Motor set in Parkinson's disease

C Robertson, K A Flowers

Abstract

Three experiments employing a five-choice button-pressing task tested the ability of Parkinsonian patients to learn and generate sequences of movement, and to switch between alternative sequences at will. It was found that patients could learn and generate individual patterns of movement normally, even complex ones involving an incompatible stimulus-response relationship. They had difficulty, however, in maintaining a sequence if two different ones had been learnt and subjects were required to switch spontaneously from one to the other within a trial. Providing external cues at the start of each sequence to guide the ordering of movements improved the stability of patients' performance. Most errors in sequencing consisted of reverting to the alternative pattern of movement. Parkinsonian subjects thus show an impairment in motor set similar to that found previously in cognitive activity.

One of the difficulties Parkinson's disease (PD) patients experience in controlling their actions is in coordinating two or more movements. In addition to the well-documented abnormalities of initiating individual movements (akinesia) and executing them (bradykinesia, hypokinesia), Parkinsonian subjects seem unable to do two things at once,[1 2] to execute two or more actions smoothly in sequence[3–5] or to generate continuous movements without visual guidance.[6 7]

These difficulties in coordination may occur simply as a consequence of the inaccuracy of execution of individual movements by Parkinsonian subjects, or they may reflect a separate higher-level impairment in response selection. The first explanation suggests that patients may be unable to integrate sequences of action because they cannot be sure what the outcome of any attempted individual movement will be and so have to monitor each one as it is executed. They can then only plan and initiate movements one at a time and not in combinations or sequences. The second hypothesis is that there may be a separate higher-level abnormality (independent of the processes involved in generating individual movements) in controlling the selection of movements in an appropriate order to fulfil an overall plan of action. Several authors have suggested that basal ganglia malfunction results in such an impairment.[8–10] Previous investigations, however, have not tried, or have not been able with the tasks used, to make a distinction between these explanations.

Previous descriptions of motor planning deficits in Parkinsonism have variously characterised them as an inability to elaborate a motor pattern or plan of action,[8] a problem of praxis,[9] or a difficulty in the automatic execution of motor plans.[10] According to Marsden,[10] a motor plan has motor programs for individual movements as its constituent elements and involves the smooth integration and sequencing of a series of motor programs. Thus while a motor program describes the characteristics of a single movement, a motor or action plan involves the selection of one or more motor programs to achieve a goal. This hierarchical model is similar to those in motor skills research which postulate a hierarchical organisation of motor control, with response selection determined by a central supervisory program assembling prepared subroutines for individual movements.[11] Thus the difficulty Parkinsonian patients have in generating sequential or simultaneous motor programs would reflect a dysfunction at the level of motor planning, implying a deficit in putting together response programs independent of any impairment in response programming of individual movements.

In another study Cools *et al*[12] considers the Parkinsonian deficit in sequential movement to be one of central programming and further to this Cools *et al*[13] coined the term "shifting aptitude" to describe the ability to rearrange "arbitrarily" the serial order of components of behavioural actions. They hypothesised that Parkinsonians have a decreased shifting aptitude for behaviour not directed by currently available sensory information, and that this diminished capacity is a behavioural impairment which manifests itself in both cognitive and motor activities.

One measure employed by Cools to test their shifting aptitude theory was a motor activity task, where subjects were asked to tap with their fingers in two sequences: (a) 1-2-3-4- and then (b) 1-3-2-4- with subjects having to change from the first to the second sequence within an allotted time. The reduction in score on the second task was taken as a measure of their difficulty in shifting from the strategy appropriate to the first task, whose score is a baseline for comparing the second sequence: this was accounted for in terms of an inability to generate finger movements spontaneously.

Department of Psychology, University of Hull, Hull
C Robertson*
K A Flowers

Correspondence to:
Dr Flowers,
Department of Psychology,
University of Hull,
Hull HU6 7RX,
United Kingdom.

Received 23 December 1988 and in final revised form 20 November 1989.
Accepted 23 November 1989

*Present address: Division of Behavioural Sciences, Humberside College of Higher Education, Hull HU6 7LU, United Kingdom.

This task can be criticised, however, for a lack of controls. It is not clear that what was tested was specifically the ability to "shift aptitude", that is, switch from one sequence to another, because there was no procedure to establish if subjects could produce each of the requisite sequences individually. Nor, having switched from the first to the second sequence, were patients tested for long enough without a time constraint to see if they could at any point reach the same level of performance as control subjects. Moreover, there was no control for the possibility that the deficit was due to an inability to make use of external cues. Thus the evidence put forward by Cools *et al* is equivocal and their hypothesis requires more rigorous testing. Hopefully, this investigation provides such a test.

Cools' definition of shifting aptitude—"the ability to reorganise behaviour according to the requirements of the task"—is very similar to those of Buchwald *et al*,[14], Denny-Brown and Yanagisawa[15] and Flowers and Robertson.[16] The latter described Parkinsonian patients as having a difficulty with maintaining a mental "set". Flowers and Robertson[16] define set as "a state of brain activity which predisposes a subject to respond in one way when several alternatives are available." The essential characteristic of set is that it operates in circumstances where the response is not determined solely by the information in the stimulus, either because it is initiated ahead of the stimulus or because there are several equally possible alternative responses and the choice has to be determined internally by the subject according to the goal currently in operation. Flowers and Robertson showed such an effect in a choice discrimination task (the Odd-Man-Out test) where subjects had to utilise two rules alternately on successive trials. Parkinsonian subjects had difficulty in using the rules appropriately, although they had no difficulty in performing the reasoning task itself. Like Cools, they suggested that an instability of set was a behavioural characteristic that applied to both mental and motor activities in Parkinsonian patients. The experiments here were designed to replicate the effect in a motor task to test this hypothesis, that is, to see if Parkinsonian subjects show a similar instability in motor set for arm movements to their lability of cognitive set in the mental reasoning task.

