

## Dopamine-Dependent Frontostriatal Planning Deficits in Early Parkinson's Disease

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Three groups of medicated and nonmedicated patients at different stages of Parkinson's disease and a group of neurosurgical patients with localized frontal lobe excisions were assessed on 2 novel tests of planning and spatial working memory. Results demonstrate that, like other tests of frontal lobe dysfunction, planning and spatial working memory are vulnerable in nonmedicated patients with mild Parkinson's disease and suggest that certain aspects of the planning impairment in these patients may be ameliorated by dopaminergic therapy. Specifically, with medication there was an improvement in accuracy of planning, but not in latency, in a series of problems based on the Tower of London test of planning. The results in terms of the frontostriatal, dopamine-dependent nature of some of the cognitive deficits found in early Parkinson's disease versus the apparent dopamine-independent nature of deficits in other cognitive processes are discussed.

As may be expected from the intimate relation that exists between the basal ganglia and the frontal cortex (Alexander, Delong, & Strick, 1986), recent neuropsychological evidence suggests a substantial role for frontal lobe dysfunction in the cognitive profile of patients with Parkinson's disease (Bowen, Kamienny, Burns, & Yahr, 1975; Canavan et al., 1989; Downes et al., 1989; Lees & Smith, 1983; Owen et al., 1992; Scatton, Javoy-Agid, Rouquier, Dubois, & Agid, 1983; Taylor, Saint-Cyr, & Lang, 1986). Although few direct comparisons have been made between patients with frontal lobe damage and patients with Parkinson's disease, similar patterns of cognitive impairment have been observed in the two groups in many studies. For example, deficits on the Wisconsin Card Sorting Task, a commonly used clinical index of frontal lobe damage

(Drewe, 1974; Milner, 1963; Nelson, 1976; Robinson, Heaton, Lehman, & Stilson, 1980) and on related tests of attentional set-shifting ability have been widely reported in patients with Parkinson's disease (Bowen et al., 1975; Brown & Marsden, 1988; Canavan et al., 1989; Gotham, Brown, & Marsden, 1988; Lees & Smith, 1983; Pillon, Dubois, L'Hermitte, & Agid, 1986; Taylor et al., 1986). However, recent evidence suggests that the similar attentional set-shifting deficits observed in frontal lobe patients and in patients with Parkinson's disease may actually involve fundamentally different, though related, cognitive processes that may be functionally dissociated (Owen, Roberts, et al., 1993). Moreover, in Parkinson's disease these processes may be differentially affected by dopaminergic medication (Owen, Roberts, et al., 1993; also see Lange et al., 1992).

Although clinically impaired sorting or set-shifting has been a dominant feature in the description of patients with frontal lobe damage, other specific neuropsychological impairments that may be unrelated to the patients' performance on such tasks have also been reported. Most notably, frontal lobe patients are often described as lacking normal executive control over action, as exemplified by their deficits in the cognitive aspects of planning on the Tower of London test (Shallice, 1982). Planning deficits were also reported in patients with Parkinson's disease (Morris et al., 1988), although it is not clear whether this deficit is truly frontal in behavioral or neural terms. To investigate this issue two recent assessments of planning ability, the first in a group of neurosurgical patients with localized excisions of the frontal lobes (Owen, Downes, Sahakian, Polkey, & Robbins, 1990) and the other in three groups of patients at different stages of Parkinson's disease (Owen et al., 1992), were made with a computerized version of the Tower of London task. This test is formally similar to the

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This research was supported by a program grant from the Wellcome Trust to Trevor W. Robbins, Barry J. Everitt, and Barbara J. Sahakian. We thank Pat Rabbitt for allowing us access to control participants drawn from the North East Age Research panel at Newcastle University, Newcastle upon Tyne, United Kingdom, and Jo Iddon for her invaluable assistance with data extraction. We also thank Julien Doyon and Viviane Sziklas for critically appraising the manuscript of this article.

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Table 1  
Summary of Previous Results

Task	Patient group				
	Frontal	Temporal	NMP	MP-mild	MP-severe
Spatial working memory					
Accuracy	I	I <sup>a</sup>	U	I	I
Strategy score	I	U	U	U	U
Tower of London					
Accuracy	I	U	U	U	I
Initial thinking time	U	U	U	I	I
Subsequent thinking time	I	U	U	U	U
Attentional set-shifting	I	U	I	I	I

Note. Frontal = frontal lobe damage; temporal = temporal lobe damage; NMP = nonmedicated Parkinson's disease; MP-mild = medicated Parkinson's disease, with mild clinical symptoms; MP-severe = medicated Parkinson's disease, with severe clinical symptoms. I = impaired performance; U = unimpaired performance.

<sup>a</sup>Impaired only at the most challenging levels of difficulty.

one used by Shallice (1982) to assess planning in patients with anterior lesions. In comparison with control subjects, the frontal lobe group required more moves to complete the planning problems and produced fewer perfect solutions. Initial thinking, or planning time, was unimpaired in these patients, although the amount of time spent thinking on line (i.e., subsequent to the first move) was significantly prolonged (see Table 1). This pattern of impairment appears to be specific at the cortical level because no deficits were observed in a group of neurosurgical patients with temporal-lobe damage (Owen, 1992).

A frontal-like impairment in solution accuracy was also observed in medicated patients with Parkinson's disease but only in those patients with severe clinical symptoms (Owen et al., 1992). This result concurs fully with an earlier report by Saint-Cyr, Taylor, and Lang (1988), who found no impairment in problem-solving accuracy in a combined group of medicated and nonmedicated patients with mild Parkinson's disease on the operationally similar, three-disk "Tower of Toronto" task. However, in that investigation the relation between accuracy and latency of response in patients with Parkinson's disease was not addressed. In the study by Owen et al. (1992), medicated patients with both mild and severe clinical symptoms were also slower than control subjects to initiate solutions to the planning problems. The study also included a nonmedicated Parkinson's disease group with mild clinical symptoms. Importantly, in these *de novo* patients, all aspects of planning ability were preserved.

In general, the results of these investigations are in agreement with previous studies that have suggested that parkinsonian patients are impaired on tasks that involve self-directed behavioral planning (Morris et al., 1988; Taylor et al., 1986). However, close inspection of the pattern of deficits in patients with frontal lobe damage and patients with Parkinson's disease suggests that important differences may exist between the two groups in terms of the precise cognitive and neural mechanisms involved. For example, in the two studies that we described earlier, impaired accuracy on the Tower of London task was found to correlate significantly with impaired performance on a test of spatial working memory in both frontal lobe patients and in patients with Parkinson's disease (Owen et al., 1990; Owen et al., 1992). Qualitatively, however, the two

groups differed in terms of their performance on this latter task. Although the frontal lobe group was impaired on a measure of task strategy, the parkinsonian group performed normally in this respect (Table 1). Thus, planning ability may be adversely affected by spatial working memory deficits in both frontal lobe patients and in patients with Parkinson's disease, although the precise cognitive mechanisms responsible may not be identical. The parkinsonian and frontal lobe patients previously studied also differed in the extent to which their planning behavior was characterized by prolonged initial thinking, or planning time. Thus, medicated Parkinson's disease patients with mild clinical symptoms were significantly slower but nonetheless accurate in initiating their solutions (Morris et al., 1988; Owen et al., 1992), although the opposite pattern was observed in patients with frontal lobe damage (Owen et al., 1990). Moreover, slowness of thinking in the parkinsonian group, a possible correlate of bradyphrenia, was specific to the planning phase of the task because, unlike the frontal lobe group, prolonged subsequent thinking time was not observed in these patients. Finally, unlike in any of the other patient groups, both planning and spatial working memory were spared in the group of nonmedicated patients in the earliest stages of Parkinson's disease (see Table 1). This contrasts markedly with the severe impairment observed in these patients in tests of sorting or attentional set-shifting ability (Owen et al., 1992; for similar patterns of results, see Downes et al., 1989; Lees & Smith, 1983; Owen, Roberts, et al., 1993) and may suggest a limited anatomical focus for the cognitive deficits that occur early in the course of Parkinson's disease. An alternative possibility, which must be addressed, is that planning and spatial working memory may be affected in early Parkinson's disease but that deficits remain undetected, if the tasks used to test these abilities are insufficiently challenging for these patients.

