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Authors

Harrington, DL
Haaland, KY

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SEQUENCING IN PARKINSON'S DISEASE

ABNORMALITIES IN PROGRAMMING AND CONTROLLING MOVEMENT

by DEBORAH L. HARRINGTON[1,2] *and* KATHLEEN YORK HAALAND[1,2,3]

(From the [1]Veterans Administration Medical Center and Department of Psychology, University of New Mexico, the [2]Department of Neurology, University of New Mexico Medical School, and the [3]Department of Psychiatry, University of New Mexico Medical School, Albuquerque, NM, USA)

SUMMARY

Central programming deficits in Parkinson's disease (PD) were studied in two reaction time (RT) experiments. In Experiment 1, PD patients and controls performed sequences of hand postures that varied in length, the number of different postures (repetitive vs heterogeneous), and the delay interval before movement. Before movement, the PD group planned repetitive movements like controls whereas for heterogeneous sequences RT increased less with sequence length for the PD group, implying less preprogramming. The interresponse time (IRT) data from repetitive sequences showed that the PD group had difficulty controlling movement such that IRTs were faster when sequences were longer, thus allowing more time to schedule the termination of the sequence during the course of movement. For heterogeneous sequences, the PD group made more errors and were slower than controls when changing hand postures, suggesting a deficit in switching between different responses. While RT decreased with a longer delay similarly for both groups, IRT_1 continued to improve only for the PD group but similarly for both types of sequences, suggesting a deficit specific to programming the first response. In Experiment 2, subjects made decisions about the number of different hand postures contained within a sequence. PD patients' decision times improved more with a longer delay only for heterogeneous sequences, suggesting a problem in identifying the number of different hand postures. The results have implications for levels of motor dysfunction in PD which emphasize the influence of sequence length and complexity.

INTRODUCTION

Part of the motor problem observed in Parkinson's disease (PD) has been attributed to central programming deficits although explanations for these deficits are disputed. The present study examines whether abnormalities in programming are found both before and during the execution of hand posture sequences, and whether such deficits vary depending on the complexity of sequences.

Early evidence suggested that once a predictable movement was initiated, PD patients could carry out the motor program if the movement was externally guided (Bloxham *et al.*, 1984; Day *et al.*, 1984). Some studies have shown that PD impairs the ability to use advance information to initiate and select movements (Bloxham *et al.*, 1984; Sheridan *et al.*, 1987; Pullman *et al.*, 1988), but others have found no such deficit (Rafal *et al.*, 1984, 1987; Stelmach *et al.*, 1986). Discrepant findings concerning the nature of cognitive deficits in PD are due in part to the level of analysis. Abnormalities are not always seen when the amount of subject-initiated organization is minimized,

Correspondence to: Dr D. L. Harrington, Psychology Service (116B), Veterans Administration Medical Center, 2100 Ridgecrest Drive SE, Albuquerque, NM 87108, USA.

such as when subjects are highly practised (Stelmach *et al.*, 1986), when the same response is repeated on successive trials (Rafal *et al.*, 1984), or when movement is externally guided (Bloxham *et al.*, 1984; Day *et al.*, 1984). When subjects must independently construct an internal motor representation to guide movement, cognitive deficits seem to be more evident (Flowers, 1978; Stern *et al.*, 1983, 1984). Such deficits are also evident in motor learning (Harrington *et al.*, 1990) where it is important to independently develop strategies that will improve performance. Motor planning in PD has been less well studied using tasks that require more organizational processing such as the sequencing of movements. Although one study of finger sequencing (Rafal *et al.*, 1987) found that PD patients used advance information to retrieve subprograms from a motor program, which was presumably constructed before the RT interval, others have shown that PD patients do not evidence normal programming of repetitive finger key presses (Stelmach *et al.*, 1987). Programming deficits also have been reported in PD during the sequencing of two distinct movements; the duration of individual movements was longer when performed sequentially than in isolation for PD patients only, suggesting a deficit in switching from one motor program to another (Benecke *et al.*, 1987*a*, *b*).

Although there is consensus that PD patients can construct a motor program, it is not clear whether the output from motor programs is qualitatively similar to that of normals or whether motor programs are optimally used during movement. Recent data showing PD patients can learn a motor task such as rotary pursuit but the amount of learning is reduced (Harrington *et al.*, 1990) suggest they may not make normal use of motor programs even when movement is externally guided and predictable. These issues can be addressed by examining programming processes before and during more complex movements such as sequencing where an internal motor representation must be independently assembled and utilized to control multiple movements.

The purpose of the present experiments was to improve understanding of cognitive deficits in PD as they relate to planning motor sequences independent of purely motor factors. The first objective of Experiment 1 was to determine whether motor deficits in PD are due to a difficulty in using advance information about sequences to improve initiation. If this is the case, RTs should not improve as much for PD patients as for controls when they are given more time to plan the sequence. Secondly, the effect of sequence complexity on PD patients' ability to plan sequences prior to movement was examined by contrasting RT performance on sequences containing different (heterogeneous) or the same (repetitive) hand postures. If PD patients can utilize advance information to plan repetitive sequences they should show no effect of sequence length on RT, similar to normal controls (Harrington and Haaland, 1987), suggesting that repetitive movements are planned as a unit. As for heterogeneous sequences, RT increases with sequence length for controls as they must assemble a motor program containing different subprograms, one for each response in the sequence. If PD patients evidence difficulty constructing a motor plan for heterogeneous sequences, sequence length should have less of an effect on RT in comparison with controls as they may not be programming information about all responses in the sequence. Difficulty using motor plans to control the execution of hand posture sequences was examined by comparing groups on the pattern of interresponse times (IRTs). If PD patients plan repetitive sequences as a single unit and use the output from the motor plan optimally, IRTs should not be affected

by sequence length. For heterogeneous sequences, PD patients may have difficulty switching between motor programs which will increase the duration of IRTs, particularly those that require changes in hand postures. Experiment 2 examined whether programming difficulties found for PD patients in sequencing were in part related to problems determining the number of different types of hand postures contained within a sequence.