Motor set can be described as the characteristic of an action plan which determines the kind of movement or sequence of movements to be executed to fulfil the goal or intention contained within the plan. (It is not concerned with the parameters of movement such as force, timing or precision but rather with the general description of the movement for example, press button A rather than B, or push rather than pull the handle.) A secondary aspect of this process is the ability to alter the sequence where appropriate, either in response to a change in environmental circumstances or with a change in goal. Therefore, set functions (a) to maintain a series of movements within the parameters of the action plan to achieve a given goal; (b) to exclude other competing possible sequences of action; and (c) to react to any events requiring a change in the motor sequence by initiating a new movement program or sequence of programs. When there is a breakdown of set, the action plan will be disrupted and there is likely to be an inability to maintain the task. Therefore, failure to achieve an action plan may be a consequence of the failure to maintain motor set (as distinct from other deficits such as miscalculating what the appropriate movement should be, mistiming the onset of action with events in the external world, or failing to coordinate the components of complex actions, all of which could equally well disrupt the execution of a motor plan, even though the subject's initial selection of responses was correct within the plan).

To explore the concept of motor set difficulties in Parkinsonism resulting in poorly executed action plans, three experiments were performed designed to reveal whether patients can a) learn and execute repeatedly different response sequences; and then b) change from one sequence to another within an action plan. The intention was to distinguish between the ability on the one hand to understand, remember and generate spontaneously the correct motor sequences, and on the other, to initiate or restrain them at will. The test used a sequential button-pressing task, and was devised to give a measure of response selection accuracy independent of the subjects' performance of the chosen movement, because the interest here was in the subjects' choice of response as distinct from their speed or accuracy of execution.

EXPERIMENT 1

Method

Experimental task

The experimental task required subjects to make a series of discrete movements in a given order in various repetitive sequences. The display consisted of five red push-button microswitches which could be illuminated as stimulus lights by LEDs inside them. They were mounted on a board sloping at 30° from the horizontal (figure) and placed equidistant around a sixth similar green button, so that a subject could see all the red switches while resting the index finger of the preferred hand on the centre green button. (For the purposes of analysis and description the lights will be referred to as 1, 2, 3, 4, and 5 numbered clockwise from the bottom left-hand corner, but the numbers did not appear on the actual display.) The buttons measured 15 mm in diameter and were spaced 10 cm apart, so that the subjects' choice of response was never in doubt and they were easily able to hit the button of their choice each time.

During initial training trials, subjects were required to move from the centre button to a peripheral target button when it lit up, to press the button (causing it to go out) and then return

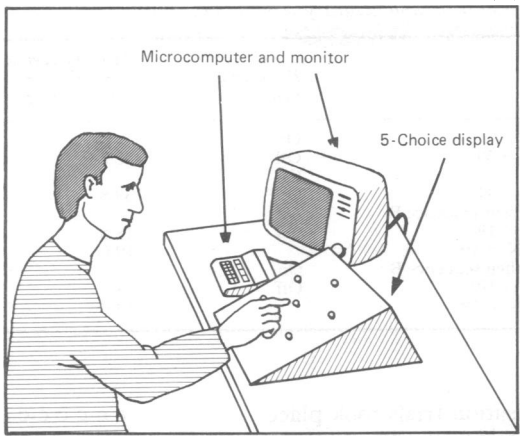

Figure Arrangement of 5-choice task display and apparatus.

to the centre. Upon returning to the centre green button, the next red button would illuminate indicating the next target. Again the subject moved to the illuminated peripheral target button, pressed it and returned to the centre, whereupon the next button lit up, and so on. Subjects continued in this manner until the lights stopped, indicating that the sequence had finished. This arrangement produced a continuous series of movements in and out from the centre button, the sequence of peripheral (outer) buttons being constant within a trial but varying from trial to trial. On later training and test trials subjects were required to follow or generate spontaneously first one sequence and then the other, and the essential interest was in their ability to maintain each action plan and to switch between them when required.

Subjects

Parkinsonian subjects were drawn from a pool of patients who attended the Parkinson's disease clinic at Hull Royal Infirmary. In view of the cognitive component of the experiments, it was decided to test mild to moderate PD patients, to reduce the possibility of including cases with dementia or depression. Patients were judged independently by a neurologist providing an assessment of their suitability for testing, and that the diagnosis was not complicated by other concomitantly existing diseases or syndromes. Patients were assessed as mild (score 1–7) or moderate (score 8–12) according to the Webster clinical severity rating scale.[17] Ten PD patients with ages ranging from 50 to 72 years (mean 60·0 SD 5·2) participated. Overall Webster ratings ranged from 5 to 12 (mean 8·0, SD 4·0) and duration of symptoms from one to 15 years (mean 7·0, SD 4·0). Informed consent was obtained from each subject to take part in the study.

At the time of testing patients were stable on their individual drug regimens. Patients received a combination of drugs which included anticholinergics (for example, Artane) and dopaminergics (for example, Sinemet, Madopar and/or Bromocriptine.)

The control group comprised 10 local volunteers and patients' spouses and were matched with the Parkinsonian group for age and educational background. None were taking drugs which affected the central nervous system and none had a history of neurological disease or head injury. Ages ranged from 50 to 70 years (mean 60·0, SD 4·0).

Experimental design

For this experiment only four of the peripheral buttons were used in the sequences. The button not used was the top centre (button No 3); the reason for this is explained below. A single sequence used four outer buttons and a trial comprised 40 outer button responses (80 responses in all). Each trial was equivalent in length, but could contain either ten repetitions of a single sequence or five repetitions of two different sequences.

The first sequence of outer buttons was 2-4-1-5-. This sequence of four lights was repeated ten times, which comprised one training trial. A minimum of three trials were presented to all subjects during this learning phase. The instructions to all subjects were uniform. They were to follow the lights and learn the sequence so that they would be able to reproduce it later.

After three trials had been completed (a total of 120 outer button responses) subjects were given a test trial to determine if the sequence had been learnt. For this purpose they were requested to reproduce the sequence by pressing the buttons in the correct serial order, but the lights did not illuminate. The computer recorded the button presses and displayed them on a visual display unit for inspection. In all cases the sequence was correct for all 10 cycles of the four-light sequence which made up the test trial, so subjects then proceeded to learn the second sequence (5-1-4-2-), the procedure for which was exactly the same as for the first. It was again followed by a test trial to establish that the sequence had been learnt.

