient group included 11 men and 4 women with mild idiopathic PD in Hoehn & Yahr Stage I.

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Their mean age was 61.8 ± 10.9 years, ranging from 46 to 77 years; average disease duration was 3.3 ± 3.0 years. The right upper extremity was involved in seven patients; the left was involved in the remaining eight. Six of the patients were drug naïve; three were treated with deprenyl alone, four received levodopa/carbidopa only, and the remaining two were treated with both dopamine agonists and levodopa/carbidopa. When tested, all patients were drug-free for at least 12 hours.

The first group of normal controls, six men and four women, was of comparable age to the PD group. Their mean age was 57.4 years (±10.7; range 45 to 71 years), not statistically different from the PD group. We also tested a group of younger normal volunteers. They were three women and six men, with mean age of 24.1 years (±2.7 years; range 22 to 28 years).

In recruiting normal subjects, the following exclusion criteria were used: 1) history of neurologic or psychiatric illness; 2) exposure to neuroleptic agents or drug use; 3) medical history of hypertension, cardiovascular disease, or diabetes mellitus; and 4) abnormal results on neurologic examination.

Methods. General features of the motor tasks are reported in detail in previous publications.[23,25,26] Briefly, subjects moved a cursor on a digitizing tablet with their right hand. Movements were out and back from a central starting point to one of eight targets (circles) displayed on a computer screen (figure 1). For all motor tasks, instructions were to make movements without corrections and reversing sharply inside each target circle. Graying of the target circle indicated successful hits. The target always appeared in synchrony with a tone at 1-second intervals. Target extent was 3.2 cm. Testing was done in separate trial blocks of 90 seconds each (a total of 90 movements per trial block). A computer sampled hand positions at 200 Hz and controlled the experiments.

Subjects learned to perform the following tasks in one or two training sessions 1 or 2 days before testing. Training was complete when performance was stable in all the tasks.

The tasks differed by having different target arrays (see below) and different temporal instructions: in the timed response instruction, subjects were instructed to synchronize hand reversal in the target with the tone[25]; in the reaction time instruction, responses were to be initiated only after the tone.

The tasks used were as follows:

1) CCW: a timed-response task where targets appeared in a predictable counterclockwise order. Subjects had to reach the target in synchrony with the tone. Thus, they had to initiate movements before target and tone were presented.
2) RAN: a reaction time task where targets were presented in a pseudorandom, nonrepeating, and unpredictable order. Subjects were required to reach for each target as soon as possible, minimizing reaction time but avoiding target anticipation. For each subject, we found the floor value of the reaction time distribution; i.e., the lowest onset time in the RAN block. There were no movements (anticipatory or not) to incorrect targets; thus, floor onset times were used as the criterion below which movements were considered to be anticipatory in the sequence learning paradigms described below.
3) SEQ: the eight targets were presented in a pseudorandom repeating order without repeating elements. Subjects were informed that a sequence was to be presented and were instructed to learn the order of the sequence while reaching for the targets, to anticipate successive targets, and to reach each target in synchrony with the tone. Thus, they were asked to start their performance in a reaction-time mode and to shift to a timed-response mode while learning the sequence. Learning of each sequence was tested in two consecutive block trials of 90 seconds each (SEQ1 and SEQ2). At the end of each block, subjects were asked to indicate the order of the sequence verbally. For each subject we used two different target sequences. Because no significant difference was found between the two, for each subject we used average values.
4) VSEQ: during an initial 90-second block, subjects were presented with a repeating sequence of eight targets and asked to learn it by attending to the display without moving. Learning was also assessed in a subsequent block of 90 seconds, where subjects were to reach for the same target sequence as per SEQ. As per SEQ, we averaged the two VSEQ sequences. Verbal reports about the sequence order were taken at the end of each 90-second block.