EXPERIMENT 1

Methods

Subjects

Twenty-four patients with Parkinson's disease (PD) and 20 neurologically intact control subjects were studied. PD patients and controls were right-handed and matched for age and educational level (*see* Table 1). The PD group consisted of 25% females and the control group had 53% females but sex was not related to performance on any of the experimental tasks. The average duration of PD was 6 yrs (SD = 7) and the mean age of onset was 60 yrs (SD = 8). All but one PD patient were being treated with dopaminergic drugs.

TABLE 1. DEMOGRAPHICS AND PERFORMANCE OF CONTROL AND PARKINSONIAN SUBJECTS ON ANCILLARY TESTS

	Control group			*Parkinsonian group*		
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*
Age	65	8	51–80	66	6	54–77
Education	12	2	8–15	12	2	4–15
Information (WAIS-R)[1]	12.6	2	9–16	11.4	3	5–18
Mini-Mental State	29.4	1	27–30	27.7*	2	25–30
Block Design (WAIS-R)[1]	8.7	2	4–13	6.4*	2	4–11
Line Orientation[2]	27.7	4	19–33	24.3*	5	16–32
Wechsler Memory Quotient	122.6	12	99–143	105.2*	15	76–137
Beck Depression Inventory[3]	5.5	4	0–14	11.7*	7	0–29
NYU Disability Scale[4]				19.8	16	1–51

* $P < 0.01$ for t tests comparing controls and PD subjects. [1] Scale scores (mean = 10 ± 3). [2] Scores corrected for age (scores less than 20 are considered impaired). [3] Scores greater than 9 are indicative of depression. [4] Scores are sums across all items with a score of zero reflecting no disability and a score of 100 representing complete disability. Scores of 40 or greater suggest considerable disability.

A board-certified neurologist assessed parkinsonian status using two different instruments. On the Hoehn and Yahr (1967) severity scale 37% were classified in Stage 1 (mild, unilateral involvement), 17% in Stage 2 (bilateral involvement), 42% in Stage 3 (mild to moderate gait disturbance), and 4% in Stage 4 (marked gait disturbance). On the New York University (NYU) Disability Scale (Lieberman, 1974) most patients showed no rigidity (71%), tremor (54%), dyskinesia (96%), postural abnormality (63%), or gait problems (67%). For bradykinesia, 54% of the patients showed impaired motor speed and 83% showed impaired amplitude of movement. Five patients received total scores of 40 or greater on this scale which reflected considerable disability (*see* Table 1).

Neuropsychological data are described in Table 1. There were no significant differences between the groups on the Information subtest from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981). Although the PD group performed more poorly on the Mini-Mental State Examination (MMS)

(Folstein *et al.*, 1975) ($F(1,41) = 13.6$, $P < 0.001$), all scores were within the normal range. The PD group also performed more poorly on Judgement of Line Orientation (Benton *et al.*, 1983) ($F(1,41) = 6.7$, $P < 0.025$), Block Design Subtest on the WAIS-R ($F(1,41) = 14.9$, $P < 0.001$), and on all subtests of the Wechsler Memory Scale (Wechsler, 1945) except Orientation ($F(1,41) = 16.3$, $P < 0.001$ for the Memory Quotient). An examination of the distributions of these scores showed that 2 PD patients (8%) scored more than 2 SDs below the control group mean on all three of these tests, 3 (13%) did so on two of these tests, and 5 (21%) performed in this range on only one of these tests. This suggests patients were not generally impaired on all tests although PD patients as a group demonstrated mild cognitive deficits. On the Beck Depression Inventory (Beck *et al.*, 1961), the PD group was more depressed than controls ($F(1,41) = 10.3$, $P < 0.01$).

Procedures

The experimental task required subjects to execute sequences of hand postures. Fig. 1 is a diagram of the apparatus which was interfaced with a computer and contained a row of 5 vertical plates which required contact with the side of the hand, a row of 5 recessed buttons which required contact with the index finger, and a row of 5 handlebars which required the 4 fingers to wrap around the bar from underneath. Subjects wore gloves equipped with metal contacts. The start plate was located to the left of the manipulanda, and subjects always moved from the left to the right using their right hand. When a change in hand posture was made, subjects moved to the right diagonally (up or down) to the next manipulandum. A monitor presented pictorial displays of the motor sequences that described the type of manipulandum associated with each response and its location on the apparatus.

Subjects started each trial by resting their index finger on the start plate which caused a pictorial display of the sequence to appear on the monitor. After a random delay of 250 ms or 2000 ms, a tone signalled

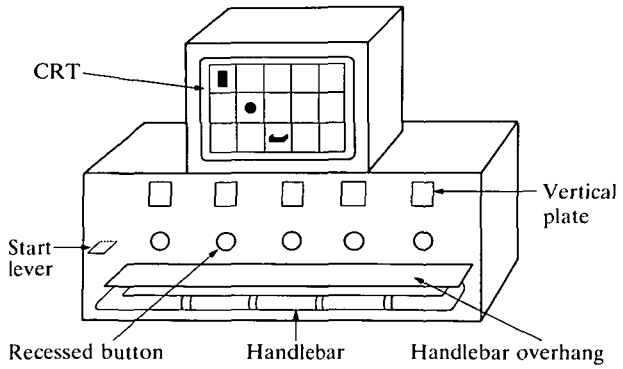

FIG. 1. Diagram of the hand posture sequencing apparatus. A monitor (cathode ray tube, CRT) presented pictorial displays of the sequence.

TABLE 2. HAND POSTURE SEQUENCES FOR EXPERIMENT 1*

	Sequence length				
Sequence type	*1*	*2*	*3*	*4*	*5*
Repetitive	P	PP	PPP	PPPP	PPPPP
	B	BB	BBB	BBBB	BBBBB
	H	HH	HHH	HHHH	HHHHH
Heterogeneous		PB	PBP	PBPP	PBPPP
		HB	HBH	HBHH	HBHHH

* The letters P, B, and H designate plate, button, and handlebar responses.

subjects to begin the sequence. On completion of the last response in the sequence, the visual display terminated. Reaction time (RT) was measured from the onset of the imperative stimulus to when subjects lifted their finger from the start plate. The first interresponse time (IRT_1) was measured from the end of the RT interval to the completion of the first response (i.e., contact with manipulandum), and subsequent IRTs were measured from the completion of one response to the completion of the next response. An error trial was recorded when subjects took longer than 2000 ms to initiate the movement or to execute a single hand posture or if they executed the wrong hand posture.