In this study we used two novel tasks to investigate further the neuropsychological, neuropharmacological, and neuroanatomical basis of planning deficits in patients with Parkinson's disease. A modified version of the computerized Tower of London task was designed to examine the relation between thinking (planning) time, problem difficulty, and solution accuracy in this patient group and, for comparison, in a group of neurosurgical patients with frontal lobe excisions. Subjects

were required to study each of the original Tower of London problems and then to decide how many moves would be required to reach an ideal solution (i.e., with the minimum number of moves) without actually moving any of the balls. Because the ideal solution is no longer defined explicitly, the number of possible solutions that must be explored before the perfect solution is identified is correspondingly greater. Inevitably, this places an increased load on the processes of working memory, which are essential for any analytical problem of this type. Accordingly, this task may prove more sensitive to incipient planning deficits in patients with early Parkinson's disease, which may not be detected with previous versions of this task.

The previous studies have suggested that spatial working memory is an important contributor to planning on the Tower of London task because performance on planning and spatial working memory tasks is correlated in both controls and patients with frontal lobe damage (Owen et al., 1990; 1992). Given the apparent sparing of spatial working memory early in the course of Parkinson's disease, we also used a novel spatial sequence task to measure the capacity of active working memory in the patient groups.

Several recent studies have suggested that frontal lobe deficits in parkinsonian patients may be significantly affected by L-dopa medication (Bowen et al., 1975; Downes et al., 1989; Owen et al., 1992). In fact, in a recent study of patients with severe Parkinson's disease, performance on the spatial working memory and planning tasks deteriorated after withdrawal of L-dopa, whereas performance on other nonfrontal tests was unaffected (Lange et al., 1992). In our study, therefore, the effects of medication in Parkinson's disease were examined by comparing patients who were early in the course of the disease and had not yet received any medication with those who also had mild clinical symptoms but who were already stabilized on dopaminergic therapy. Because recent studies have emphasized the need to take account of the severity of clinical symptoms when assessing cognitive deficits in Parkinson's disease (e.g., Owen, Beksinska, et al., 1993; Owen et al., 1992; Taylor et al., 1986), a third group of patients, who were medicated and had severe clinical symptoms, was also included.

## Method

### Participants

*Frontal-lobe patients.* The 17 frontal lobe patients included in this study had all undergone unilateral or bilateral frontal lobe surgery at the Maudsley Hospital Neurosurgical Unit, London. Ten of these patients had right-side frontal lobe excisions: Four had undergone right frontal lobectomy; for 2, an aneurysm of the anterior communicating artery had been clipped; in 3 patients a right-side meningioma had been removed; and for 1, a benign astrocytoma had been resected. Five of the patients had left-side frontal lobe excisions; all had undergone unilateral surgery for the relief of intractable epilepsy. The remaining 2 patients had undergone bilateral frontal meningioma removal. Examples of the main lesion types are shown in Figure 1. The frontal lobe patients were tested, on average, 5 years, 1 month after their operation, although the time elapsed since surgery varied from 3 to 312 months. As this factor was not statistically related to performance on either of the neuropsychological tasks, we do not give it further

consideration in the main analyses of effects. Thirteen patients in this group were on anticonvulsant medication at the time of testing, although none of these patients were toxic. All were seen as outpatients.

Seventeen healthy control subjects were chosen to match the frontal lobe patients as closely as possible with respect to age and premorbid verbal IQ as estimated by the National Adult Reading Test (Nelson, 1982). These subjects were recruited from local advertisements in the London and Cambridge (United Kingdom) areas.

*Parkinson's disease patients.* The 56 parkinsonian patients included in this study were all outpatients at the Maudsley Hospital (London), Queen Elizabeth Hospital (King's Lynn), or Addenbrooke's Hospital (Cambridge). Patients were referred consecutively by the consultant neurologist if a diagnosis of idiopathic Parkinson's disease was reached, in the absence of clinical dementia or depression. Patients with a significant medical history not related directly to their Parkinson's disease (e.g., stroke or head injury) were not referred for the study. The severity of clinical symptoms was also assessed by the neurologist according to Hoehn and Yahr's (1967) 5-point rating scale. In cases in which medicated patients were experiencing response fluctuations, the rating referred to the on rather than the off condition.

Twenty-two of these patients were early in the course of the disease and had not yet received any medication (nonmedicated Parkinson's disease group; NMP). In this group, clinical symptoms were rated as either Stage I (13 patients) or Stage II (9 patients), according to Hoehn and Yahr's (1967) scale.

The remaining 34 patients were all receiving L-dopa preparations either alone or in combination with other medication. All were responding well, and none were suffering from a confusional state at the time of testing. Twenty of these patients had mild to moderate clinical symptoms (mild, medicated Parkinson's disease group; MP-mild) and were rated, on Hoehn and Yahr's (1967) scale, as Stage I (8 patients) or Stage II (12 patients). In addition to their dopaminergic medication, 2 of these patients were receiving anticholinergic medication (orphenadrine or benzhexol) at the time of testing. Fourteen of the patients in the medicated Parkinson's disease group had more severe clinical symptoms (severe, medicated Parkinson's disease group; MP-severe) and were rated as Stage III (6 patients) or Stage IV (8 patients). Five of these patients were receiving anticholinergic medication (orphenadrine or benzhexol) in addition to their dopaminergic medication at the time of testing.

Exclusion criteria for the MP patients included clinical dementia assessed on both the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) and the Kendrick Object Learning Test (Kendrick, 1985). Specifically, only patients who scored above 24 (out of 30) on the MMSE and 23 or above on the Kendrick Object Learning Test were included. Patients with significant affective disturbance were also identified with the Geriatric Depression Scale (Yesavage et al., 1982) and excluded from this study. This self-administered, 30-item questionnaire is particularly suited for the assessment of depression in parkinsonian patients because it contains few somatic items that may relate directly to the patients' physical disability. The NMP group was not given the Mini-Mental State Examination, the Kendrick Object Learning Test, or the Geriatric Depression Scale on a formal basis. However, none of the NMP patients included in this study showed any signs of clinical dementia or significant affective disturbance during extensive neurological and neuropsychological evaluations.

Three groups of healthy control subjects ( $N = 56$ ) were chosen to match the three parkinsonian groups as closely as possible with respect to age and premorbid verbal IQ as estimated by the National Adult Reading Test. Again, these subjects were recruited from local advertisements in the London and Cambridge areas and from a large pool of control volunteers at the North East Age Research panel (Newcastle upon Tyne, United Kingdom). Informed consent was obtained from all