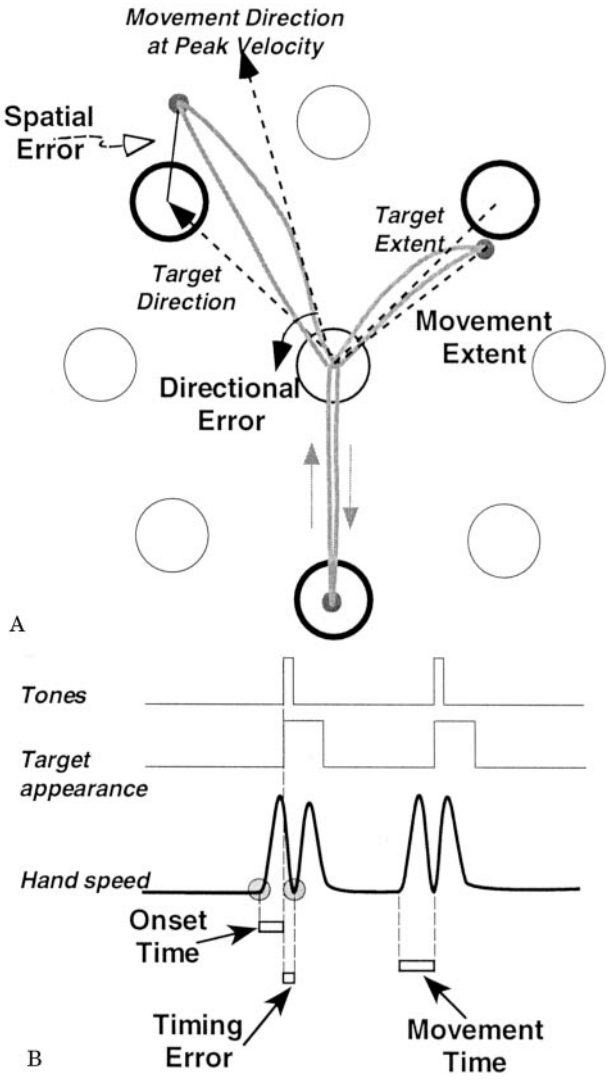

Figure 1. Spatial (A) and temporal (B) variables measured for each movement. (A) Movements to three of the eight targets starting from a common point. For two movements, spatial error, directional error at the peak velocity, and movement extent are shown with target direction, target extent, and movement direction at the peak velocity. (B) The occurrences of tones and target are shown with the velocity temporal profile for two movements. Measurements for onset time, movement time, and timing error are also illustrated.

Data analysis. As detailed in previous reports,[23,25,26] for each movement we identified movement onset, peak velocity, peak acceleration, and movement reversal position and computed the following measures (see figure 1):