Table 2 presents the two types of sequences (repetitive or heterogeneous) which were blocked. Block order was randomized across subjects. Each of the 23 different motor sequences was presented 8 times across blocks in a random order. If subjects made an error, the trial was repeated randomly at the end of the block of trials. Subjects were required to complete correctly 2 practice trials of each of the 23 sequences.

Results

The analyses used a mixed model design with group as the between subject factor and posture, delay interval, and sequence length as the repeated factors. Trend analyses were performed on effects involving sequence length. Separate analyses of variance (ANOVAs) were conducted for each measure. Repetitive and heterogeneous sequences were analysed separately.

Repetitive sequences

Errors. There were no differences between groups in the percentage of errors before the imperative stimulus (4%) or the percentage of errors during movement (1%).

Reaction time. The PD group did not show slower RTs, and RT improved as much for the PD group as for controls with a longer delay interval ($F(1,41) = 102.6$, $P < 0.0001$) (Table 3). Fig. 2A shows that sequence length did not interact with group ($P > 0.05$), suggesting that both groups programmed repetitive sequences similarly. Pooling across groups, RT varied with sequence length ($F(4,164) = 4.1$, $P < 0.01$), but this was due to faster RTs for isolated hand postures ($F(1,42) = 7.1$, $P < 0.01$) relative to sequences of postures regardless of delay interval. For both groups, the type of hand posture interacted with delay interval ($F(2,82) = 9.8$, $P < 0.001$) so that with a 250 ms delay, RTs were longer for button (mean = 530) than plate (mean = 514) or handle responses (mean = 494) ($F(2,84) = 14.8$, $P < 0.001$); at the longer delay interval RT did not vary with type of hand posture. This finding shows that the PD group did not show any deficits in constructing a motor program for specifying muscle groups.

Interresponse times. Table 3 shows that for IRT_1, the performance of the two groups varied with delay ($F(1,41) = 5.1$, $P < 0.05$) so that while IRT_1 was slower for the PD group regardless of delay interval ($F(1,41) = 7.0$, $P < 0.01$), it improved with a longer delay interval for the PD group only ($F(1,23) = 21.6$,

TABLE 3. MEAN (SE) REACTION TIME AND IRT_1 (ms) AS A FUNCTION OF DELAY INTERVAL

	Controls			*Parkinsonians*		
	Delay interval (ms)			*Delay interval (ms)*		
	250	*2000*	*Difference*	*250*	*2000*	*Difference*
Repetitive						
Reaction Time	485	336	149*	534	360	174*
	(33)	(13)	(24)	(32)	(17)	(21)
IRT_1	523	503	20	664	606	58*
	(30)	(28)	(10)	(36)	(33)	(13)
Heterogeneous						
Reaction Time	492	353	139*	561	379	182*
	(32)	(15)	(19)	(28)	(20)	(19)
IRT_1	576	557	19	756	691	65*
	(30)	(28)	(10)	(40)	(38)	(14)

* $P < 0.01$ for the difference between the 250 ms and 2000 ms delay intervals.

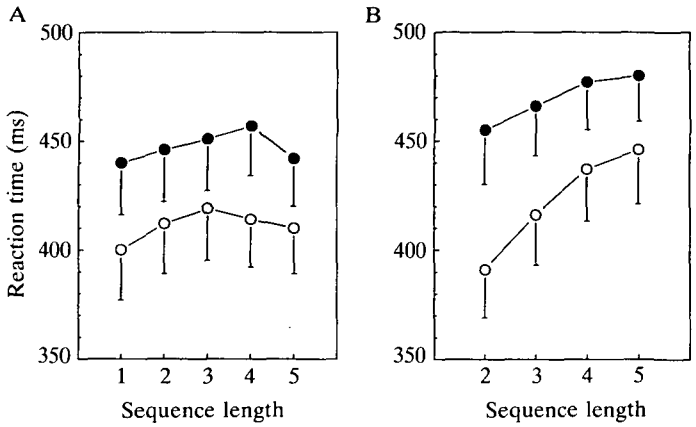

FIG. 2. Reaction time as a function of sequence length. A, mean reaction times with SE bars for repetitive sequences averaged over delay interval. B, mean reaction times with SE bars for heterogeneous sequences averaged over delay interval. Filled circles = parkinsonian patients; open circles = controls.

$P < 0.0001$). For both groups delay interval did not affect IRT_2 through to IRT_5 or reduce the effect size of sequence length on IRT_1.

Fig. 3 shows that the two groups also performed differently as a function of sequence length ($F(4,164) = 7.3$, $P < 0.001$). Although it took longer for PD patients to execute the first response regardless of sequence length ($F(1,41) = 10.0$, $P < 0.01$), IRT_1 varied with sequence length for the PD but not the control group (*see* fig. 3A) such that the first hand posture was executed faster as sequence length increased ($F(1,23) = 35.5$, $P < 0.001$ for linear trend). Similarly, figs 3B and C show that for IRT_2 and IRT_3 group also interacted with sequence length ($F(3,123) = 3.2$, $P < 0.05$ and $F(2,82) = 5.4$, $P < 0.01$) such that for controls there were no sequence length effects whereas for the PD group the time to execute the second and third posture decreased as sequence length increased ($F(1,23) = 22.3$, $P < 0.001$ for linear trend and $F(1,23) = 6.6$, $P < 0.05$ for quadratic trend of IRT_2; $F(1,23) = 23.1$, $P < 0.001$ for linear trend of IRT_3). However, fig. 3D shows that for IRT_4, execution time was longer for sequences of 4 than 5 responses for both groups.