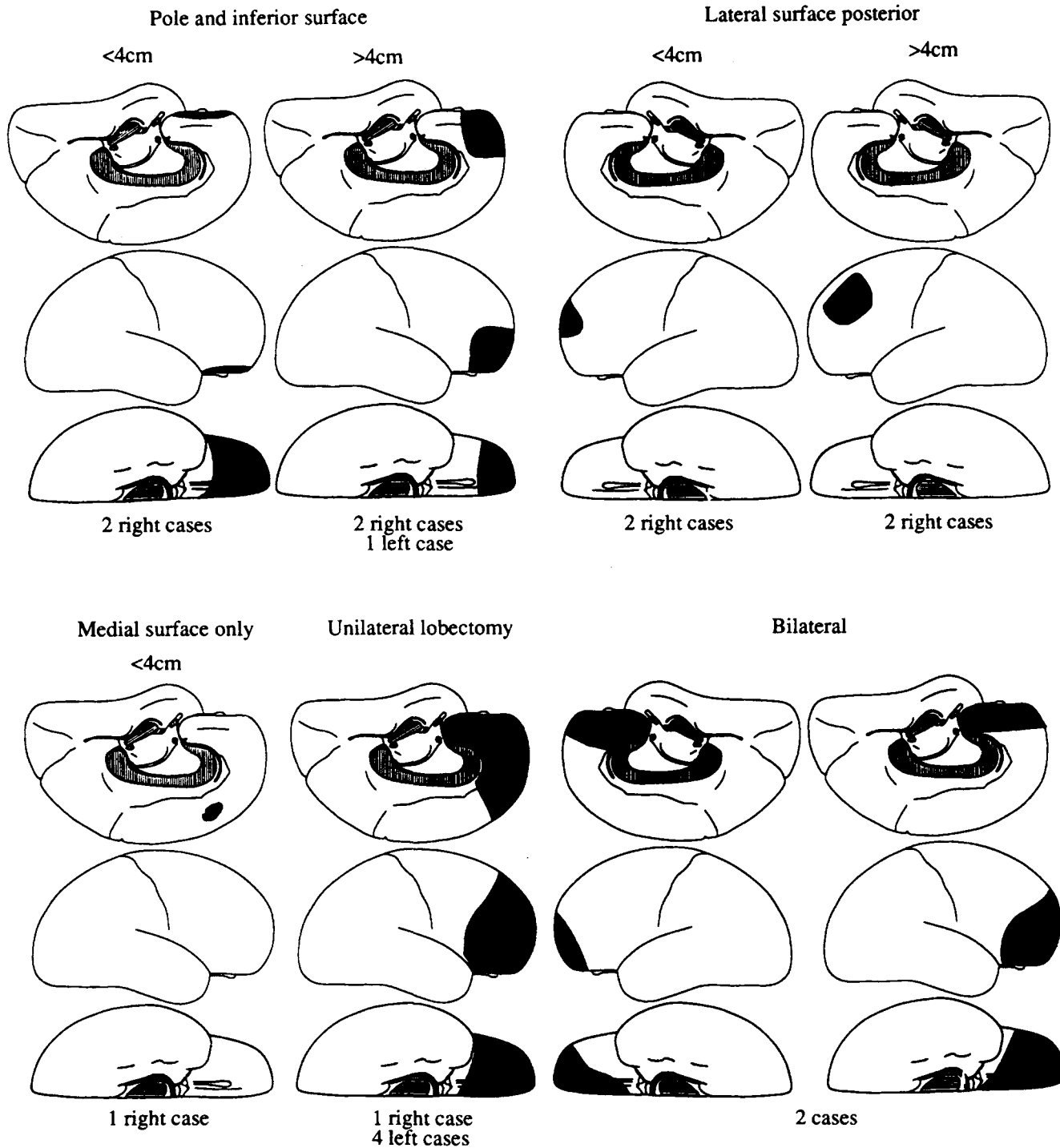


Figure 1. Diagrams of the extent of frontal lobe excisions in several representative cases. The diagrams are based on the neurosurgeons' drawings at the time of operation. Blackened areas define the lesion site.

patients and control subjects before the neuropsychological testing session.

Table 2 shows a summary of characteristics for the frontal lobe patients, the three groups of patients with Parkinson's disease, and the four matched groups of healthy control subjects.

One-way analysis of variance confirmed that the frontal lobe, NMP,

MP-mild, and MP-severe groups were all well matched with their respective control groups in terms of age,  $F(1, 32) = 0.12$ ,  $F(1, 42) = 2.68$ ,  $F(1, 26) = 1.16$ , and  $F(1, 18) = 3.11$  (all  $ps > .05$ ), and estimated verbal IQ,  $F(1, 32) = 0.27$ ,  $F(1, 42) = 2.32$ ,  $F(1, 26) = 2.16$ , and  $F(1, 18) = 1.48$  (all  $ps > .05$ ). It was not possible to match the groups precisely with respect to gender. However, separate analyses of

Table 2  
*Characteristics of Subjects*

Subject group	<i>n</i>	Men	Women	Age (in years)		Verbal IQ	
				<i>M</i>	<i>SEM</i>	<i>M</i>	<i>SEM</i>
Frontal							
Experimental	17	9	8	46.53	4.39	108.8	2.9
Control	17	7	10	44.41	4.20	110.8	2.5
NMP							
Experimental	22	13	9	58.59	2.29	109.4	1.7
Control	22	7	15	52.41	3.00	113.4	2.0
MP-mild							
Experimental	20	13	7	59.65	1.73	107.3	2.3
Control	20	7	13	53.80	3.26	111.0	2.5
MP-severe							
Experimental	14	10	4	66.67	2.03	107.4	2.9
Control	14	3	11	61.08	3.04	112.3	3.5

*Note.* Verbal IQ was estimated using the National Adult Reading Test (Nelson, 1982). Frontal = frontal lobe damage; NMP = nonmedicated Parkinson's disease; MP-mild = medicated Parkinson's disease, with mild clinical symptoms; MP-severe = medicated Parkinson's disease, with severe clinical symptoms. All control groups were normal volunteers.

combined control scores, frontal lobe scores and combined parkinsonian group scores confirmed that there were no significant effects of gender within the data. Similarly, a recent analysis of data collected with the Cambridge Neuropsychological Test Automated Battery (CANTAB) computerized Tower of London test from over 240 normal control volunteers has verified that this test is not sensitive to gender differences (Robbins et al., 1994).

### Procedure

*Modified Tower of London task.* The computerized test was essentially a modified version of the CANTAB Tower of London task (for detailed description, see Owen et al., 1990; Owen et al., 1992). The task was programmed and run on an IBM (Armonk, NY) PS2 Model 30, 286 personal computer with an Intasolve (Colchester, United Kingdom) Taxan 770+ touch sensitive monitor. Subjects were seated approximately 0.5 m from the screen, and it was explained that they would respond to stimuli by touching the screen.

*Training.* The subjects were trained with six practice problems from the CANTAB computerized Tower of London task (Owen et al., 1990; Owen et al., 1992). In this task two sets of three colored balls are presented, one in the top half of the screen and one in the bottom half of the screen. They were described to the subject as "snooker" or "pool" balls because they appeared to be hanging in pockets or socks. There were three pockets in each half of the screen, one that could clearly hold three balls, one that could hold two balls, and one that was filled by just one ball. On each trial, a red ball, a blue ball, and a green ball were placed in predetermined positions in the pockets of each of the two displays. The subjects were asked to rearrange the balls in the bottom display so that their positions matched those of the balls in the top display. A ball could be moved by first touching it and then by touching an empty position in one of the other pockets. Importantly, illegal moves, such as trying to place a ball high in a pocket when there was no other ball beneath the position or trying to remove a ball when there was another sitting above it in the same pocket, were carefully explained to the subject, and if attempted, such moves evoked no response from the computer. Only once subjects were entirely familiar with the rules governing the movement of balls and the concepts involved with solving the Tower of London problems were they given the revised form of the task.

*Testing.* As in the original task, two sets of colored balls were used, one in the top half of the screen and one in the bottom half (Figure 2). However, in this modified version, the numbers 1, 2, 3, 4, and 5 were

also printed in large 3 × 3 cm boxes across the bottom of the screen. At the beginning of each trial, the six pockets appeared empty on the screen. After a 1-s delay, a beep from the computer alerted the subject to the screen, and the balls appeared, again in predetermined positions in both displays. With each trial the position of the balls was varied so that the problem could be solved after a minimum of one to five moves. The subjects were now instructed to examine the position of the balls and then to imagine how they might rearrange the balls in the bottom display to match the ones in the top without actually moving any of the balls. For any given problem, the subjects were asked to find the simplest solution, that is, the one that required the fewest moves. The movement of the balls was governed by the same rules that the subject had learned in the previous training session. Once the ideal solution had been found, the subjects were asked to count the number of moves involved and then to respond simply by touching the corresponding number on the bottom of the screen. If the response was correct, the word *congratulations* appeared in the center of the screen, and a large, green check mark was placed over the appropriate response box. If the response was incorrect, the words "try again" appeared in the center of the screen, and a large red cross was placed over the response box that had been touched. The subjects were then required to try again and to continue in this manner until the correct response box was selected.

Importantly, while solving the problem, subjects could touch any part of the screen, but this did not alter the position of any of the balls. The importance of accuracy was emphasized. The subjects were encouraged not to guess but to continue to work on the problem until they were sure that they had found the ideal solution. They were first given two assisted one-move problems and two assisted two-move problems for practice and to ensure that the instructions had been fully understood. After this they were given 14 test trials that consisted of the 12 original Tower of London problems (e.g., 2 two-move problems, 2 three-move problems, 4 four-move problems, and 4 five-move problems; see Owen et al., 1990; Owen et al., 1992; Shallice, 1982) and 2 additional one-move problems. The 14 problems were arranged in pseudorandom order, which was consistent across subjects.