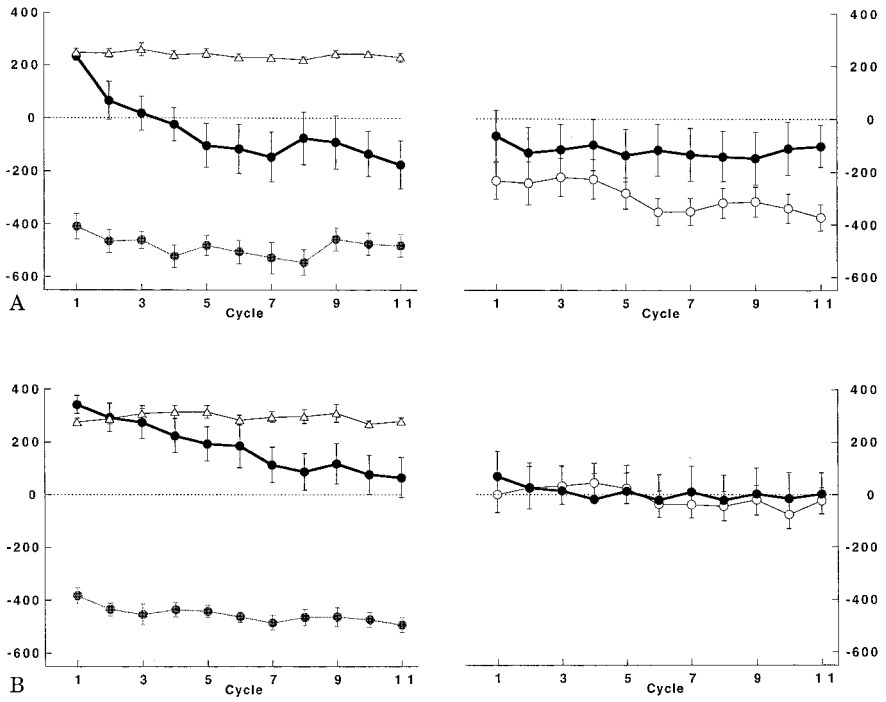

Figure 2. Mean onset times in RAN, CCW, SEQ, and VSEQ plotted as a function of cycles. Values for RAN are represented by empty triangles and a thin line, CCW by gray filled circles and a thin line, SEQ by black filled circles and a thick line, and VSEQ test by empty circles and a thin line. Analysis was performed on mean data of two different sequences in both normal subjects and patients with PD, because no significant difference was found between the time course of the two. Mean and SD per cycle for the normal age-matched control group are shown in (A) and for the patients with PD of Group 1 in (B). On average, onset time of SEQ1 (left panels) decreased with cycles, indicating target prediction and, thus, sequence learning. A repeated measures ANOVA (groups and cycles) found a difference between the two groups [$F(1,23) = 5.79$, $p < 0.03$] and an effect of cycles [$F(1,230) = 18.5$, $p < 0.0001$], without interaction between groups and cycles. For SEQ2 (right panels), repeated measures ANOVA did not find effect of cycles, groups, or interaction between the two. For VSEQ test, there was an effect of groups [$F(1,23) = 7.3$, $p < 0.02$] and cycles [$F(1,230) = 3.9$, $p < 0.0001$], but no interaction between the two factors. In normal controls, comparison between the onset times of SEQ2 and VSEQ test revealed an effect of cycles ($p < 0.0001$) and tasks ($p < 0.03$) with interaction between cycles and tasks ($p < 0.009$). In patients with PD, this comparison yielded no significant results.

1) Spatial error: the shortest distance of the end point from the center of the target.
2) Extent error: the difference between target extent and movement extent.
3) Directional error at the peak velocity: the difference in degrees between the direction of the vector from the starting point to the target and that of the vector from the starting point to the movement peak velocity. Correct responses were defined, on the basis of this variable, as movements with directional error of 22° or less at peak velocity. Such errors occurred more frequently in the sequence learning tasks, when subjects were instructed to predict upcoming targets, but they were rare (less than 5%) in RAN. Spatial and timing measures of these incorrect movements were excluded from statistical analysis.
4) Movement time: the time from movement onset to the end point.
5) Onset time: the time from target and tone presentation to movement onset. Depending upon the experimental time constraint, this measure corresponds to the movement latency or the reaction time. Negative values indicate responses that were initiated before the tone.
6) Timing error: the time from target and tone presentation to movement end. In this case, negative values indicate responses that ended before the tone.

For the sequence learning conditions (SEQ and VSEQ), we also quantified the retrieval of the target sequence during movement execution. All the movements with onset times lower than RAN floor value and directed to the correct target were regarded as reflecting anticipation, subject prediction, and learning, and, thus, successful retrieval of previously acquired targets. For each variable, we computed means and variances across the correct movements of the entire trial block, as well as for each complete cycle of eight targets. At the end of each trial block, subjects were asked to indicate on the screen the order of the sequence. The number of total correct target locations reported by each subject from 0 (unawareness of a repeating sequence) to 8 (complete correct sequence) represented a declarative score, an additional measure of the explicit learning achieved.

Repeated measures analysis of variance (ANOVA) with post hoc comparisons was performed to assess the effect of group and cycles. Declarative scores and the number of correct anticipatory movements per trial block were compared using regression analysis. All analyses were considered significant for $p < 0.05$. All statistical procedures were performed with STATVIEW 5.0 (Abacus Concepts, Berkeley, CA).

Results. No indices of motor execution and learning of the right and left hemiparkinsonian patients were significantly different. Also, there was no difference between the performance of treated and naïve patients. Their data were thus combined for comparison to normal controls.