Having learnt the two sequences separately, subjects were then instructed that they were to learn to produce them successively within one trial. The signal to switch sequences would be the illumination of the top red button (Number 3) which needed to be pressed to switch it off. Thus subjects were to follow the first sequence as the lights came on; when the top button lit up they were to press it to turn it off and then continue with the second sequence. The switch occurred half-way through the trial. The purpose of this phase of the experiment was to familiarise subjects with the conditions of the "set" task. Two trials of this task familiarisation were given.

At this point subjects had completed six learning trials plus two test and two task familiarisation trials. They then did two "switching" trials: this constituted the test proper. In these trials they were required to reproduce the first and then the second sequences in the same manner as in the task familiarisation trials, but the four red lights for the sequences did not illuminate. The only lights involved were the green reference button and the top centre button which indicated when to switch sequences. After these trials

Table 1 Experiment 1: Order of trials and accuracy scores in test trials

Trial	Task	Peripheral lights	Mean number correct responses per subject per trial: Control group	PD group
1, 2, 3	Follow sequence A	On		
4	Test sequence A (N = 39)	Off	38·3	38·0 (U = 33, NS)
5, 6, 7	Follow sequence B	On		
8	Test sequence B (N = 39)	Off	38·8	38·9 (U = 49, NS)
9, 10	Follow sequence A, then sequence B	On		
11, 12	Test sequence A (N = 19)	Off	18·5	9·8 (U = 15, p < 0·01)
	then sequence B (N = 19)		19·0	7·9 (U = 5, p < 0·01)
13, 14	Follow sequence A, then sequence B	On		
15, 16	Test sequence A (N = 19)	Off	19·0	10·7 (U = 10, p < 0·01)
	then sequence B (N = 19)		19·0	12·0 (U = 15, p < 0·01)

two additional familiarisation trials took place followed by two further test trials. The order of trials is summarised in table 1.

Rationale for scoring

Subjects were given scores for the number of outer button presses made in the correct order within each sequence or half-sequence. Within any sequence string each correct response is determined by what the preceding response was and then, in its turn, designates the next response. Therefore, the method of analysis employed here was a running score of pairs of responses, with each button press compared to its predecessor to see if it followed in the correct sequence or not, and if not, what kind of error it was. As sequence B was the reverse of sequence A, all responses could be put into one of four categories:

i) a correct response (following the designated sequence)

ii) a response appropriate to the alternative sequence (following the reverse pattern to the one currently required)

iii) a repetition of the previous response (same button as before)

iv) an "error" response which did not fit into any of the above categories (pressing the fourth possible button)

This method is preferred to one where, for instance, the number of complete strings of sequences (four responses) are scored and aggregated. Such a method would fail to distinguish individual errors, protracted error sequences or different kinds of errors determined by the criteria for scoring given above.

Criteria for scoring

The method is shown in the examples.

Example 1

2415241524152415 3 5142514251425142

First Sequence — Change-over Response — Second Sequence

A typical printout is shown in example 1 for a trial with 38 possible correct responses from two sequences (1st = 2-4-1-5- and 2nd = 5-1-4-2-) the numbers corresponding to the peripheral buttons pressed. The first sequence is reproduced five times giving a total of 20 responses; however, because of counting pairs of responses the total number of correct responses can only be 19 per half trial and 38 for a complete trial of two sequences.

c c c c c c c a a a a a a a a c c c c

First sequence

Example 2

2 4 1 5 2 4 1 5 1 4 2 5 1 4 2 5 2 4 1 5

Number correct (c) = 11

Number of alternatives (a) = 8

Total 19

Second sequence

c c c c c c c a a a a c c a a c c c c

5 1 4 2 5 1 4 2 4 1 5 2 5 1 5 2 5 1 4 2

Number correct (c) = 13

Number of alternatives (a) = 6

Total 19

Example two shows the method of scoring for alternative responses as intrusions into the currently required sequence.

Example 3

First sequence

c c c c a r a e c c c a a a a r a a a

2 4 1 5 2 5 5 1 2 4 1 5 1 4 2 5 5 1 4 2

Number correct (c) = 7

Number of alternatives (a) = 9

Number of repetitions (r) = 2

Number of errors (e) = 1

Total 19

Example three shows the method of scoring for alternative, repetition and error responses.

Statistics

Non-parametric Mann-Whitney, Wilcoxon and Chi-square tests were used for statistical analysis because of the ceiling effects and skewed distributions found for control subjects in most cases.

Results

Table 1 shows the total scores for the learning test trials (Trials 4 and 8; Sequences 1 and 2) for the Parkinson's disease and Control groups. At this stage no significant differences emerged in the number of correct responses. Table 1 also shows the results for the switching test trials (Trials 11, 12, 15 and 16) where the differences between Parkinson's disease and Control scores were highly significant for both sequences, on a Mann-Whitney U-Test (results in Table 1 are pooled for clarity of presentation but the effect was significant for each trial separately.) Thus while Parkinsonian subjects were able to reproduce each sequence on its own with few errors, they produced

Table 2 Experiment 1: Parkinsonian error distribution on switching trials (mean error per subject)

	Sequence (A)				Sequence (B)			
Trial	Alternative	Repetition	Error	χ^2	Alternative	Repetition	Error	χ^2
11	4·6	2·3	1·8	15·38 ($p < 0.001$)	7·9	2·3	0·6	81·06 ($p < 0.001$)
12	7·4	1·9	0·5	81·45 ($p < 0.001$)	7·9	3·0	0·5	72·23 ($p < 0.001$)
15	5·4	2·0	0·7	43·63 ($p < 0.001$)	5·2	2·8	1·0	29·60 ($p < 0.001$)
16	6·0	1·3	1·3	51·37 ($p < 0.001$)	3·1	1·5	0·4	19·00 ($p < 0.001$)

significantly more errors when having to continue the "set" task. Scores for each sequence were about equal in all test trials in both subject groups, none of the differences between Sequence A and Sequence B scores reaching significance on a Wilcoxon test.

Table 2 shows the number of Alternative, Repetition and Error responses made by the Parkinsonian group in the switching test trials (Controls were not included because they produced very few errors). In all sequences a Chi-square analysis showed a significant effect, with Alternative responses constituting the great majority of errors. Thus where patients make mistakes they involve predominantly reverting to the alternative sequence of actions.