### Spatial Working Memory Task

This computerized task was designed to place an increasingly large load on active, spatial working memory. The subjects were required to

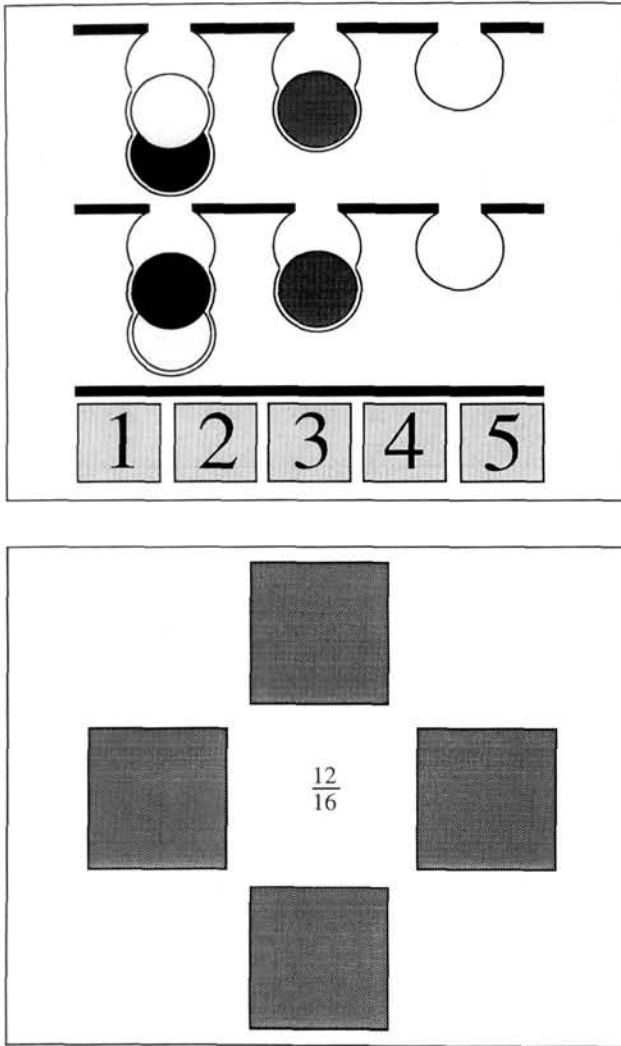


Figure 2. Modified Tower of London planning task and spatial sequence generation task. For the Tower of London task, subjects were asked to calculate how many moves were required to match the two sets of colored balls. In the spatial sequence generation task, subjects were asked to generate as many novel four-box sequences as possible.

generate as many different four-box sequences as possible from four large, red squares arranged symmetrically around the center of the screen (Figure 2). They were instructed to produce as many sequences as possible without repetition, by touching each of the four response boxes in turn. A given sequence could start and end with any of the four squares except every sequence had to include each of the boxes. Thus, there were 24 possible four-box combinations. As each box was touched, it changed color for 10 ms and a high-pitched beep sounded for the same duration. At the end of each sequence (i.e., when the fourth box was touched), a middle-pitched beep sounded if that sequence was a novel one, but a much lower pitched beep sounded if that combination of boxes was in fact a repetition of an earlier sequence. In addition, a constantly updated fraction, presented in the center the boxes, informed the subjects how many sequences had been attempted (denominator) and how many of those were actually novel (numerator). Subjects were allowed to generate 24 sequences (including repetitions) with no time limit, and the main indexes of perfor-

mance were the total number of different sequences generated within 24 attempts and the number of novel sequences produced before an error (repeated sequence) was committed.

## Results

### Modified Tower of London

The main indexes of performance were the mean number of attempts to reach the correct solution and the mean thinking time for correct (first-time) solutions within each level of difficulty (one to five moves) as measured by response latency. Because the required response (i.e., a single touch) was unrelated to problem difficulty (unlike the original computerized Tower of London test), a motor-control condition was not used.

*Accuracy of performance.* The data were analyzed in two-way, split-plot analyses of variance with task difficulty (Levels 1–5) as the within-subjects variable and group (patients vs. control subjects) as the between-subjects variable. In Figure 3, the mean number of responses at each level of difficulty for the four patient groups and their matched control groups are presented.

In all four comparisons between a patient group and the matched control group, there was a significant effect of task difficulty (Table 3). Thus, as the problems became more difficult, accuracy decreased. Despite the emphasis on performance accuracy, significant impairments in the number of responses required to identify the correct solution were observed in three of the four patient groups.

For the comparison between frontal lobe patients and control subjects, there was a highly significant effect of group and a significant interaction between the group and difficulty variables (Table 3). The appropriate simple main effects were calculated and confirmed that the frontal lobe group were significantly less accurate than control subjects at solving four-move,  $F(1, 32) = 11.89, p < .01$ , and five-move problems,  $F(1, 32) = 26.14, p < .001$ .

The NMP patients were also significantly impaired in terms of performance accuracy (Figure 3 and Table 3). Again, simple main effects confirmed that these patients were significantly impaired at solving three-move problems,  $F(1, 42) = 7.25, p < .025$ , and five-move problems,  $F(1, 42) = 36.78, p < .0001$ . A trend was also observed at the level of four-move problems, although this did not quite reach statistical significance,  $F(1, 42) = 3.79, p = .058$ . In contrast, no significant impairments were observed in terms of performance accuracy in the MP-mild patients (Figure 3 and Table 3). Accuracy was impaired, however, in the MP-severe patients. Simple main effects confirmed that these patients were significantly impaired on four-move problems,  $F(1, 26) = 10.17, p < .01$ , and on five-move problems,  $F(1, 26) = 37.50, p < .0001$ . A trend was also observed on three-move problems, although this did not quite reach statistical significance,  $F(1, 26) = 4.16, p = .054$ .

These results reveal that in terms of accuracy of planning, different patterns of performance are observed in patients with frontal lobe damage and in patients at different stages of Parkinson's disease. Specifically, although frontal lobe patients

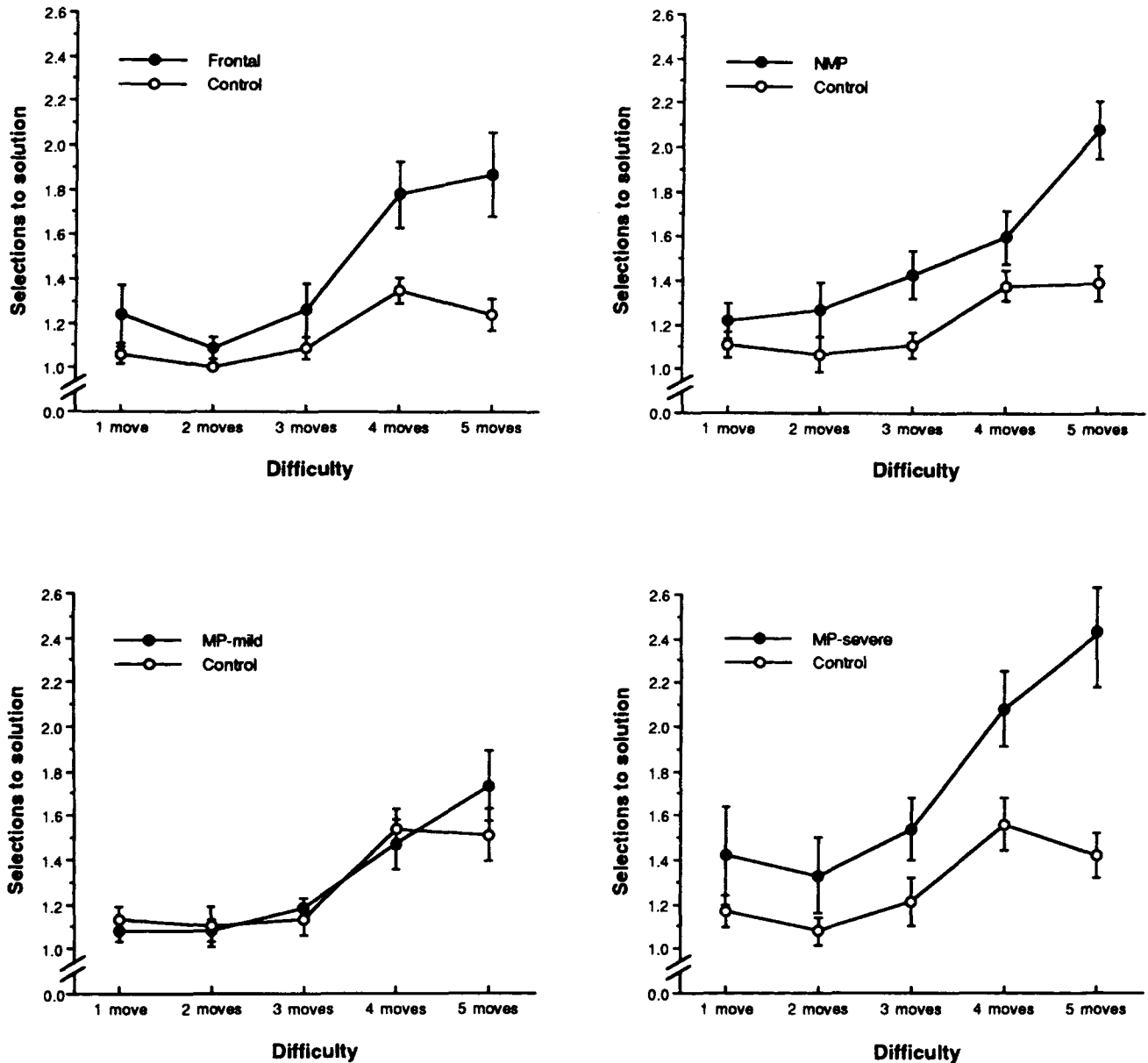


Figure 3. Number of responses needed to identify correctly the number of moves required for the ideal solution at each level of difficulty in the Tower of London task (planning accuracy). Bars represent standard errors.