Predictable and random sequences. During CCW, all patients and controls made straight movements and correctly anticipated target appearance, thus reaching the target in synchrony with the tone. Onset and movement times were not significantly different in patients with PD and age-matched controls (onset time: see figure 2; movement time: normal, 440.3 ± 13.9 msec; PD, 459.3 ± 14.1 msec), similarly to timing error (normal, −21.5 ± 74.9 msec; PD, 27.2 ± 108.4 msec) and its variability (normal, 12.5 ± 4.4 msec; PD, 13.9 ± 6.7 msec). Accuracy, measured as linear error, was similar in the two groups. Significant reductions in linear error and movement time occurred during each trial block, as previously shown.[25]

Movements performed in RAN were also straight and accurate in both patients and control groups. Reaction times were stable across each trial block in both groups (see figure 2). However, mean reaction values were higher in patients with PD [PD, 300.25 ± 65.99 msec; controls, 240.81 ± 41.2 msec, $F(1,23) = 4.5$, $p < 0.05$]. Floor reaction times were also higher in patients with PD [169.1 ± 25.5 vs 144.29 ± 15.6 msec, $F(1,23) = 7.5$, $p < 0.02$]. However, the distributions of reaction times were similar between PD and controls, because the z-min values were not statistically different (PD, 1.9 ± 0.47; controls, 1.7 ± 0.43). On average, patients with PD were more accurate (linear error: 2.3 ± 0.4 vs 3.4 ± 2.3 mm) but slower than controls (movement time: 375.1 ± 93.1 vs 321.6 ± 49.9 msec), although these differences did not attain significance.

Concurrent visual and motor sequence learning. In SEQ, some movements were in the wrong direction because subjects