Discussion

In this first experiment many patients had significant difficulties compared with control subjects in maintaining control over the sequencing of their actions when two incompatible series had to be generated in the same trial. The impairment is not a failure of memory for motor actions, because their performance on the initial test trials (4 and 8) showed that the Parkinsonian patients can reproduce the sequences separately over an equivalent period of time and number of responses. Nor, for the same reason, is the problem due to any cognitive misunderstanding. It arises as a behavioural disturbance whereby patients experience difficulty producing one sequence of actions when two or more are equally available. This is similar to the suggestion by Cools *et al*[12 13] that patients have a difficulty with "shifting their aptitude" and switching their behaviour on an arbitrary basis. But whereas that study involved separate tasks, the experiment here showed the effect with two similar motor sequences each of which subjects had been shown capable of reproducing alone.

The Odd-Man-Out mental set test used in our previous investigation[16] showed that, when there are alternatives which provide ambiguity in a cognitive decision task, Parkinsonian subjects have difficulty in suppressing the intrusion into behaviour of an alternative rule, resulting in an instability in applying the currently correct rule. Patients were not simply distracted by novelty, nor were they generally confused, because neither the third alternative, nor the common item of the group was consistently selected. In the motor set experiment reported here there was also ambiguity in the test situation and the results indicate that a similar effect was taking place. That is, the alternative sequence was intruding into the designated one and patients were fluctuating between sequences. Note that Sequence A is disrupted as much as Sequence B; thus the effect is not merely one of perseveration or forgetting to switch between sequences. Again the Error response was not selected very often, and therefore patients were not generally confused. The lack of Repetition responses also militates against the effect being a "frontal" one such as perseveration. Instead the fluctuations suggest that the Parkinsonian group are repeatedly switching between the two response sequences rather than maintaining a designated motor set.

Thus in this experiment the Parkinsonian deficit manifests itself as a lack of control over self-generated actions, where the cognitive element (understanding of the action sequence) and the motor element (ability to execute the sequences separately) are both shown to be intact. It is in the integration of the two that an operational fault appears, disrupting the planning process at the point where the appropriate behavioural strategy engages the motor mechanism. In other words, it affects the interface between the cognitive content of a movement plan and the mechanisms through which the plan finds expression. The results indicate that in patients the action plan is understood but the key ability to repeatedly execute one motor sequence whilst holding another in abeyance is compromised. Parkinsonian subjects exhibit a difficulty in executing a designated sequence while at the same time suppressing the alternative, currently unwanted, sequence. The effect occurs from the start of any trial where two sequences are primed, so it is the potential of an alternative action plan that causes the interference, not just a perseverative influence from the first sequence carrying over to the second one.

This effect has similarities with firstly, the inability of pre-frontally lesioned animals to suppress previously-acquired response patterns, reported by Settlage *et al*;[18] secondly, the report by Schwab *et al*[1] that Parkinsonian subjects cannot execute two acts simultaneously; thirdly, the involvement of basal ganglia in set postulated by Buchwald *et al*[14] or in performing a complementary inhibitory and arousal function (Denny-Brown and Yanagisawa);[15] and fourthly, Hassler's suggestion that basal ganglia perform an integrative function focusing attention on one event to the exclusion of others.[19]

EXPERIMENT 2

Several investigations[20 21] have suggested that Parkinsonian subjects need an external cue to initiate movements. If so, it might be expected that in the five-choice task patients would be able to continue a given motor sequence if it was initiated for them by light signals indicat-

ing the buttons to press. This was investigated in the second experiment.

Method

Experimental design

The experiment replicated the first, except that on some of the test trials where two sequences were to be generated signal lights were provided for the first eight responses of each sequence to guide the subjects' response selection. The remaining 11 responses constituted the test proper where no signal lights were illuminated. The aim was to see whether an initial visual cue improved the subjects' ability to maintain or switch between motor sets.

The procedure employed for learning the motor sequences was similar to Experiment 1, except that two rather than three learning trials per sequence were given. These were again each followed by a test trial to determine if learning had taken place. After the initial learning phase, two test familiarisation trials were undertaken where subjects, still following the lights, switched from sequence 1 to sequence 2. Then, after a single test trial without lights, four "preview" trials and then two further test trials were given. All the test trials were similar to those of Experiment 1, that is, reproduction of the sequences was required without any peripheral lights.

The main difference between Experiments 1 and 2 were the preview trials. In the initial stages of each sequence of preview trials subjects were given cues to aid their selection of responses. That is, the next button in sequence would always light up one step ahead of the motor response, indicating what the next choice should be. This happened for the initial eight responses, after which the remainder of the sequence had to be completed without the aid of lights.

In this condition subjects, having learnt the sequences separately and satisfactorily, were required to reproduce them together, switching from first to second. After this, subjects were given an additional cue during preview trials to aid their selection and had to reproduce the sequence during the remainder of the requisite trial. After completing four preview trials, subjects then completed two further test trials without any cues or lights illuminating. The sequences used were different from Experiment 1 but were of the same length (first sequence 4-2-5-1-; second sequence 1-5-2-4-). The sequence of trials is summarised in table 3.

Subjects

Nine Parkinsonian patients from Experiment 1 participated in Experiment 2 (one patient dropped out due to extraneous illness). Ages ranged from 54 to 72 years (mean 63, SD 7·1 years). Webster ratings were from 6 to 12 (mean 8·3, SD 2·0) and duration of symptoms were from one to 10 years (mean 5·6, SD 3·1 years). The same 10 control subjects from Experiment 1 took part in this experiment.

Results

Table 3 shows the number of correct responses in each test trial of Experiment 2. On trials 3 and 6 the results show that satisfactory learning had taken place in both groups with no significant differences between them. On Trial 9, however, (reproducing both sequences in one trial without cues) Parkinsonian and Control group performances differ for both sequences. Also the patient group's scores are significantly worse for each sequence than those on the comparable trials 3 and 6 (Wilcoxon $T = 1, p < \cdot 01$ in both cases, using pro-rated scores for comparison.) Up to this point Experiment 2 mimics the effect seen in Experiment 1.