There were no overall differences between groups in the execution of the second and third responses ($P > 0.05$); thus, once PD patients initiated a sequence of repetitive movements, execution time was not impaired, at least for the first few movements. However, for IRT_4 and IRT_5 PD patients showed significantly slower execution times than controls ($F(1,41) = 6.0$, $P < 0.025$ and $F(1,41) = 8.7$, $P < 0.01$, respectively).

Heterogeneous sequences

Errors. The percentage of errors before the imperative stimulus was approximately 4% for both groups, but the PD group made significantly more errors during movement (mean = 5.4% vs 1.2%) ($F(1,41) = 12.8$, $P < 0.001$). Further analyses showed that the PD group made significantly more errors on the first, second and third responses of the sequence when changes in hand postures were required ($F(1,41) = 10.6$, $P < 0.01$; $F(1,41) = 6.6$, $P < 0.025$; and $F(1,41) = 7.9$, $P < 0.01$), but no differences were seen on the fourth and fifth responses which required repetitions of the same hand posture.

Reaction time. The PD group did not show slower RTs for heterogeneous sequences, and RT improved for both groups with a longer delay interval ($F(1,41) = 142.3$, $P < 0.0001$) (*see* Table 3). Although it appears that the performance of the PD group improved more than that of the controls with a longer delay interval, this effect was not significant. Delay interval interacted with sequence length ($F(3,123) = 11.1$, $P < 0.001$), showing that RTs for both groups did not increase as much with sequence length (although they still increased) at a longer delay interval. This finding demonstrates that for both groups, more programming is completed with a longer delay interval.

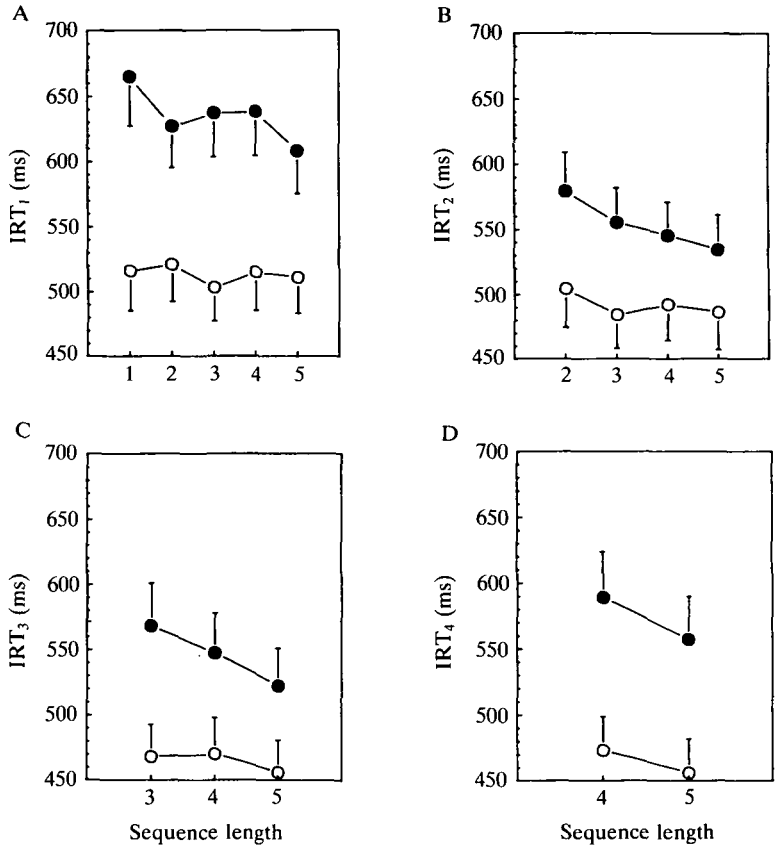

FIG. 3. Interresponse times (IRTs) for repetitive sequences as a function of sequence length. A, B, C and D designate the mean IRTs with SE bars for IRT_1, IRT_2, IRT_3 and IRT_4, respectively. Symbols as in fig. 2.

Fig. 2B shows that for heterogeneous RT, group interacted with sequence length ($F(3,123) = 3.4$, $P < 0.025$) such that for control subjects RT increased from sequence lengths of 2 to 4 and became asymptotic thereafter ($F(1,18) = 46.1$, $P < 0.001$ for linear; $F(1,18) = 16.2$, $P < 0.001$ for quadratic trend). For the PD group, only a small effect of sequence length was found, with RTs being faster for sequences containing 2 postures than those containing 4 or 5 postures ($F(1,23) = 8.6$, $P < 0.01$). There was no significant interaction of group by sequence length by delay, indicating that the smaller effect of sequence length on RTs for the PD group relative to controls was found at both delay intervals despite the finding that sequence length had less of an effect on RT with a longer delay interval for both groups.

Interresponse times. Similar to the findings for repetitive sequences, Table 3 shows that for IRT_1 delay interval interacted with group ($F(1,41) = 6.4$, $P < 0.025$) such that the execution of the first posture was faster with a longer delay interval for the PD ($F(1,23) = 22.3$, $P < 0.001$) but not control group. For both groups, delay interval did not affect IRT_2 through to IRT_5 or reduce the effect size of sequence length on IRT_1.

Fig. 4 presents the IRT data for both groups as a function of sequence length. For all IRTs, the PD group was significantly slower than control subjects regardless of sequence length ($P < 0.025$). In addition, the duration of the first IRT increased with sequence length ($F(1,41) = 22.7$, $P < 0.001$ for linear trend) similarly for both groups (*see* fig. 4A) as programming that began during the RT interval is ongoing. While

this finding implies that both groups are engaging in similar processes during the execution of the first response, the higher error rates for the PD group during IRT_1 indicates otherwise, and may suggest a speed-accuracy trade off. Fig. 4B shows that no sequence length effects were found for IRT_2 for either group, but for IRT_3 and IRT_4 figs 4C and D show that the performance for the two groups interacted with sequence length ($F(2,82) = 5.3$, $P < 0.01$ and $F(1,41) = 4.1$, $P < 0.05$) such that there was no length effect for control subjects, but IRT_3 and IRT_4 decreased with sequence length for the PD group ($F(1,23) = 12.0$, $P < 0.01$ and $F(1,23) = 12.7$, $P < 0.01$ for the linear trends). Recall that the third response involves a change in hand posture and subsequent responses are repetitions of this posture which may explain why this pattern of findings is similar to those reported for repetitive sequences.