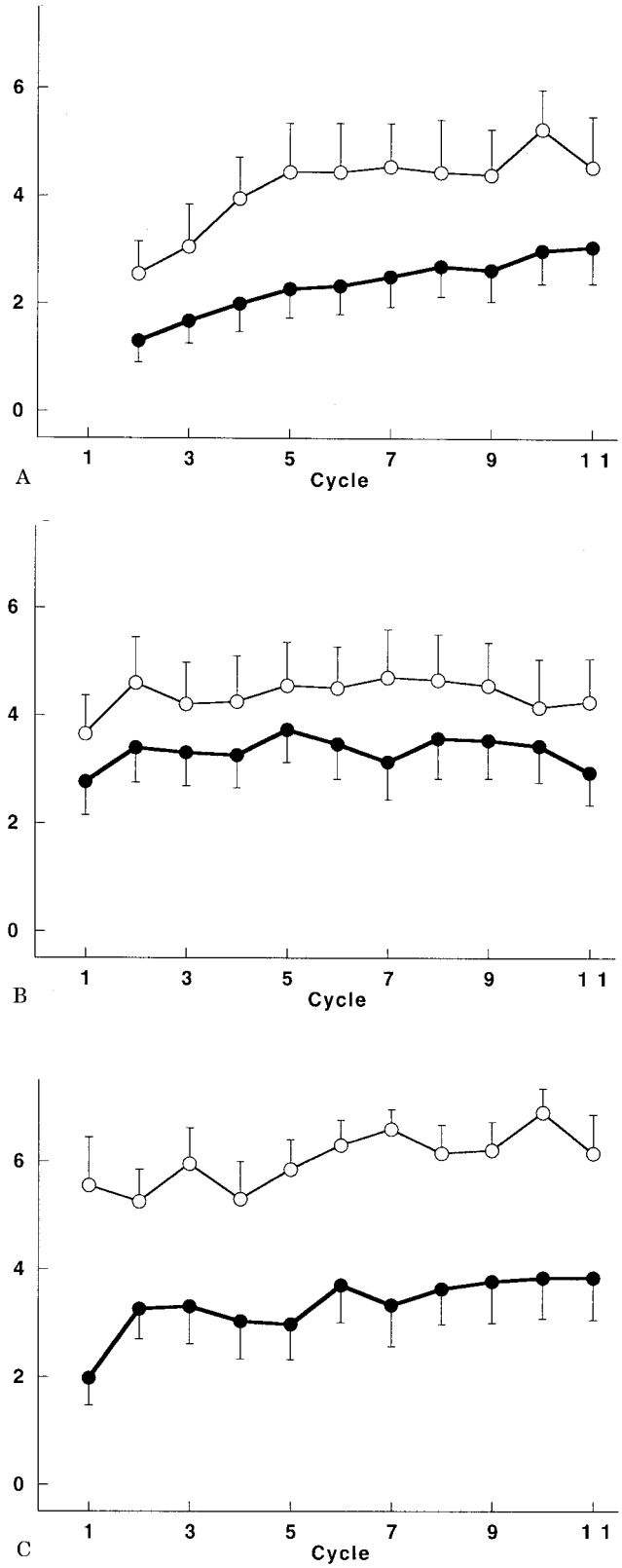

Figure 3. Retrieval of previously acquired targets in the three learning tasks. These indices are plotted as a function of cycles in control subjects (empty circles and a thin line) and patients with PD (black filled circles and a thick line). (A) SEQ1: A repeated measures ANOVA showed that target retrieval was different across cycles [F(10,207) = 11.59, $p < 0.001$*] and groups [F(1,207) = 4.34,* $p < 0.05$*], but without significant interaction. (B) SEQ2: Retrieval was not different between the two groups [F(1,23) = 1.25,* $p = 0.3$*], with an effect of cycles [F(1,230) = 2.23,* $p = 0.017$*] and no interaction between groups and cycles [F(1,10) = 0.43,* $p = 0.93$*]. (C) VSEQ test: A repeated measures ANOVA identified a main effect of both group [F(1,23) = 8.9,* $p < 0.007$*] and cycles [F(1,23) = 5.97,* $p < 0.0001$*], but no interaction [F(10,230) = 1.38,* $p = 0.2$*].*

were attempting to anticipate the upcoming target. The number of correct responses per cycle was higher in the control group for both trial blocks (SEQ1: controls, 6.91 ± 0.55; PD, 5.96 ± 0.94 [$F(1,23) = 8.3$, $p = 0.008$]; SEQ2: 6.86 ± 0.74 and 5.87 ± 1.5, $F(1,23) = 6.1$, $p = 0.02$). In both groups, correct responses increased in the course of each block [SEQ1: $F(1,230) = 2.2$, $p < 0.02$; SEQ2: $F(1,230) = 2.3$, $p < 0.02$]. Movement time was on average higher in patients with PD (410.2 ± 68.2 msec) than controls (377.6 ± 66.7 msec), although this difference did not reach significance.

Sequence learning was evident in both groups as a progressive decrease in mean onset time (see figure 2). However, in normal controls, this reduction occurred considerably earlier and more rapidly than in patients [$F(1,23) = 5.79$, $p < 0.03$]. On average, mean onset time of controls dropped below RAN reaction time floor by the second cycle. By the fourth cycle, it became negative, and by the fifth, it reached a plateau between −63 and −140 msec, corresponding to the range of values recorded during SEQ2 (see figure 2). In patients, mean onset times crossed RAN reaction time floors by the eighth cycle and stabilized around zero (range: from 70 to −22 msec) at the beginning of SEQ2. The difference in onset times between the two groups during SEQ2 did not reach significance. In this second trial block, onset times of all movements in both patients and age-matched controls occurred significantly later in CCW (see below). Similar results were obtained when onset times of correctly anticipated movements in either SEQ2 or SEQ1 (mean ± SD: −174.89 ± 177.44 msec) were compared to the corresponding values in CCW [mean ± SD: −508.90 ± 159.70 msec; $F(1,95) = 338.3$, $p < 0.0001$], suggesting that motor learning was incomplete in both groups.

Retrieval of previously acquired targets increased across cycles in both groups, but at a more rapid rate in controls than patients with PD. On average, control subjects correctly anticipated from four to five targets per cycle by the fifth cycle of the first block, whereas patients anticipated on average only three targets by the tenth cycle (figure 3).