require significantly more responses to identify the correct number of moves to solution, this deficit was particularly pronounced during the more difficult four- and five-move problems. Similarly, in NMP patients, difficulty-dependent deficits were observed, although these occurred even earlier, on the simpler three-move problems. In stark contrast, no impairments were observed in the MP-mild patients. Finally, profound deficits were observed in the MP-severe patients, and as in the NMP patients, these were most clearly evident at the more challenging levels of task difficulty.

*Latency of performance.* The mean response times for correct (first-choice) solutions within each level of task diffi-

culty are shown in Figure 4, for all four patient groups and the respective control groups. Although the data were normally distributed, significant outliers were detected in several instances (i.e., more than two standard deviations from the mean within a group). When this occurred, the data point in question was replaced by the next highest response latency in that group at that level of difficulty (see Winer, 1971, p. 51). However, only 1.43% of all latencies recorded were identified as outliers and corrected in this way. The data were again analyzed in two-way, split-plot analyses of variance with task difficulty (Levels 1–5) as the within-subjects variable and group (patients vs. control subjects) as the between-subjects variable.

Table 3  
Summary of Results

Measure and effect	Patient group											
	Frontal			NMP			MP-mild			MP-severe		
	F	df	p	F	df	p	F	df	p	F	df	p
Tower of London												
Planning accuracy												
Group	10.24	1, 32	.0005	15.10	1, 42	.0001	0.08	1, 38	ns	8.84	1, 26	.01
Difficulty	15.44	4, 128	.0001	18.02	4, 168	.0001	19.73	4, 152	.001	15.71	4, 104	.0001
Group × Difficulty	15.44	4, 128	.0001	3.98	4, 168	.0005	0.39	4, 152	ns	3.74	4, 104	.01
Planning latency												
Group	2.94	1, 32	ns	4.32	1, 42	.05	6.14	1, 38	.025	3.81	1, 26	ns
Difficulty	48.27	4, 128	.0001	34.57	4, 168	.0001	41.11	4, 152	.0001	69.37	4, 104	.0001
Group × Difficulty	1.59	4, 128	ns	3.72	4, 168	.01	4.37	4, 152	.005	7.98	4, 104	.0001
Spatial working memory												
Total score												
Group <sup>a</sup>	9.54	1, 32	.005	7.50	1, 42	.01	3.30	1, 38	ns	3.07	1, 26	ns
Novel sequences												
Group	2.40	1, 32	ns	1.28	1, 42	ns	1.26	1, 38	ns	0.08	1, 26	ns
Repetitions												
Group	5.91	1, 32	.05	0.20	1, 42	ns	0.18	1, 38	ns	0.01	1, 26	ns

Note. Frontal = frontal lobe damage; NMP = nonmedicated Parkinson's disease; MP-mild = medicated Parkinson's disease, with mild clinical symptoms; MP-severe = medicated Parkinson's disease, with severe clinical symptoms.

<sup>a</sup>For the group effect of the combined MP groups,  $F(1, 66) = 7.50, p < .01$ .

In all four comparisons between a patient group and the matched control group, there was a significant effect of task difficulty (Table 3). Thus, as the problems became more difficult, response latencies increased. However, in terms of latency for correct responses, no significant deficits were observed in the frontal lobe group (Figure 4 and Table 3).

In contrast, prolonged latencies were observed in the NMP group (Figure 4), and there was a significant interaction between the group and difficulty variables. Simple main effects were calculated and confirmed that the NMP patients were only significantly slower than control subjects at Level 5,  $F(1, 42) = 12.02, p < .0001$ .

Latencies were also significantly prolonged in the MP-mild group (Figure 4). Simple main effects were calculated and confirmed that the patient group was significantly slower than the control group at Level 4,  $F(1, 38) = 16.41, p < .001$ , and at Level 5,  $F(1, 38) = 29.23, p < .0001$ .

The MP-severe patients were also significantly slower than control subjects in identifying correct solutions, although the main effect of group did not reach significance. There was however, a significant interaction between the group and difficulty variables, and simple main effects confirmed that the MP-severe group was only significantly slower than control subjects at the most challenging level of task difficulty,  $F(1, 26) = 78.18, p < .0001$ .

These results demonstrate that in terms of planning latency, different patterns of performance are observed in patients with frontal lobe damage and in the three Parkinsonian patient groups. Specifically, the frontal lobe group was unimpaired in terms of this performance measure, whereas all three Parkinson's groups were significantly slower than control subjects in identifying the appropriate solution at the most difficult levels. Importantly, in all three groups, there was a significant interaction between the difficulty and group variables.

### Spatial Working Memory Task

The main index of performance on this task was the total number of novel sequences generated (out of a possible 24). In Figure 5, the results for the four patient groups and their respective control groups are presented. Data were analyzed in one-way analyses of variance with group (patient or control) treated as a between-subjects variable.

In terms of this measure, only the frontal lobe patients and the NMP group were significantly impaired, although in both the MP-mild and MP-severe groups, these effects approached significance (Table 3). Because there were clearly no significant differences between the two MP groups, a supplementary analysis was performed, with data collapsed across these two patient groups. In comparison with the amalgamated group of control subjects, the MP patients produced significantly fewer novel sequences overall.

These results show that both MP and NMP patients and patients with frontal lobe damage are impaired on this sequence-generation task in terms of the total number of novel sequences produced. However, because no clear differences were found between the patient groups, two further analyses were performed to establish whether the groups could, in fact, be dissociated in terms of other measures of performance. The results of these analyses showed that, in terms of the number of novel sequences generated before subjects made an error, there were no significant differences between any of the four patient groups and their respective control groups (Table 3). The associated scores for this measure were: for frontal lobe patients,  $M = 7.6, SD = 1.1$ ; for NMP patients,  $M = 7.3, SD = 0.8$ ; for MP-mild patients,  $M = 7.2, SD = 0.7$ ; and for MP-severe patients,  $M = 7.2, SD = 1.1$ . Control subject's mean scores varied from 6.7 ( $SD = 1.1$ ) to 8.5 ( $SD = 0.8$ ).