Mild versus advanced PD

The effect of disease severity was examined by comparing sequencing performance of patients with mild symptoms and those with more advanced symptoms of tremor, rigidity, and bradykinesia. PD patients with ratings on the NYU Disability Scale in the lower (scores less than 11) and upper (scores greater than 20) 38th percentile were compared. There were no differences between the groups in age, disease duration, age of disease onset, amount of tremor and rigidity, or performance on neuropsychological tests. The advanced PD group showed more severe bradykinesia ($F(1,16) = 17.4$, $P < 0.001$), and scored somewhat

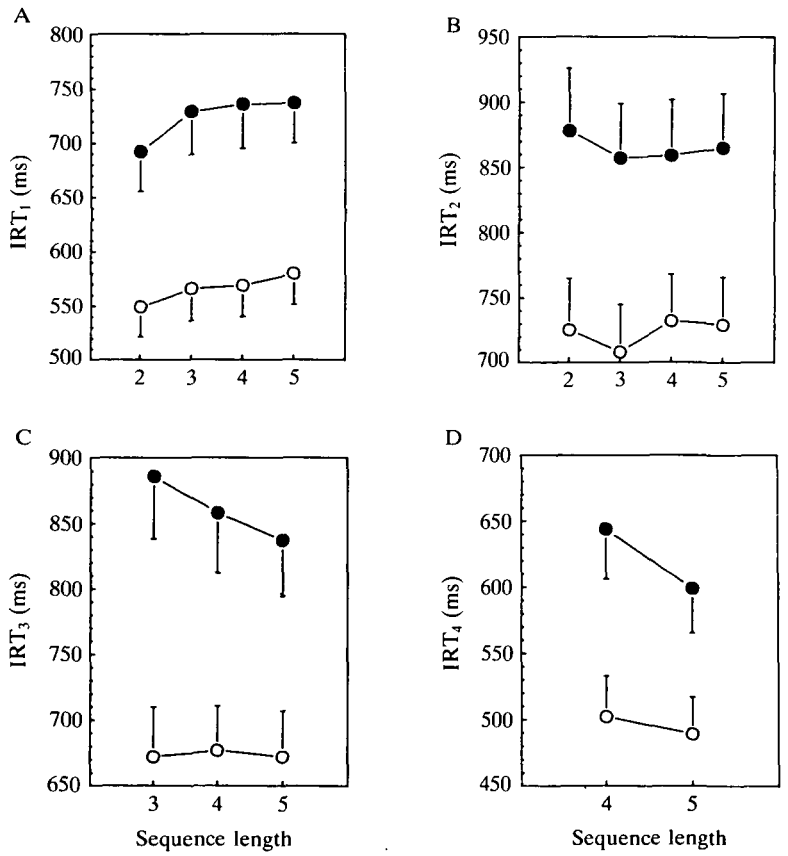

FIG. 4. Interresponse times (IRTs) for heterogeneous sequences as a function of sequence length. A, B, C and D designate the mean IRTs with SE bars for IRT_1, IRT_2, IRT_3 and IRT_4, respectively. Symbols as in fig. 2.

lower on the MMS (mean = 27.0, SD = 1.7) than the mild PD group (mean = 28.8, SD = 1.6) ($F(1,16) = 5.5$, $P < 0.05$).

The results showed that while the more advanced PD group was slower in execution and made more errors (possibly due to the slowness) ($P < 0.05$), the pattern of motor programming deficits as inferred by sequence length and delay interval effects was similar for both groups. The only exception was that sequence length sometimes had less of an effect on the IRTs of repetitive movements for the mild group than the advanced group, but mild PD patients still showed similar deficits.

Correlates of sequencing performance

To explore the relationship further between sequencing and cognitive deficits in PD, performance on clinical tests of visuospatial skills (Block Design, Line Orientation), memory and attention (subtests of the Wechsler Memory Scale), mental status (MMS), and depression (Beck Depression Inventory) were correlated with sequencing performance. The pattern of delay interval and sequence length effects was examined to determine if differences between PD and controls varied as a function of performance on these tests. Using separate regression analyses with repeated measures, none of these tests explained differences between groups in delay interval effects (i.e., group×ancillary test×delay interval) for RT or IRT_1. For heterogeneous but not repetitive RT, the Block Design subtest, Line Orientation, and the Visual Reproduction subtest of the Wechsler Memory Scale significantly interacted with group and sequence length ($P < 0.05$) such that these tests were related to the pattern of sequence length effects on RT for the PD but not the control group. As all 3 tests measure some form of visuospatial processing, z scores were computed for each test and summed, producing a composite score. In a regression analysis with repeated measures, this composite score interacted with group and sequence length for heterogeneous RTs ($F(3,117) = 5.45$, $P < 0.01$). Follow-up analyses showed that this composite score interacted with sequence length for the PD group ($F(1,22) = 8.4$, $P < 0.01$) but not controls. Table 4 presents the heterogeneous RTs as a function of sequence length effects for controls and PD patients who scored in the upper and lower 33 percentile on the visuospatial composite. This table shows that PD patients who performed better on the visuospatial tasks (i.e., within the range of normals) showed as much of an increase in RT with increasing sequence length as controls whereas those who performed more poorly showed no sequence length effects. The visuospatial composite accounted for 30% of the variance in sequence length effects on heterogeneous RT ($r = 0.55$, $P < 0.025$). Thus visuospatial skills partially predicted the extent to which PD patients programmed heterogeneous sequences prior to but not during movement. This finding

TABLE 4. MEAN (SE) HETEROGENEOUS RT (ms) FOR SUBJECTS SCORING IN THE LOWER AND UPPER PERCENTILES[1] ON THE VISUOSPATIAL COMPOSITE

	Sequence length			
	2	*3*	*4*	*5*
Controls				
Lower percentile	410	450	480	480
	(43)	(48)	(51)	(54)
Upper percentile	408	420	446	452
	(20)	(24)	(25)	(30)
Parkinsonian				
Lower percentile	565	552	562	564
	(45)	(46)	(45)	(42)
Upper percentile	397	425	436	449
	(33)	(30)	(29)	(28)

[1] Visuospatial composite scores for control subjects in the lower 33 percentile ranged between −5.31 and −1.00 and for controls in the upper 33 percentile scores ranged between 1.44 and 3.10. Visuospatial composite scores for PD patients in the lower 33 percentile ranged between −8.16 and −4.70 and for patients in the upper 33 percentile ranged between −1.84 and 2.41.

could not be attributed to disease severity as there was no difference between the mild and advanced PD groups on this composite measure. None of the clinical ancillary tests was related to the pattern of IRTs.