Declarative scores recorded at the end of each trial block (figure 4) showed a difference between groups [$F(1,23) = 11.3$, $p < 0.003$] and tasks ($p < 0.0005$). However, post hoc analysis disclosed a difference between tasks only for the parkinsonian group ($p < 0.0007$), but not for the controls. Declarative scores were highly correlated with retrieval indexes ($r^2 = 0.78$, $p < 0.0001$), suggesting that both measures are expressions of declarative learning.

Sequence learning through visual exposure. With VSEQ, we determined whether impairment in sequence learning during SEQ could have resulted from the task concurrent demands of making movements while learning. In this task, patients with PD and age-matched controls were first asked to learn the sequence by observing target appearance in a 90-second block; they were then tested in a second block as per SEQ.

In both groups, the number of correct responses increased in the course of VSEQ testing block [controls: $F(10,180) = 2.7$, $p < 0.005$; PD: $F(10,280) = 4.04$, $p < 0.0001$], not differently from SEQ2. On average, the control group had a higher number of correct movements than patients with PD [6.83 ± 0.88 vs 5.30 ± 1.76; $F(1,23) = 9.2$, $p < 0.006$].

After visual exposure to the sequence, control subjects initiated movements earlier than patients [−295.4 ± 191.1 msec vs −10.1 ± 317.7 msec; $F(1,23) = 7.3$, $p < 0.02$]. Moreover, as shown in figure 2, in controls onset times occurred earlier in this task than in SEQ2. Interestingly, onset times of correctly anticipatory movements alone in VSEQ testing block (mean ± SD: −403.3 ± 153.0 msec) were still higher than in CCW [mean ± SD: −501.9 ± 159.4 msec; $F(1,99) = 35.9$, $p < 0.0001$]. When this analysis was confined to the last three cycles, we found no significant difference between the two tasks, suggesting that in normal controls, motor

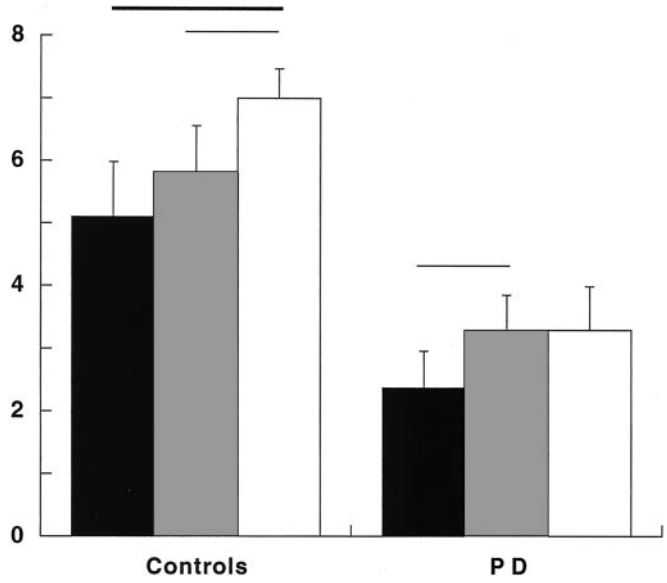

Figure 4. Declarative scores in normal controls and patients with PD. Mean declarative scores for SEQ1 (black column), SEQ2 (gray column), and VSEQ (white column) are plotted for the two groups. A repeated measures ANOVA identified an effect of group [F(1,46) = 11.332, $p < 0.003$*] and tasks [F(2,46) = 2.8,* $p < 0.0005$*]. Post hoc analysis for the control group yielded a difference between VSEQ and the other two tasks, SEQ1 [t(9) = 3.32;* $p < 0.009$*] and SEQ2 [t(9) = 2.8;* $p < 0.02$*]; there was only a marginal difference between SEQ1 and SEQ2 [t(9) = 1.77;* $p = 0.11$*]. In the PD group, declarative scores of SEQ1 were lower than SEQ2 [t(14) = 4.40;* $p < 0.0007$*] and only marginally different from VSEQ [t(14) = 1.99;* $p = 0.07$*].*