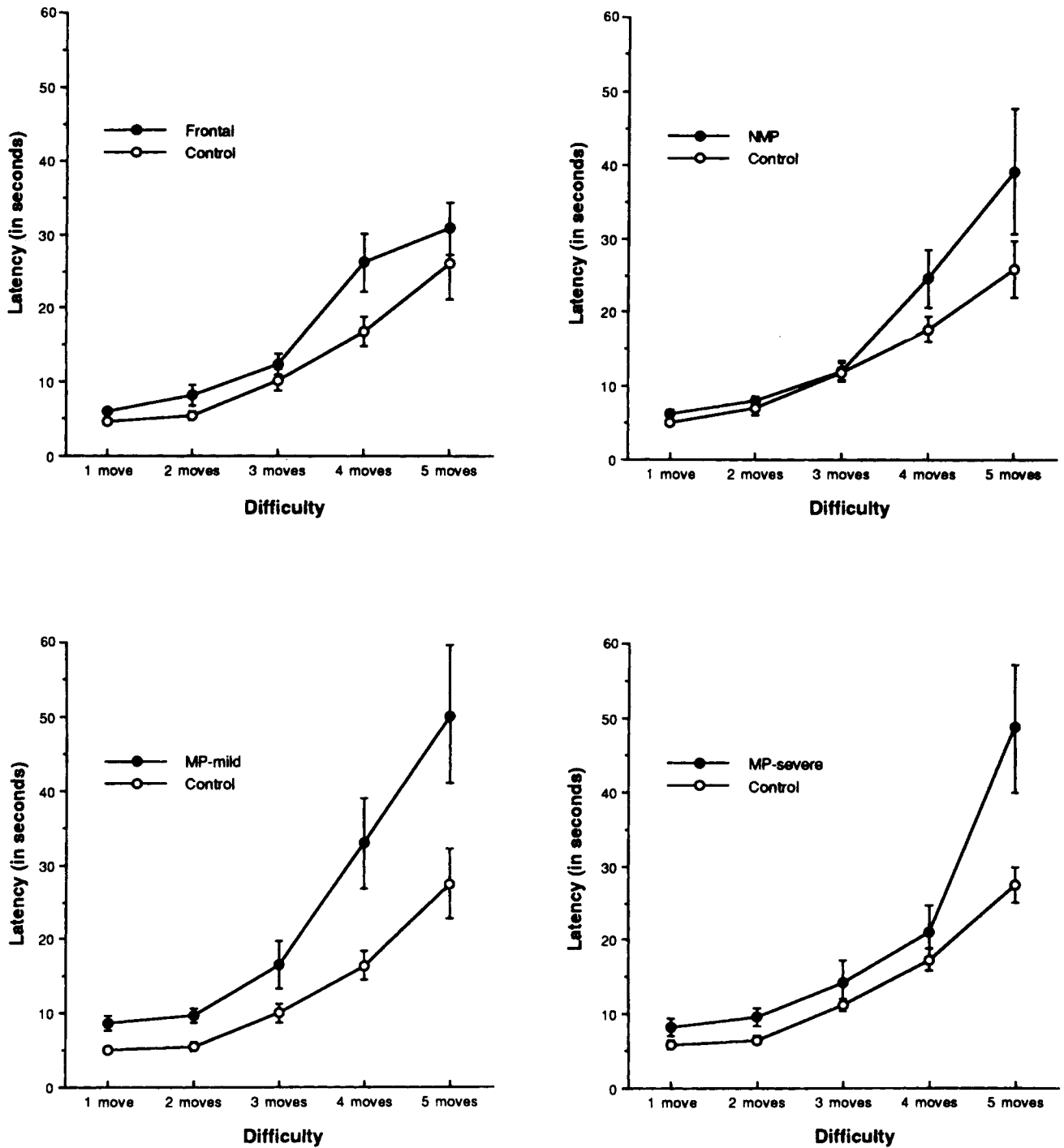


Figure 4. Response latency, for correct responses only, at each level of difficulty in the Tower of London task (planning latency). Bars represent standard errors.

A second analysis was also performed to identify whether any particular pattern of responding could be associated with poor performance on this task. The results of this analysis showed that in the period between the first error (repeated sequence) and the end of the task, the frontal lobe patients were significantly more likely to initiate any given

sequence with the same box that was used to begin the previous one (Figure 5). Similar response patterns were not observed in any of the Parkinson's disease groups (see Table 3). This repetitive tendency did not correlate with other indexes of performance in any of the patient or control groups.

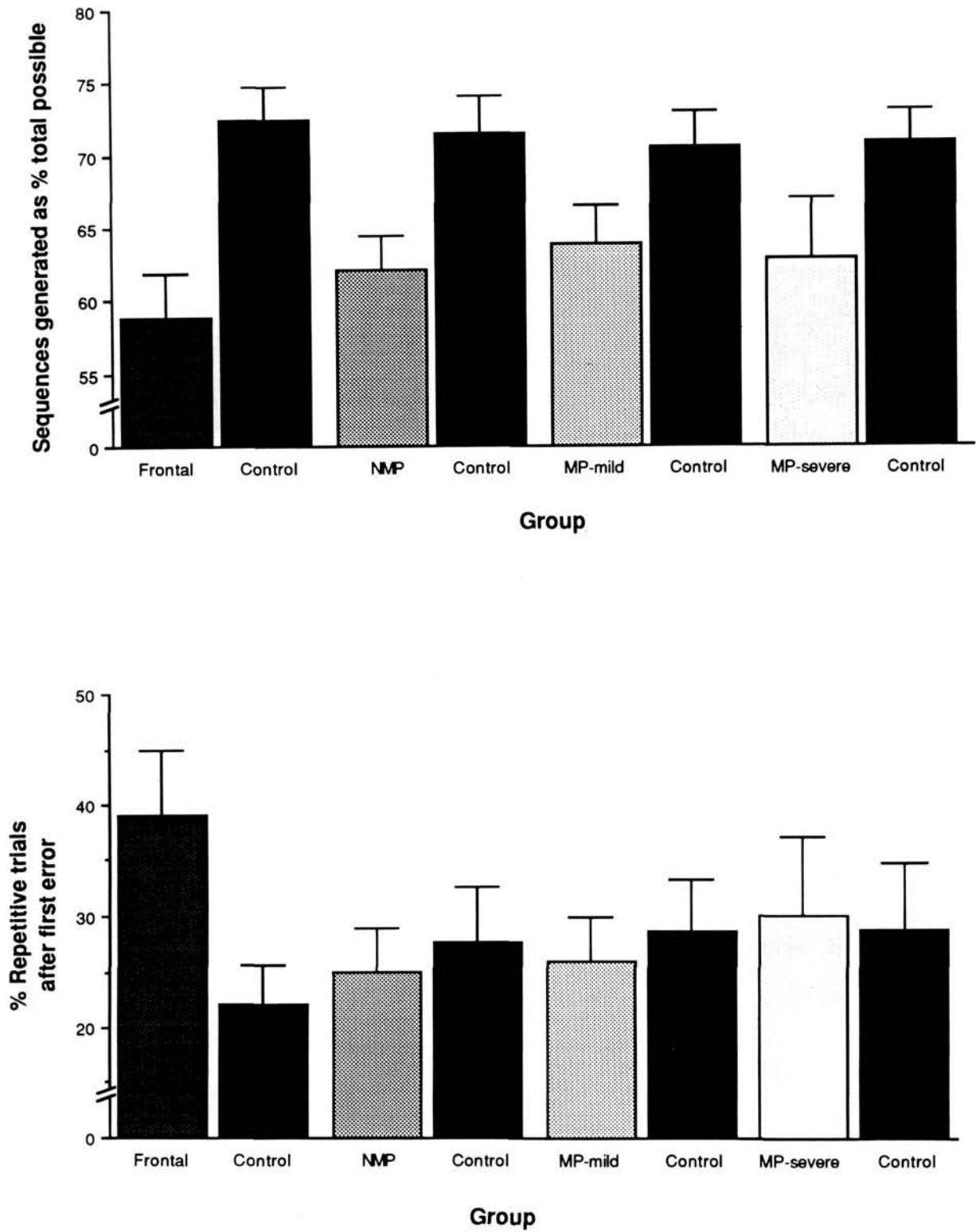


Figure 5. Spatial sequence generation task: Number of novel sequences generated, expressed as percentage of 24 possible responses, and percentage of sequences (after an error) that began with the same box used to begin the previous sequence.

### *Correlational Analysis*

To assess the general relations between the two tests, Pearson's product-moment correlation coefficients were calculated between various composite measures of performance. Specifically, on the Tower of London task, mean thinking times and selections to solution were computed, with data collapsed across the five levels of task difficulty, and were then compared with each other and with overall performance on the sequence-generation task. Separate intercorrelation matrices were generated for the combined Parkinson's disease group, for the frontal lobe group, and for the combined group of normal control subjects.

In the Tower of London task, there were no significant correlations between measures of accuracy and latency in either the frontal lobe patients or in the combined control group. In the combined Parkinson's disease group, however, mean latency for correct solutions correlated significantly with accuracy of performance on this task,  $r(27) = -.35, p < .05$ . In the control group the accuracy of performance on the Tower of London test also correlated significantly with both the total number of novel sequences produced in the spatial task,  $r(33) = -.36, p < .05$ , and the number of sequences produced before an error,  $r(33) = -.59, p < .0001$ . In the frontal lobe patients, these correlations were maintained to a high level of significance,  $r(17) = -.79, p < .0001$ , and  $r(17) = -.56, p < .01$ . In contrast, in the combined Parkinson's disease group, only the relation between planning accuracy and the number of sequences produced before an error was maintained,  $r(36) = -.43, p < .005$ . Planning latency on the Tower of London task failed to correlate significantly with any other measure of performance in any of the patient or control groups.