Discussion

The delay interval findings for both types of sequences showed that before movement, PD patients were able to use advance information to improve their RTs similarly to controls, but only PD patients continued to show additional benefits of a longer delay interval during the first IRT. The fact that delay interval reduced the effect of sequence length on heterogeneous RT for both groups but had no such effect on IRT_1 slope for either sequence type suggested that longer delays affected different processes before and during movement. For heterogeneous sequences, a longer delay prior to movement appears to influence programming of the entire sequence as a longer delay reduces RT slope. In contrast, for both sequence types the execution of the first response improved similarly with a longer delay, which did not affect the IRT_1 slope, suggesting that faster response times were not related to the composition of responses contained within the sequence. Instead, the effect of delay interval on IRT_1 appears specific to the first response.

Whereas before movement both groups appeared to plan repetitive movements as a single unit, once movement began the PD group performed differently and these effects could not be attributed solely to general slowness as, again, IRT slopes were not affected by delay interval. Instead, the IRT data suggest that during movement execution the PD group engages in some aspects of programming that controls have otherwise completed.

As for heterogeneous sequences, the PD group showed less programming before movement even at the longer delay interval as their RTs were less affected by sequence length, and during movement they continued to show programming deficits. Higher error rates for the first hand posture imply programming deficits for more complex sequences as no such errors were found for repetitive sequences. This may reflect a continuation of similar programming deficits seen during RT as the pattern of sequence length effects was similar for RT and IRT_1 but not for the other IRTs. Higher error rates, along with slowed IRTs for movements involving hand posture changes but not repetitions, also suggested a deficit in switching between different motor programs. Sequence length effects on IRT_3 and IRT_4 similar to those reported for IRTs of repetitive sequences, again were indicative of ongoing programming in the PD patients.

EXPERIMENT 2

One aspect of planning a sequence of movements is to resolve how many different types of responses are contained within the sequence. The results from Experiment 1 suggest this possibility as before movement the PD group appeared to plan heterogeneous but not repetitive sequences differently from controls. Experiment 2 was designed to test whether this component of planning was impaired in PD. Stimulus sequences similar to those in Experiment 1 were used, and the task was to indicate whether the sequences contained 1, 2, or 3 different hand postures. All subjects from Experiment 1 participated in this study.

Methods

The experimental task required subjects to press 1 of 3 possible keys in a row to specify the number of different types of hand postures in a sequence. Half of the subjects pressed the 3 keys from left to right with the thumb, index, and middle fingers to designate 1, 2 or 3 different hand postures; the others did the opposite.

The experimenter controlled the onset of the sequence display on the monitor. After a random delay of 250 or 2000 ms an imperative tone was presented. On completion of the response, the simulus display terminated. RT was measured from the onset of the tone to when subjects depressed a key. An error was measured when subjects made the wrong response or took longer than 2000 ms to respond, or responded before the imperative stimulus.

The stimulus displays contained sequences that were constructed similar to those in Experiment 1 except that only 3 or 5 posture sequences were used. Three different types of sequences were presented: (1) repetitive sequences of button or plate postures (1 posture); (2) heterogeneous sequences of plate and button postures (2 different postures); and (3) heterogeneous sequences of plate, button, and handlebar postures (3 different postures). Each of the 8 different stimulus sequences was presented 8 times across blocks in a random

order. If subjects made an error, the trial was repeated randomly at the end of the block of trials. During practice, subjects successfully completed 2 trials of each sequence type at both delay intervals.

Results

The ANOVAs used a mixed model design with group as the between subject factor and delay interval, sequence length and sequence type (i.e., 1, 2 or 3 different postures) as the repeated factors. Of interest were the effects of group and the interactions of group with the repeated factors. Repetitive sequences of button responses were not included in the analyses so that the beginning hand posture was the same (i.e., plate) across sequence types.

Errors. There was no difference between PD and control groups in the percentage of errors before the imperative stimulus (2%) or the percentage of delayed response errors (1%). Regardless of condition, the PD group made more incorrect responses (2%) than the controls (0.4%) ($F(1,41) = 8.0$, $P < 0.01$).

Reaction time. The PD group did not show slower RTs than controls and there was no significant interaction of group×sequence length which indicated decision times were similar between groups regardless of sequence length. Group interacted with sequence type and delay interval ($F(2,82) = 5.1$, $P < 0.01$). Follow-up analyses found no differences between PD and control subjects in RTs, regardless of condition. For both groups there was a significant effect of sequence type at the 250 but not the 2000 ms delay interval such that RTs were longer for 2 and 3 posture sequences than repetitive sequences. However, Table 5 shows

TABLE 5. MEAN DECISION TIMES (SE) IN SIMPLE RT (ms) AS A FUNCTION OF DELAY INTERVAL

Sequence type	*Controls*	*Parkinsonians*
Repetitive		
250	567 (52)	612 (48)
2000	383 (17)	373 (15)
Difference	184 (41)	238 (43)
Two postures		
250	651 (55)	814 (61)
2000	373 (16)	388 (20)
Difference*	278 (45)	425 (55)
Three postures		
250	690 (69)	844 (60)
2000	397 (18)	370 (18)
Difference**	293 (57)	474 (53)

* $P = 0.052$ and ** $P < 0.025$ for the difference between groups in the amount of improvement with a longer delay.

that the amount of improvement with a longer delay varied between groups as a function of sequence type. There was no difference between groups in the amount of improvement with a longer delay for repetitive sequences, but for 2 and 3 posture sequences, a longer delay interval improved decision times more for the PD than the control group ($F(1,41) = 4.0$, $P = 0.052$ and $F(1,41) = 5.5$, $P < 0.025$, respectively).