Scores on Trials 10 to 13 (preview condition) are also shown in Table 3. On these preview trials significant between-group differences were found on Trial 10 for both sequences and on Trial 11 for the second sequence only; on Trials 12 and 13 scores were not significantly different. Therefore, over the second half of the preview condition the Parkinsonian performance showed marked improvement. On these latter trials 12 and 13 the pro-rated Parkinsonian scores for both sequences do not differ significantly from the comparable scores of trials 3 and 6 (all Wilcoxon tests not significant), and all are better than those of trial 9, although with the reduced number of responses scored in these trials only one score

Table 3 Experiment 2: Order of trials and accuracy scores in test trials

Trial	*Task*	*Peripheral lights*	*Mean number correct responses per subject per trial*	
			Control group	*PD group*
1, 2	Follow sequence A	On		
3	Test sequence A (N = 39)	Off	39·0	37·9 (U = 28, NS)
4, 5	Follow sequence B	On		
6	Test sequence B (N = 39)	Off	39·0	38·6 (U = 31, NS)
7, 8	Follow sequence A, then sequence B	On		
9	Test sequence A (N = 19),	Off	19·0	11·6 (U = 2, p < 0·01)
	then sequence B (N = 19)		19·0	11·8 (U = 10, p < 0·01)
10	Test A + cues (N = 11),	On first 8 responses	11·0	7·4 (U = 14, p < 0·05)
	then B + cues (N = 11)	Only	11·0	5·7 (U = 9, p < 0·01)
11	Ditto	Ditto	11·0	8·1 (U = 28, NS)
			11·0	5·4 (U = 9, p < 0·01)
12	Ditto	Ditto	11·0	8·3 (U = 22, NS)
			11·0	7·6 (U = 22, NS)
13	Ditto	Ditto	11·0	9·1 (U = 27, NS)
			11·0	8·8 (U = 27, NS)
14	Test sequence A (N = 19),	Off	19·0	13·2 (U = 10, p < 0·01)
	then sequence B (N = 19)		19·0	13·4 (U = 5, p < 0·01)
15	Ditto	Off	19·0	15·6 (U = 10, p < 0·01)
			19·0	14·7 (U = 15, p < 0·05)

Table 4 Experiment 2: Parkinsonian error distribution on switching trials (mean errors per subject)

	Sequence (A)				*Sequence (B)*			
Trial	*Alternative*	*Repetition*	*Error*	χ^2	*Alternative*	*Repetition*	*Error*	χ^2
9 (No cues)	4·6	1·8	1·2	12·61 ($p < 0·01$)	4·0	2·0	1·2	9·26 ($p < 0·01$)
10 (Cues)	2·0	0·8	0·6	7·75 ($p < 0·05$)	2·8	1·3	1·1	8·47 ($p < 0·05$)
11 (Cues)	1·9	0·6	0·3	12·54 ($p < 0·01$)	3·0	1·6	1·0	8·92 ($p < 0·05$)
12 (Cues)	1·2	1·0	0·4	3·25 (NS)	1·6	1·3	0·4	5·60 (NS)
13 (Cues)	0·8	0·6	0·6	0·47 (NS)	0·9	0·8	0·6	0·72 (NS)
14 (No cues)	2·8	2·0	1·0	7·42 ($p < 0·05$)	3·1	1·4	1·0	12·04 ($p < 0·01$)
15 (No cues)	2·1	0·6	0·7	12·20 ($p < 0·01$)	2·7	0·8	0·8	15·21 ($p < 0·001$)

reaches statistical significance (trial 13 sequence A Wilcoxon $T = 6, p < ·05$). Scores for the final test trials (14 and 15), however, show that this improvement does not carry over when the cues are removed; here again there is a significant deficit in the Parkinsonian group (and the scores are all significantly worse than those of trials 3 and 6, and not significantly different from those of trial 9)—even after all the practice undergone in the course of the experiment.

Table 4 shows the distribution of Alternative, Repetition and Error responses for the Parkinsonian group in the test trials of Experiment 2. These reach significance on a Chi-square test on Trials 9, 14 and 15 (no-cue trials) and on the first two cued trials (Trial 10 and 11). On the second two trials with cues, however, the distribution flattens out, largely because of a reduction in the number of errors in the Alternative category. There are fewer errors of this type in all the cued trials than in any of the non-cued trials, but with the small numbers in the former the differences only reach significance for Trials 12 and 13 compared to Trial 9 (Wilcoxon $T = 6, p < ·05$ or better for both sequences using pro-rated scores). Alternative error scores did not differ between cued trials nor between non-cued trials, nor were there any changes in the relative occurrence of the other kinds of error from trial to trial.

Taken together, these results indicate that Parkinsonian subjects show signs of an improvement in performance when given visual cues at the start of a sequence. They could not maintain this improved performance, however, when the cue is no longer available.

Discussion

The introduction of a visual cue during the preview test trials in Experiment 2 influenced the Parkinsonian group to the extent that they were better able to maintain their motor set. This result suggests that when given the opportunity to make use of an external cue to help select their responses the Parkinsonian group are capable of improving upon their previous no-cue performance levels. In the no-cue trials patients had to initiate response selection for themselves. However, without the initial cue to assist them, patients were unable to reproduce earlier levels of performance. Thus, the motor set required continuous stimulation or arousal from an external source to select appropriate actions because this was not being adequately achieved internally.

In this respect Parkinsonian patients are displaying an effect comparable to that shown in frontal lesions by Pinto-Hamuy and Linck.[22] In serial activity each correct response is contingent on the previous action and in turn serves to order and anticipate the next action. With an initial correct sequence of actions in the preview condition the plan is adequately represented for the actions to proceed step by step. But in the immediately following non-cue test trials, there was no external indication of what the next action should be, and because patients could not adequately provide the input internally, mistakes began to be made.

EXPERIMENT 3

The third experiment tested the possibility that the PD impairment is in remembering or combining action sequences, especially where two have to be held in store and accessed in the same trial. Subjects were first asked to learn two component sequences with cues, and to reproduce them without cues, and were then required to combine the two sequences into a single longer one. As an added load on the memory/performance system, subjects were asked to make a transformation on the display, so that they pressed a button different from the one that lit up each time. Any difficulty subjects have in organising and planning action sequences should, therefore, show up on this incompatible stimulus-response layout, especially if the difficulty involves holding and/or combining two elements, or holding more than a certain amount of material in the memory at one time. This complex combination of elements, however, did not involve a problem of set, as it did not require switching between alternative and incompatible sequences.