### *Effects of Laterality and Lesion Location*

The initial analysis combined left-lesion, right-lesion, and (in two cases) bilateral patients within the frontal lobe group. We also examined the data for possible effects of laterality of lesion in this patient group. Owen et al.'s (1990) study revealed no differences relating to side of lesion in slightly larger groups of frontal lobe patients on tests of planning or spatial working memory. There were again, in this study, no significant differences between the frontal lobe subgroups on any measure of performance. Notably, however, in both tasks the performance of the bilateral frontal lobe group was worse than either of the unilateral lesion groups, although the small group size precluded any formal statistical analysis of this effect. In spite of this trend, when the 2 bilateral subjects were excluded from the main analyses, the overall pattern of results was unchanged.

These results suggest that the deficits observed in tests of planning and spatial working memory in patients with frontal lobe excisions are not disproportionately related to damage to one or other hemisphere.

To examine further the effects of lesion location in this patient group, unilateral subjects were regrouped according to both the size of the lesion ( $< 4 \text{ cm}^2, n = 5$ ;  $> 4 \text{ cm}^2, n = 5$ ; and complete frontal lobectomy,  $n = 5$ ) and the site of the lesion (pole and inferior surface,  $n = 5$ ; lateral surface posterior,  $n =$

4; and medial surface only,  $n = 1$ ). Although formal comparisons between groups were limited by unequal and small group sizes, no effects of significance were observed.

### *Discussion*

The results of this study reveal distinct patterns of cognitive impairment in patients with frontal lobe damage, nonmedicated patients with Parkinson's disease, and medicated parkinsonian patients with mild or severe clinical symptoms. In a computerized test of planning, the frontal lobe group required more attempts to identify correct solutions, particularly during the more challenging four- and five-move problems. However, response latencies, or thinking times, for correct solutions were not significantly prolonged in this group. Conversely, significantly prolonged selection latencies were observed in a group of medicated parkinsonian patients with mild clinical symptoms, although in these patients, planning accuracy was preserved. Finally, in nonmedicated Parkinson's patients and in medicated patients with severe clinical symptoms, deficits of both accuracy and latency were observed.

The results of this investigation both confirm and extend previous findings (see Table 1) in which planning deficits have been demonstrated in both frontal lobe patients (Owen et al., 1990; Shallice, 1982) and patients with Parkinson's disease (Morris et al., 1988; Owen et al., 1992). The results also provide important new information in regard to the nature of cognitive dysfunction in nonmedicated patients in the early stages of Parkinson's disease.

Although the test that we used was conceptually similar to that adopted in previous studies, certain modifications were made to improve the sensitivity of the task and to examine further the relation between the contrasting patterns of deficit observed in these patient groups. Specifically, the modified planning task used in this study required subjects to evaluate and solve the problems in full, without actually moving any of the balls. Consequently, it was no longer possible to compromise initial planning time (i.e., time before a response was made) in favor of on-line consideration of the problem during the execution of the solution (i.e., subsequent thinking time). This modification served to encourage subjects to plan the solution in full, before they initiated a response, and provided important information about the relation between thinking (planning) time, problem difficulty, and solution accuracy. The effects of this alteration may be seen most clearly by comparing the performance of control subjects in this study with those studied previously by Owen et al. (1992) with an earlier version of this task. All four control groups in this study exhibited clear, difficulty-dependent, monotonic increases in thinking time, which were not consistently observed in the previous study. This modification was also designed to improve the sensitivity of the test by increasing the load on active working memory during the initial search for possible solutions. Because the ideal solution (in terms of number of moves) was no longer defined a priori, the number of possibilities that had to be considered before the most appropriate solution was identified was significantly increased. In this study the initial thinking times among control subjects during the more challenging four- and five-move problems were approximately twice as

long as those observed previously (Owen et al., 1992), which may reflect the additional time required to consider all possible solutions.

This methodologically refined form of the Tower of London test, which minimizes the motor requirements of the task but also increases the time spent thinking about solutions, has recently proved ideal for functional imaging studies with positron emission tomography. Preliminary results suggest significant involvement of the prefrontal cortex in the planning phases of this task (Rogers et al., 1994).

The pattern of deficits exhibited by the frontal lobe group is broadly similar to that observed previously in a larger group of patients with frontal lobe damage (Owen et al., 1990). Deficits were observed in terms of accuracy of planning, but initial thinking or planning times were not significantly different from control subjects. One may have expected to see prolonged thinking times in the frontal lobe group, given those patients' profound difficulty with solving these problems and the fact that prolonged subsequent thinking times on an earlier version of this task were reported previously (Owen et al., 1990). In Owen et al.'s (1990) study, however, prolonged subsequent thinking time in frontal lobe patients was assumed to reflect the additional time required to revise and refine a solution after an inadequately planned, or impulsive, attempt to solve the problem. Because performance on the modified Tower of London task used in this study was measured by a single response, the results further suggest that the behavior of frontal lobe patients in tests that require forward thinking or planning is indeed impulsive; that is, these patients initiate a response, or make the first move, before they have successfully generated an appropriate solution to the problem, a view consistent with the conclusions of other investigators (e.g., Stuss & Benson, 1984).

The deficit on the Tower of London task in patients with frontal lobe damage has previously been considered in terms of the component processes required for efficient planning (Owen et al., 1990). Planning accuracy was found to relate to impaired performance on a self-ordered search task designed to assess the efficiency of spatial working memory. Moreover, in the frontal lobe group, this impairment was shown to relate to the inefficient use of a repetitive searching strategy known to improve performance on this task (Owen et al., 1990). Planning accuracy in this study was also correlated with performance on an entirely novel test of spatial working memory, both in control subjects and, particularly, in patients with frontal lobe damage, which confirms that working memory is a major contributor to some aspects of planning on the Tower of London task. Although no obvious deficits in the strategic self-ordering of responses were found in the frontal lobe group, their behavior was characterized by a unique tendency to repeatedly generate sequences that began with the same box. This pattern, although not detrimental to performance in this task, may be akin to the stuck-in-set form of perseveration (Sandson & Albert, 1984, 1987) that has been widely reported in patients with frontal lobe damage (Drewe, 1974; Milner, 1963; Nelson, 1976; Owen, Roberts, et al., 1993; Robinson et al., 1980).

Our results also extend previous findings in patients with Parkinson's disease (Lange et al., 1992; Owen et al., 1992) and

have considerable significance for the pattern of cognitive deficits observed at the earliest stages of this neurodegenerative disorder. For example, an important finding in previous studies was the apparent sparing of planning and spatial working memory functions in nonmedicated patients with mild clinical symptoms (Owen, Beksinska, et al., 1993; Owen et al., 1992). In contrast, deficits on tests of sorting or attentional set-shifting, which are also assumed to depend on the integrity of the prefrontal cortex, have been reported in several studies of *de novo* patients (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Downes et al., 1989; Lees & Smith, 1983; Owen, Roberts, et al., 1993; Owen, Roberts, Polkey, Sahakian, & Robbins, 1991). Using two novel tasks, we demonstrate that planning and spatial working memory may also be vulnerable at the earliest stages of Parkinson's disease.

One factor that complicates our understanding of the profile of cognitive impairments in Parkinson's disease is the potential role of medication. It is possible that some of the deficits that have been reported in Parkinson's disease may be attributable to various aspects of medication, because both L-dopa (Gotham et al., 1988) and scopolamine (Dubois et al., 1987) can adversely affect cognitive performance in these patients. However, medication clearly cannot account for the planning and spatial working memory impairments observed in the NMP group in this study. In fact, the pattern of deficits exhibited by the group of medicated patients with a similar degree of clinical disability (MP-mild) suggests that certain aspects of the planning impairment in Parkinson's disease may be ameliorated by dopaminergic medication. Specifically, although planning times were, if anything, longer in this group than in the NMP patients, no deficit in planning accuracy was observed. This result substantiates two recent studies, which have shown that under certain conditions, L-dopa can selectively improve performance on tests that are sensitive to frontal lobe dysfunction (Lange et al., 1992; Owen, Roberts, et al., 1993). It also suggests that impaired planning accuracy in Parkinson's disease occurs as a consequence of damage to the striatal dopaminergic projections, although possible effects of L-dopa on nonstriatal mechanisms cannot be ruled out. For example, parkinsonian patients also exhibit dopamine loss in the prefrontal cortex (Scatton et al., 1983), which may contribute to the frontal-lobe planning deficits observed in these patients.