Mild versus advanced PD patients

There was no difference between groups in the number of errors before the imperative stimulus, but Mann-Whitney U tests showed that the advanced PD group made more delayed response errors (mean = 3.8 vs 1.8) and more incorrect responses (mean = 3.0 vs 1.1) than the mild PD group ($P < 0.05$). Severity group interacted with delay interval ($F(1,16) = 9.2$, $P < 0.01$) such that patients with more advanced symptoms had longer RTs only for the 250 ms delay interval ($F(1,16) = 9.1$, $P < 0.01$). The advanced

PD group also showed more overall improvement (mean = 527) with a longer delay interval than the mild PD group (mean = 229) ($F(1,16) = 9.2$, $P < 0.01$). These findings were not influenced by sequence type or length suggesting that group differences were most likely due to the greater motor slowness of the advanced PD group.

Correlation of visuospatial skills

Of interest in this analysis was whether the pattern of delay interval and/or sequence length effects differed for PD and controls depending on their score on the visuospatial composite described in Experiment 1. A regression analysis with repeated measures showed that visuospatial skills did not explain differences between these groups in delay interval (i.e., group×composite×delay), sequence type effects (i.e., group×composite×type), or the combination of delay interval and sequence type effects (i.e., group×composite×delay×type). This suggests that making decisions about the number of different responses contained in a sequence is largely independent of visuospatial skills.

Discussion

Although RTs were not slower for PD patients, they had more difficulty determining the number of different postures in complex sequences as their decision times improved more with a longer delay only for these sequence types. This suggests that one reason underlying preprogramming problems for heterogeneous sequences (Experiment 1 RT findings) in PD may be difficulties forming an internal representation of the sequence. Specifically, problems in resolving the number of different responses could impair organizing or grouping responses according to a strategy so as to facilitate programming and subsequent decoding during execution.

GENERAL DISCUSSION

The PD patients showed different types of programming deficits depending on the complexity of sequences which was suggestive of abnormalities in several levels of motor programming. Prior to movement, RTs for sequences of repetitive hand postures did not vary with length for either group whereas for heterogeneous sequences RTs for the PD group were less influenced by sequence length. This latter finding was true even when more time was available to preprogram despite the fact that at a longer delay interval the RT slope increased less with sequence length for both groups, suggesting that all subjects had completed more programming. If the PD group was simply slower in constructing a motor program for the sequence, the RT slope might be expected to increase rather than decrease with a longer delay, similar to that of the controls at the 250 ms delay. Instead, it appears that regardless of delay interval in PD a motor program is assembled that is dissimilar to that of controls. Higher error rates in PD for the first response of heterogeneous but not repetitive sequence lengths, despite normal increases in the duration of IRT_1 with sequence length also support this conclusion. IRT_1 errors for PD patients did not decrease with a longer delay which further supports the view that this deficit was not due to slowness per se in programming sequences but rather to problems in programming more complex sequences.

Although PD patients were able to use advance information to improve their RTs, as others have shown (Stelmach *et al.*, 1987), unlike controls they continued to benefit from a longer delay during the first IRT. The percentage improvement in IRT_1 with a longer delay (9%) was considerably less than for RT (32%), but was similar for both sequence types. It may take longer for PD patients to construct a motor program for the entire sequence such that programming continues during the execution of the first response. As previously discussed, this hypothesis predicts an interaction of group×

delay interval × sequence length for heterogeneous RT such that PD patients show more evidence of programming with a longer delay, which was not the case. Further, because the delay interval effect was similar between sequence types and did not affect the size of the sequence length effect on IRT_1, it appears that it is not the overall complexity of the sequence but, rather, the first response that benefits from additional time. This argument suggests the delay effect on IRT_1 may reflect slowed activation of the motor program for the first hand posture as EMG studies show the pattern of antagonist and agonist activity is normal but delayed in PD (Hallett *et al.*, 1977), or may reflect impaired programming of force-time parameters of movement in PD which would also produce slowing (Stelmach and Worringham, 1988). In any case, while longer delays prior to movement allowed all subjects to plan more about the sequence (i.e., reduction in RT slope with a longer delay), during the execution of the first response additional time only affected the programming of the first response.

The finding that PD patients showed faster IRTs for longer sequences (regardless of delay) suggests a separate deficit in using motor programs to control execution. Similar effects have been reported for choice RT in normal controls where the latency of the first key press became faster as the number of responses prior to an uncertain response within a sequence increased, suggesting a model where movement begins before the sequence is entirely programmed (Rosenbaum *et al.*, 1987). Extending this model to control processes during movement, the PD group had difficulty scheduling the termination of a sequence such that hand postures contained in longer sequences were more quickly executed because they had more time to identify the end of the sequence while they were executing the beginning responses. Execution of shorter sequences had to be delayed in order to plan the termination of the sequence which occurs earlier than for a longer sequence. Sequencing deficits of this type have been reported elsewhere showing that PD patients make more errors than controls in the number of repetitive finger taps in a sequence (Stelmach *et al.*, 1987).

For heterogeneous sequences, the pattern of sequence length effects differed across IRTs for both groups, suggesting that these sequences were not programmed as a single unit. While both groups show similar sequence length effects on IRT_1 and IRT_2, again PD patients made more errors executing the first hand posture. This may reflect ongoing problems (beginning during RT) assembling a motor plan for the sequence while simultaneously programming the physical parameters for the first movement. Difficulties coordinating two or more processes have been reported in PD for the performance of simultaneous movements (Benecke *et al.*, 1986) and the coordination of eye and hand movements (Warabi *et al.*, 1988).