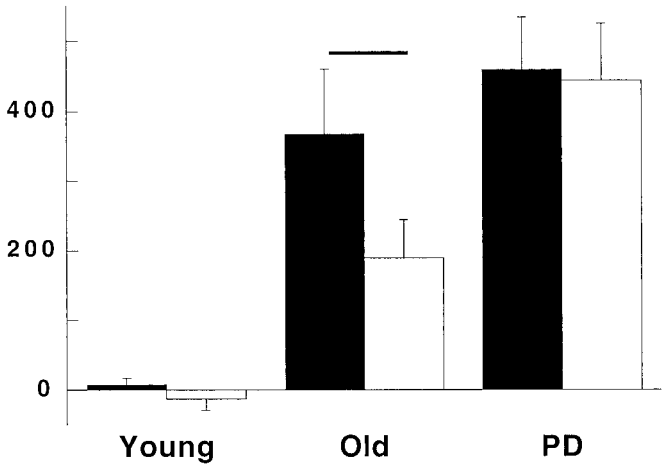

Figure 5. Difference between onset times between CCW and SEQ2 (white column) and VSEQ test (black column). Mean differences and SD are plotted for three groups of subjects: young subjects, older controls, and patients with PD. A repeated measures ANOVA (groups and task differences) identified an effect of groups [F(2,31) = 11.7, $p < 0.0003$*] and tasks [F(1,2) = 5.2,* $p < 0.03$*]. Post hoc tests revealed that the delta between the two tasks was different only for the group of older controls [t(10) = 1.98;* $p < 0.02$*].*

learning was complete before the end of VSEQ testing block. In the patient group, onset times fluctuated around zero in both VSEQ testing block and SEQ2, with no difference between the two tasks.

Other learning indexes were consistent with these results. Target retrieval in VSEQ was lower in patients with PD than in controls [$F(1,23) = 8.9$, $p < 0.007$] (see figure 3). Similarly, declarative scores taken after a 90-second block of visual exposure and before motor execution showed a difference between groups [$F(1,23) = 11.3$, $p < 0.003$] and tasks ($p < 0.0005$). Post hoc analysis disclosed difference between VSEQ and SEQ1 for the control group ($p < 0.009$). Analysis for this difference in PD showed a trend toward significance ($p = 0.07$) (see figure 4).

No significant correlation was found between verbal scores obtained after SEQ1, SEQ2, and VSEQ and mean movement times of either CCW or RAN.

Sequence learning in young subjects. A group of young normal subjects was tested to determine if aging itself might impair sequence learning. Indeed, sequence learning for both SEQ and VSEQ was faster in young subjects than in the older control group described in the previous paragraphs. In young subjects, the average number of correct responses was 7.3 ± 0.93 for SEQ1, 7.7 ± 0.58 for SEQ2, and 7.7 ± 0.45 for VSEQ. SEQ average onset times fell below the floor of RAN reaction time (mean ± SD: 144.5 ± 17.0 msec) by the second cycle and, by the third, became negative. From the fourth cycle, young subjects reached and remained at values comparable to CCW until the end of this trial block as well as in the following SEQ2. No significant differences were found between onset times of SEQ2, VSEQ testing block, and CCW. This finding is illustrated in figure 5, where average differences in onset time between SEQ2 and CCW, as well as between VSEQ testing block and CCW, are plotted for young subjects, old normal controls, and patients. Whereas both differences were close to zero in the younger group, onset time in SEQ2 was on average 367 msec and 459 msec higher compared to CCW in older normal subjects and patients with PD. However, the difference between VSEQ testing block and CCW was only 189 msec in older normal subjects, whereas in the patient group it was, on average, 444 msec and, thus, not significantly different from their SEQ2 − CCW difference.

Discussion. The questions addressed in the current study were whether sequence learning is impaired in early PD; whether such an impairment relates to explicit learning, which involves working memory and attention; and whether slower learning can be dissociated from bradykinesia. We found that patients with early PD learned novel motor sequences at a lower rate than their age-matched controls. Reduced learning rates were obtained with specifically designed tasks that emphasize explicit sequence learning and pose high demands on working memory and attention. Finally, by using kinematically equivalent reaching tasks to analyze the time course of explicit sequence learning and general motor performance, we showed that this learning deficit did not reflect impairments in motor execution or bradykinesia.