Importantly however, the profound deficit in terms of latency of thinking in all three groups of Parkinson's disease patients suggests that they also have deficits that are not necessarily attributable to dysfunctioning of circuitry, which includes the prefrontal cortex. Because this increase in latency varied as a function of task difficulty in all three parkinsonian groups, it is clearly not related to any basal slowing of reaction time but, rather, represents a specific slowing of cognitive processes, a possible correlate of bradyphrenia. Slowed thinking in patients with Parkinson's disease has been interpreted in a number of ways (Morris et al., 1988; Rogers, 1986; Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988; Watts, Macleod, & Morris, 1988; for discussion, see Owen et al., 1992), although little is known about the neural substrates responsible. Rogers, Lees, Trimble, and Stern (1987) proposed that bradyphrenia in Parkinson's disease and psychomotor retardation in primary depressive illness may be closely related and

that the dopaminergic system may be involved in both. In our study the lack of effect of L-dopa and of frontal lobe damage on thinking times suggests that neither the dopaminergic mechanisms in the striatum nor the prefrontal cortex itself, mediate this aspect of planning ability. It remains possible, however, that prolonged thinking times are striatal in nature and are improved by L-dopa medication (see Lange et al., 1992) but that this relative improvement is masked by the effects of disease progression. There is, as yet, little relevant evidence in experimental animals, although the presence of a range of nonstriatal forms of pathology in Parkinson's disease, including noradrenergic, serotonergic, and cholinergic deafferentation of the cortex (Agid, Ruberg, Dubois, & Pillon, 1987) suggests that slowed thinking may arise from one or more of these alternative forms of pathology. Cortical Lewy bodies may also be implicated in Parkinson's disease (Byrne, Lennox, Lowe, & Godwin-Austin, 1989; Gibb, Luthert, Janota, & Lantos, 1989), although these are most evident in the later stages of the disease and cannot, therefore, account for the profound deficits observed in the NMP group. Clearly, further studies to compare groups of patients at different stages of Parkinson's disease, tested both on and off their L-dopa medication, are required before this issue can be fully resolved.

Anticholinergic medication is also unlikely to play a significant role in the pattern of cognitive deficits observed in this study because only 7 of the 34 MP patients were receiving such preparations. In addition, a supplementary analysis confirmed no obvious differences between these patients and the remainder of the MP group.

The pattern of deficits observed in the MP-severe patients was, if anything, worse than that observed in either of the other parkinsonian groups, on almost all aspects of task performance. The fact that MP-severe patients exhibited profound deficits in planning accuracy, a pattern not observed in the MP-mild group, strongly suggests that the beneficial effects of L-dopa medication on cognitive performance may decline in more elderly patients or in the later stages of the disease. These findings are also consistent with the results of several recent studies that have described a progressive pattern of cognitive deficits in Parkinson's disease with increasing clinical disability (Owen, Beksinska, et al., 1993; Owen et al., 1992). It is important to point out that the reported increase in severity and general broadening of intellectual deficits may not be restricted to functions ascribed to the frontal lobes. For example, in Owen, Beksinska, et al.'s (1993) investigation, only patients in the more advanced stages of Parkinson's disease were shown to be impaired on a test of delayed matching-to-sample for complex patterns (see also Sahakian et al., 1988). This task is sensitive to deficits in neurosurgical patients with temporal-lobe or amygdalohippocampotomy damage but not to deficits in patients with damage to the frontal lobes (Owen, Sahakian, et al., *in press*).

Some of the planning deficits observed in the patients with Parkinson's disease may also be attributable to impaired spatial working memory, given that both medicated and nonmedicated groups were significantly impaired in the spatial sequence-generation task. However, although it was not possible to distinguish between parkinsonian patients and patients

with frontal lobe damage on this task, recent evidence suggests that different cognitive processes may be responsible for the similar impairments observed in the two groups. In particular, although spatial working memory deficits have been linked to deficient executive or organizational processes in patients with frontal lobe damage (Owen et al., 1990), no strategic deficits have been found in patients with Parkinson's disease on the same task (Owen, Beksinska, et al., 1993; Owen et al., 1992). In fact, the pattern of deficits observed in Parkinson's patients is almost identical with that observed in neurosurgical patients with temporal-lobe or amygdalohippocampotomy damage (Owen, Morris, et al., 1993) and may therefore reflect an impairment of mnemonic rather than strategic mechanisms. In addition, the significant association between planning accuracy and the total number of novel sequences generated on the working memory task observed in this study's control subjects and frontal lobe patients was disrupted in the combined parkinsonian group. This further strengthens the possibility that impaired spatial working memory in Parkinson's disease is not truly frontal in either behavioral or neural terms.

The precise neural mediation of functions as complex as planning are not known, although the relation between spatial working memory and the prefrontal cortex is now well established. Monkeys with bilateral damage to the area around the sulcus principalis exhibit profound and selective deficits in spatial tasks that require memory for the location of objects (Funahashi, Bruce, & Goldman-Rakic, 1989; Goldman & Rosvold, 1970; Goldman, Rosvold, Vest, & Galkin, 1971; Gross & Weiskrantz, 1964; Passingham, 1985; for review, see Goldman-Rakic, 1990). In humans, a recent positron emission tomography study showed increased activation in the right prefrontal cortex during performance of a spatial working memory task with a nonsignificant increase in the homologous area of the left hemisphere (Jonides et al., 1993). In addition, using a formally similar version of the Tower of London task to the one we used, Rezai et al. (1993) reported increased cerebral blood flow in both left and right mesial prefrontal cortex of normal control subjects, measured with single photon emission computerized tomography. As a group, our frontal lobe patients were anatomically heterogeneous, and no obvious associations were observed between the performance indexes and either the size, the site, or even the side of the lesion. In general, however, more profound deficits were observed in the 2 patients with bilateral lesions. This latter result is particularly interesting given that, experimentally, the relation between working memory processes and damage to the prefrontal cortex is most often investigated in animals with bilateral frontal lobe lesions (Funahashi et al., 1989; Passingham, 1985; Petrides, 1991).

The finding that planning function in Parkinson's disease is impaired in a different manner from that seen in frontal lobe patients suggests that the study of these different disorders may enable us to dissociate different aspects of task performance that may depend on different elements within frontostriatal loops, such as those suggested by Alexander et al. (1986). Accuracy and efficiency of planning, for example, appears to be mediated by mechanisms within the frontostriatal system, although speed of thinking may be modulated by neurotransmitter systems of subcortical origin that innervate

either or both the cortex and the caudate nucleus. Future studies will aim to define which regions of frontostriatal circuitry are responsible for the dopamine-dependent effects observed in this investigation and extend the results to include longitudinal studies of parkinsonian patients tested before, and then after, receiving medication. This and other detailed comparisons between patients with Parkinson's disease and patients with different pathology of the corticostriatal system (e.g., Owen & Robbins, 1993c; Robbins et al., 1992; Robbins et al., 1994) are thus enabling us to define the precise role of its various elements in complex cognitive functions.

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Received December 27, 1993  
 Revision received March 14, 1994  
 Accepted March 16, 1994 ■

**UNITED STATES POSTAL SERVICE** Statement of Ownership, Management, and Circulation (Required by 39 U.S.C. 3685)

1. Publication Title: *Neuropsychologia*

2. Issue Frequency: Quarterly

3. Issue Date for Circulation Data Below: October 1994

4. Issue Frequency: 4 No. of Issues Published Annually: 4 Annual Subscription Price: \$25; Number, 5407; \$502/issue.

5. Complete Mailing Address of Known Office of Publication (Street, City, County, State, and ZIP+4) (Not Printer):  
 70 First Street, NE, Washington, DC 20002-4242

6. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not Printer):  
 750 First Street, NE, Washington, DC 20002-4242

7. Full Name and Complete Mailing Address of Publisher, Editor, and Managing Editor (Do Not Leave Blank):  
 American Psychological Association, 750 First Street, NE, Washington, DC 20002-4242

8. Owner (Name and Complete Mailing Address):  
 Nelson A. Rockefeller, Ph.D., Psychology Service, 1115B3, Department of Veterans Affairs Med. Ctr., 3550 La Jolla Village Dr., San Diego, CA 92161

9. Managing Editor (Name and Complete Mailing Address):  
 Thomas Kadish, American Psychological Association, 750 First Street, NE, Washington, DC 20002-4242

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PS Form 3526, October 1994 (See Instructions on Reverse)

13. Publication Title: *Neuropsychologia*

14. Issue Date for Circulation Data Below: July 1994

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