Method

Experimental design

The purpose of this experiment was to test the ability of subjects a) to perform two separate mental transformations of information in selecting their responses, b) to combine two transformed sequences together in one trial, c) to learn a single motor sequence on the basis of their understanding, and d) to execute the learnt motor sequence without stimulus lights.

The experiment was structured so that contained within the relationship between buttons was a latent motor sequence which subjects would eventually learn and reproduce. Subjects were first required to learn specific relationships between the five red peripheral buttons. Thus they had to press, not the button that illuminated each time, but one of the other buttons, according to the following associations:

Light 1 on—press button 3
Light 3 on—press button 1

Light 2 on—press button 5
Light 5 on—press button 4
Light 4 on—press button 2

For the purposes of learning, these associations were divided into two sub-units, one between lights 1 and 3, and one between lights 2, 5 and 4. These two sub-units were learnt separately in order to first establish the stimulus-response relationship for each button, and were then combined on later trials. All subjects first learnt the relationship between lights 1 and 3 over two trials of 50 responses each. To test that subjects had learnt the relationship a third trial (Trial 3) was completed in which the lights came on in a pseudo-random manner instead of the fixed sequence of previous trials; subjects were required to press the other button each time as before.

After the first relationship had been learnt the second sub-unit was introduced for subjects to learn the association between lights 2, 5 and 4. Three trials of 50 responses each were performed (Trials 4, 5 and 6) followed by a test trial (Trial 7) where the peripheral lights were illuminated in a random order.

In the next phase the sub-units were combined. Subjects, following the lights, pressed the buttons in accordance with the learnt stimulus-response associations in a continuous repetitive sequence. This phase comprised five trials of 50 responses each (Trials 8–12) during which subjects were told to learn the latent button sequence of 1-3-5-4-2- which was not apparent from the sub-units but was embedded in the combination. After five sequence-learning trials, subjects proceeded to the test phase. The test was to reproduce the combined sequence by pressing the buttons in the correct serial order without any illumination of the red lights. The test phase comprised five trials of fifty responses each (Trials 13–17).

Subjects

Ten Parkinsonian patients, ranging in age from 54 to 73 years (mean 62, SD 7·6 years) took part. Webster ratings ranged from 3 to 10 (mean 7·0, SD 2·2) and duration of symptoms from one to 12 years (mean 7·0, SD 3·6 years). Ten controls were tested, ranging in age from 54 to 67 years (mean 61·0, SD 4·5 years).

Results

Table 5 shows accuracy scores for the initial sub-unit test trials, with a perfect score for the first sub-unit (Trial 3) and satisfactory performance scores for the second sub-unit (Trial 7) in both subject groups. Scores for Trials 8–12 (following the two sub-units combined) and Trials 13–17 (generating the resultant pattern independently) also show no marked differences between the groups overall. (The results have been pooled for clarity, but the same effect was found in each of the five trials of each condition separately.)

Discussion

This experiment indicates that the Parkinsonian group: 1) are capable of understanding a mental transformation of information and can combine two separate transformations; and 2) are capable of learning a single motor sequence on the basis of this understanding; and 3) can execute the resulting motor sequence accurately. The results provide support for the interpretation of the previous experiments. They show that, at the cognitive level the Parkinsonian group had no overt problems learning a plan of action. They could adequately hold two separate patterns of stimulus-response relationship involving a transformation, and then integrate this information to undertake further learning to acquire a latent sequence.

To test if subjects had learnt the sequence they had to execute it under conditions similar to those in Experiments 1 and 2. The results indicate that all subjects had learnt equally well and could execute the sequence without any particular difficulties. Thus the effects seen in the motor set task cannot be explained as an inability to undertake new learning. On the contrary, Parkinsonian subjects are quite capable of "running off" a single motor sequence on the basis of newly learnt material.

General discussion

The main points of these experiments are, first, that the Parkinsonian group had significant difficulties maintaining one motor set against an alternative. Second, that when given a visual cue as an aid the Parkinsonian group were better able to maintain a motor set, but that this improvement was not maintained when the visual cue was removed. Third, that patients were capable of integrating information from external sources into a single motor sequence and then could execute the sequence without difficulty. Their problem therefore is centred not on the formation, learning or execution of a particular sequence of action, but at a higher level, that is, in the selection and maintenance of one plan of action to direct current activity against competition from alternatives. The results support the suggestion by Cools *et al*[13] that Parkinsonism disrupts shifting aptitude,

Table 5 Accuracy of response selection in experiment 3—test trials

Trial	*Task*	*Peripheral lights*	*Mean number correct responses per subject per trial*	
			Control group	*PD group*
1, 2	Follow sequence A	On		
3	Test sequence A (N = 49)	On	49·0	49·0
4, 5, 6	Follow sequence B	On		
7	Test sequence B (N = 49)	On	48·1	47·6 (U = 45, NS)
8, 9, 10, 11, 12	Follow sequences A + B combined (N = 49)	On	48·3	46·1 (U = 35, NS)
13, 14, 15, 16, 17	Test sequences A + B combined (N = 49)	Off	47·9	46·2 (U = 37, NS)

or in our terms behavioural set, and do so with experiments specifically designed to control the ability of patients to learn and perform the requisite action sequences independently and hence for the ability to carry out both the cognitive and motor components involved in the task.

In contrast to Cools' description of the deficit, however, the difficulty here was not so much one of the central programming of actions, but rather an inability to keep apart two plans of action, especially where these overlap and have the potential to interfere with each other. Thus in situations where alternatives are available patients experience difficulties with controlling the independent generation of motor sequences which they have previously learnt. This difficulty manifests itself as a problem not with the cognitive element of the task (patients understand what they have to do), nor with the organising of compound or sequential action as such (patients can handle even high-information-loaded tasks as in the third experiment), but rather with the selection and maintenance of one motor plan rather than another which might be equally appropriate in the current situation. It is thus a difficulty at the interface between decision and action where general intentions or plans for action select particular movements (which may be already stored as a repertoire of well-practiced programmes or may be constructed on-line for present use) for their fulfilment.