Apart from the above programming deficits, the results also suggested that PD patients have difficulty switching between different responses, similar to others (Benecke *et al.*, 1987*a*, *b*). For heterogeneous sequences IRT_2 and IRT_3 were longer for PD than control subjects whereas for repetitive sequences no such differences were found at these response positions. PD patients also made more errors when changing hand postures but not when executing repetitions of a hand posture. This experiment did not examine whether this deficit was independent of problems programming motor parameters for individual responses. However, the fact that PD patients make more errors when initiating the first movement in a heterogeneous but not a repetitive sequence, would seem to imply that some other aspect of sequencing is also impaired.

Correlations of neuropsychological tests with sequencing performance revealed that for heterogeneous sequences only, poor visuospatial skills but not general cognitive functioning were related to deficient motor programming prior to but not during movement. This implies the visuospatial composite is more indicative of programming associated with the initial organization of responses rather than execution processes. Experiment 2 suggested that identifying the number of different hand postures contained within heterogeneous sequences may contribute to programming deficits in PD. Interestingly, poor visuospatial skills in PD were not related to slower decisions about the number of different postures, suggesting that this factor may influence motor programming independently.

Little is known about the role of visuoperceptual or visuospatial skills in motor programming, in part because of the multifaceted nature of these skills. There have been several reports of deficits in PD on a variety of visuospatial or visuoperceptual tests that minimize or eliminate motor output (Pirozzolo *et al.*, 1982; Boller *et al.*, 1984), but no study has related these deficits directly to motor programming. Studies with normal subjects have demonstrated that spatial aspects of some types of movements are represented in the motor program (Stelmach and Teulings, 1987). Stern *et al.* (1984) found that in PD poorer performance on drawing tests (which have a motor component) was related to greater difficulty performing predictable movements without visual cues. These studies, together with our findings and reports of visuospatial deficits in PD, introduce the possibility that the basal ganglia may be involved in integrating perceptual and motor systems for constructing motor programs. Still, visuomotor or visuospatial deficits have not always been observed in PD (Brown and Marsden, 1986; Taylor *et al.*, 1986).

Our results suggest that programming sequences require a variety of cognitive processes including: (1) identification of all responses; (2) ordering and grouping of the responses; (3) programming the physical parameters of responses; (4) resolving the termination of movement; and (5) controlling switching among different responses. Specifically, the absence of an RT slope for repetitive sequences, together with similar decision times in both groups for these sequences in Experiment 2, suggested that one level of programming may be identifying whether all responses are the same. PD patients seem to be able to perform this level of analysis normally. However, when all responses are not the same, Experiment 2 showed that PD patients had problems identifying the number of different responses. Based on the output from this process, responses are ordered and grouped. Repetitive sequences tend to be grouped as a single unit whereas the unit of analysis for heterogeneous sequences may be the hand posture, although structural aspects of these sequences could result in higher level grouping strategies (Povel and Collard, 1982). It is proposed that this level of programming is partially dependent on a visuospatial analysis, as only PD patients with poor visuospatial skills showed no evidence of programming heterogeneous sequences prior to movement. Another level of programming which was also impaired in PD was suggested by the IRT findings for repetitive movements and involves resolving where the sequence terminates spatially. The greater errors and slowness in PD when executing hand posture changes may also suggest abnormalities in a central executive process that controls switching between different motor programs. Finally, a level of programming related to controlling the physical parameters of individual movements was suggested by the delay effects on

IRT_1 for the PD patients only. This level may directly relate to the symptoms of bradykinesia whereas the other programming levels characterized in the present study may be more related to cognitive deficits frequently reported in PD that affect both motor and nonmotor task performance and learning, but are not closely related to bradykinesia. Thus different mechanisms may explain deficits in different levels of motor programming which raises the question, to which we now turn, of whether the basal ganglia regulate all or only some of these mechanisms.

Neuroanatomical correlates

Our results suggest that the basal ganglia play a role in several processes associated with the organization and control of hand posture sequences but two qualifications must be mentioned. The first is that the importance of different parts of the basal ganglia need to be specified as the neuroanatomical connections of the putamen and the caudate nucleus are different with the putamen projecting primarily to the supplementary motor area and the caudate projecting to the dorsolateral and lateral orbitofrontal cortex. These circuits probably serve different behavioural functions (Alexander *et al.*, 1986). Recently it has been suggested that the putamen is involved in early stages of PD and both putamen and caudate function are compromised in patients with more advanced symptoms (Nahmias *et al.*, 1985). The present study did not find qualitative differences in sequencing deficits between patients with mild and those with more advanced symptoms which may implicate the putamen and, more generally, the motor circuit in the programming and control of sequential movements. However, a study of rotary pursuit learning with the same sample of PD patients found motor learning deficits in the advanced but not mild PD group (Harrington *et al.*, 1990). One reason for this apparent discrepancy may be that motor learning requires skills more dependent on caudate function and the complex loops whereas it has been shown that the supplementary motor area is especially important for programming sequences of different finger movements (Roland *et al.*, 1980). This introduces a second limitation which is that the specific conribution of the basal ganglia to different levels of motor programming cannot be discerned without knowledge of how patients with damage to other neuroanatomical areas perform on these tasks.

A related issue concerns whether deficits in the present study apply only to motor tasks. One proposal is that the same processes which are involved in motor tasks and are performed at the level of basal ganglia can also influence nonmotor tasks (Alexander *et al.*, 1986). Planning deficits in PD have been observed on nonmotor tasks and conceptualized by some investigators as a shifting or switching disorder that did not appear to be due to frontal abnormalities in the PD patients studied (Cools *et al.*, 1984; Morris *et al.*, 1988). In the present study, there is some evidence consistent with a dysfunctional mechanism for switching or simultaneously coordinating several levels of programming such that processes normally proceeding in parallel become more serial. Some of our other findings, however, suggest the possibility of abnormalities in other mechanisms such as deficient motor program construction and a slowness programming physical parameters of responses. Future studies examining levels of programming on comparable motor and nonmotor tasks which require organizational processing may provide some insight into this issue.

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