Learning a motor sequence requires a series of implicit and explicit processes including integration of visual and proprioceptive information, acquisition and retrieval of spatial and temporal associations, and performance optimization. In contrast to the usual serial reaction time tasks,[20,27] the SEQ task used in this study promotes the explicit acquisition of the sequence order. Both patients and controls learned the sequence consciously and could verbalize it. The corresponding declarative score was highly correlated with the retrieval index derived from motor performance measures. Moreover, learning was

predictably much faster than with implicit protocols, as subjects were informed of the presence of a sequence and instructed to learn it. The results obtained using SEQ1 (see figure 2) demonstrate that the initial rate of learning was dramatically slower in our patients with early PD compared to controls. This impairment of explicit learning was confirmed by the low declarative scores of patients with PD both at the end of SEQ1 and after visual learning in VSEQ.

The profound slowing of explicit learning in PD seen in ours and in other learning tasks[28-30] likely reflects early deficits in attention and working memory resources.[3,31] Successful performance in our sequence learning tasks depends upon working memory, given that successive targets must be compared to the ones that previously occurred. The multiple explicit requirements of the task likely place further demands on attention, thereby retarding sequence acquisition even in the early clinical stages of the disease. In addition, our results in a recent PET study[23] suggest that these learning abnormalities may reflect changes in the brain organization involving premotor and prefrontal circuitry utilized in learning. In control subjects, the earliest stages of learning are dependent on activity of the caudate, putamen, and DLPFC. In early stage PD, these regions may not be functioning optimally[32,33] and the learning process is subserved, perhaps less efficiently, by other prefrontal regions and by the rostral supplementary motor area.[23] This compensatory adjustment may be more effective in tasks with fewer attentional and working memory requirements, such as VSEQ, where concurrent movements are not required. Nevertheless, our data show that PD patient performance remains subnormal even in the absence of concomitant movement. Interestingly, the rate of motor sequence learning was reduced in older controls compared to a group of young subjects. In the older controls, the defect resulted primarily from interference produced by the concurrent motor task when a sequence was learned with simultaneous movement execution.

Spatial and temporal accuracy as well as movement times of patients with PD were normal in CCW, a task that demands predictions of the time and locus of the upcoming target as well as the duration of the movement, but requires neither stimulus-response translation or substantial new learning.[25] The rhythmic appearance of target and tones in our timed-response paradigm may encourage the development of anticipatory movements in patients with PD by reinforcing and maintaining attention at a high level.[34-37] This finding and the lack of correlation between movement times in all tasks and indexes of declarative learning strongly suggest that the reduced acquisition rate in PD is not a consequence of bradykinesia.

Our findings of early deficits in explicit sequence learning complement previous ones demonstrating impaired implicit learning in severely affected patients.[8-10,17,19] In addition, our timed-response paradigm allowed us to evaluate an important later aspect of implicit learning that had not been assessed previously. The specific instruction to make anticipatory movements to reach the targets as they appear requires taking account of movement time and dynamic effects in programming movements. Normal subjects learn to do this without awareness, but only once they are able to predict the targets correctly. Indeed, both in young and older control groups, onset times during SEQ approach those of CCW only when declarative scores are high. Thus, the ability to accurately program the time of onset of each movement relies upon achieving a substantial declarative knowledge of the sequence. This suggests that these two learning processes—i.e., declarative learning and movement optimization—may occur separately. Patients with PD with comparatively lower declarative scores and retrieval indexes did not achieve full declarative knowledge by the end of these testing blocks. Although during learning their onset times declined at a relatively slower rate than in controls, it is not possible to determine whether this was the result of impairment in explicit visual learning or because of an additional deficit in the optimization process. Further psychophysical and imaging studies will be required to determine the time course of the transformation of the sequence declarative knowledge into an optimized motor performance in controls and patients with PD.

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