Impairment of set therefore is not a cognitive deficit in terms of loss of understanding of the task, or of information, memory or reason necessary to plan it, and cannot therefore be explained as a manifestation of incipient dementia, although it may appear so when subjects behave in an erratic way as they change suddenly from one plan to another. Also dementia is an unlikely explanation for the effect because patients in experiment 3 were able to carry out the rather complex requirements of learning two transformed sequences and amalgamating them quite normally. Nor could any dyskinesia, psychomotor retardation from depression or drug effects account for the deficits for the same reason; if they were having a deleterious effect on patients' ability to perform the first experiments, they should surely have disrupted performance on experiment 3 also.

Nor is the difficulty specifically a motor one in the sense of the ability to assemble and execute individual movements (although this may well be separately impaired in tasks where the accuracy, timing or force of movements are to be controlled) or the ability to store programs for movement in motor memory. It seems rather to occur higher up in the system, where motor plans are selected or formulated. In particular it appears to involve the ability to organise action independently of real time events and immediate external sensory cues. Parkinsonian patients appear tied to sensory cues and find it difficult to initiate movements independently of them.[6 7 20 21] It seems that the "internal model" which would normally guide behaviour in such situations is lacking. Such a model could be thought of as storing, in computer terms, algorithms for action, or "schema"[23] which contain the rules for combining subroutines of particular movements which by virtue of their combined function produce the action originally decided on.

Motor control theorists such as Schmidt[23] emphasise that motor memory in learnt skills is unlikely to involve the direct storage of movement programs per se, as this would be inefficient and wasteful in terms of processing and storage space in the nervous system. Many variables would have to be stored, including all the degrees of freedom necessary for a movement. In preference to the notion of storing motor programs, they suggest that what is stored is the schema or algorithm for the action. This contains the abstract rules for fitting together relevant actions to carry out the overall plan, the values of which may be changed to suit current requirements. Thus the central representation of a movement is not a finite array of stored programs, but rather a means by which different combinations of movements matched to behavioural requirements can be generated. This process is referred to by Schmidt as a process of rule generation. During the learning of a task data are thrown away but, instead of the motor program itself, the rule is retained to be used again in similar situations.

On this basis, akinesia may stem from an inability to select and/or maintain internal control over the algorithms which generate actions, even though perceptual and motor mechanisms are in themselves intact. The problem is not in operating the algorithm (because patients can run off a single sequence) but in running an internally selected algorithm that contains the correct sequence of actions and not an alternative. Therefore, akinesia is not only a delay in the initiation of movement but also a disruption in the choice between actions at the junction box of perceptual-motor activity, that is, an instability of set. This high-level impairment can apply equally to cognitive (decision-making or active perception) activities or to overt motor actions, so that it is not surprising that similar effects to those reported here have been found in cognitive tasks[16] and perception of ambiguous figures.[24]

The present motor set impairment, where knowing what to do cannot be properly integrated with the motor mechanism for actually performing the action, parallels that reported by others. For example Schwab[1 25] showed that Parkinsonian subjects have a difficulty in performing two voluntary actions at the same time. The impairment is especially marked where a previously selected action from a number of alternatives had to be maintained, that is, a task involving set. This may explain the sporadic "freezing" experienced by many Parkinsonian patients in the middle of ongoing actions, even where well-practiced activities such as walking are concerned. Note also that directing patients' attention to a visual cue to initiate their actions may help them overcome freezing.)

The similarity of such planning difficulties with results from our previous cognitive task[16] also parallels that found in more general intellectual tasks by Taylor *et al.*[26] They

present evidence that in their Parkinsonian sample there were no deficits involving occipital, parietal or temporal cortices. Also that patients had no real memory weakness for organised information. Results from four tests, however, (Rey Auditory-Verbal Learning Test, Wisconsin Card-Sorting Test, Bead and Tapper Test, and Delayed Recall Test) clearly distinguished Parkinsonian from control subjects, not because they were related but because they shared one common element; all require the need for "self-directed planning in forming context-dependent associations or strategies." This function has been accredited to the frontal lobes.[27 28] It is further argued that since the Supplementary Motor Area (SMA) is considered responsible for planning actions which are guided by internal rather than external cues[29 30] and that SMA is the main target outflow of the inner sector the globus pallidus[31] evidence presented concerning deficits on these four tests supports the notion of disturbed outflow from basal ganglia involving activity in the frontal cortex thought to play a role in self-directed behavioural planning.

The picture of Parkinsonian disturbance which emerges from this investigation is of a difficulty in controlling the selection of motor responses at the level of specifying the details of an action plan, that is, at the "junction box" between perceptual/decision and motor activity. This junction box may be located in the basal ganglia where striatum can be regarded as selecting between inputs and pallidum as selecting motor outputs. If this system utilises dopamine for this purpose, then it would fit Rolls'[32 33] suggestion that this neurotransmitter sets the threshold for firing in striatum. A change in environmental stimuli may be detected by the striatum which selects one stream of behavioural output, but with the possibility of switching to another if a higher priority input is received. Thus, a low threshold setting but maximal information transmission could facilitate a switch in behavioural output, whilst simultaneously another segregated pathway in striatum may have a high threshold and therefore minimal information transmission, which could act as a method of suppressing another behavioural output. Therefore, neurophysiologically the basal ganglia is a system whereby segregated parallel pathways[34] are either maximised or suppressed utilising dopaminergic nigrostriatal inputs. Given the extensive connections of the basal ganglia to frontal cortical areas[34 35] it is not surprising that similar characteristics can be found in the performance of any task, whether cognitive or motor, which involves decisions and the control of actions. Parkinson's disease can therefore be regarded as a disease which affects all aspects of the patients' behaviour.

This work was supported by the Parkinson's Disease Society of Great Britain. We are indebted to Dr J M S Pearce for access to patients under his care and to Dr Iris Pearce for providing the clinical assessments and Webster ratings of the Parkinsonian subjects. We are also grateful to Mr R Wallis for technical assistance, Mr S McCloud for computer programs and Mr J Spencer for photographic work.

1 Schwab RS, Chafetz ME, Walker S. Control of two simultaneous voluntary acts in normals and in Parkinsonism. *Arch Neurol Psychiat (Chicago)* 1954;**72**:591–8.
2 Benecke R, Rothwell JC, Dick JPR, Day BL, Marsden CD. Performance of simultaneous movements in patients with Parkinson's disease. *Brain* 1986;**109**:739–57.
3 Schwab RS, Zieper I. Effects of mood, motivation, stress and alertness on the performance in Parkinson's disease. *Psychiatrica et Neurologia (Basel)* 1965;**150**:345–57.
4 Flowers KA. Some frequency response characteristics of parkinsonism on pursuit tracking. *Brain* 1978;**101**:19–34.
5 Benecke R, Rothwell JC, Dick JPR, Day BL, Marsden CD. Disturbance of sequential movements in patients with Parkinson's disease. *Brain* 1987;**110**:361–79.
6 Flowers KA. Lack of prediction in the motor behaviour of Parkinsonism. *Brain* 1978;**101**:35–52.
7 Stern Y, Mayeux R, Rosen J, Ilson J. Perceptual motor dysfunction in Parkinson's disease: a deficit in sequential and predictive voluntary movement. *J Neurol Neurosurg Psychiatry* 1983;**46**:145–51.
8 Joubert M, Barbeau A. Akinesia in Parkinson's disease. In: Barbeau A, Brunette J-R, eds. *Progress in neuro-genetics*. International Congress Series No 175. Amsterdam: Excerpta Medica, 1969.
9 Sharpe MH, Cermak SA, Sax DS. Motor planning in Parkinson patients. *Neuropsychologia* 1983;**21**:455–62.
10 Marsden CD. The mysterious motor function of the basal ganglia: the Robert Wartenburg lecture. *Neurology (Ny)* 1982;**32**:514–39.
11 Rosenbaum DA. Hierarchical organisation of motor programs. In: Wise SP, ed. *Higher Brain Functions*. New York: Wiley, 1987.
12 Cools AR, Jaspers R, Schwarz M, Sontag KH, Vrijmoed de Vries M, Van den Bercken J. Basal ganglia and switching motor programs. In: McKenzie JS, Kemm RE, Wilcock LN, eds. *The basal ganglia: structure and function. Advances in behavioural biology Vol 27*. New York: Plenum Press, 1984.
13 Cools AR, Van den Bercken JHL, Horstink MWI, Van Spaendonck KPM, Berger HJC. Cognitive and motor shifting aptitude disorder in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1984;**47**:443–53.
14 Buchwald NA, Hull CD, Levine MS, Villablanca J. The basal ganglia and the regulation of response and cognitive sets. In: Brazier MAB, ed. *Growth and development of the brain*. New York: Raven Press, 1975.
15 Denny-Brown D, Yanagisawa N. The role of the basal ganglia in the initiation of movements. In: Yahr MD, ed. *The Basal Ganglia* (Assoc Res Nerv Men Dis Publ Vol 55). New York: Raven Press, 1976.
16 Flowers KA, Robertson C. The effect of Parkinson's disease on the ability to maintain a mental set. *J Neurol Neurosurg Psychiatry* 1985;**48**:517–29.
17 Webster DD. Critical analysis of the disability in Parkinson's disease. *Mod Treatment* 1968;**5**:257–82.
18 Settlage P, Zable M, Harlow HF. Problem solution by monkeys following bilateral removal of the prefrontal areas. VI: Performance on tests requiring contradictions in reactions to similar and to identical stimuli. *J Exp Psychol* 1948;**38**:50–65.
19 Hassler R. Striatal control of locomotion, intentional actions and of integrating and perceptive activity. *J Neurol Sciences* 1978;**36**:187–224.
20 Bloxham CA, Mindel TA, Frith CD. Initiation and execution of predictable and unpredictable movements in Parkinson's disease. *Brain* 1984;**107**:371–84.
21 Wing AM, Miller E. Basal ganglia lesions and psychological analyses of the control of voluntary movement. In: Evered D, O'Connor M, eds. *Functions of the basal ganglia*. CIBA Foundation Symposium No 107. London: Pitman, 1984.
22 Pinto-Hamuy T, Linck P. Effect of frontal lesions on performance of sequential tasks by monkeys. *Exp Neurol* 1965;**12**:96–107.
23 Schmidt RA. The schema as a solution to some persistent problems in motor learning theory. In: Stelmach GE, ed. *Motor control: issues and trends*. New York: Academic Press, 1976.
24 Talland GA. Cognitive functions in Parkinson's disease. *J Nerv Ment Dis* 1962;**135**:196–205.
25 Talland GA, Schwab RW. Performance with multiple sets in Parkinson's disease. *Neuropsychologia* 1964;**2**:45–53.
26 Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease. *Brain* 1986;**109**:845–83.
27 Milner B, Petrides M. Behavioural effects of frontal lobe lesions in man. *Trends in neuroscience* 1984;**7**:403–7.
28 Luria AR. *The working brain*. London: Penguin, 1973.
29 Wise SP, Strick PL. Anatomical and physiological organization of the non-primary motor cortex. *Trends in Neuroscience* 1984;**7**:442–6.
30 Goldberg G. Response and projection. A reinterpretation of the premotor concept. In: Roy EA, ed. *Neuropsychology of apraxia and related disorders*. Amsterdam: North-Holland, 1986.
31 Schell GR, Strick PL. The origin of thalamic inputs to the pre-motor and supplementary motor areas. *J Neuroscience* 1984;**4**:539–60.
32 Rolls ET, Thorpe ST, Madison SP. Responses of striatal neurones in the behaving monkey: 1. Head of the caudate nucleus. *Behav Brain Res* 1983;**7**:179–210.
33 Rolls ET. Responses of neurones in different regions of the striatum of the behaving monkey. In: McKenzie JS, Kemm RE, Wilcock LN, eds. *The Basal Ganglia: Structure and Function*. New York: Plenum Press, 1984.
34 Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann Rev Neuroscience* 1986;**9**:357–81.
35 Passingham RE. From where does the motor cortex get its instructions? In: Wise SP, ed. *Higher brain functions*. New York: Wiley, 1987.