Comparative neuropsychology of parkinsonian syndromes

A.M. OWEN and T.W. ROBBINS

ABSTRACT

Medicated and non-medicated patients at various stages of Parkinson's disease (PD) were compared to groups of neurosurgical patients with localised frontal lobe lesions in order to define as precisely as possible, which frontal lobe functions are involved in the pathology of PD and the extent to which this involvement is related to disease severity and medication. The patient groups were compared on a comprehensive battery of computerised, neuropsychological tests, designed to decompose complex cognitive functions into their constituent elements. On the basis of these initial findings, direct comparisons were made between groups of patients with PD, progressive supranuclear palsy or Steele-Richardson-Olzsewski syndrome (SRO) and multiple system atrophy (MSA), matched for overall clinical disability. The three basal ganglia disorders were associated with a distinctive pattern of cognitive deficits on tests of frontal lobe function although there were subtle qualitative differences between the the groups and by comparison with patients with frontal lobe damage. The results have important implications for the concept of 'fronto-striatal' cognitive deficits mediated by parallel, functional corticostriatal circuits.

INTRODUCTION

Characteristic patterns of cognitive impairment have now been reported in groups of patients with various basal ganglia disorders including Parkinson's disease (PD), Huntington's disease (HD) and progressive supranuclear palsy (or Steele-Richardson-Olszewski syndrome, SRO) (1). However, the relationship between these deficits in terms of common neural and neuropsychological mechanisms has yet to be well defined. Some investigators have suggested that many of the cognitive deficits observed are similar to a syndrome of 'subcortical dementia' (2,3). However, others have favoured a more specific, 'frontal' or 'fronto-striatal' basis for these impairments, emphasizing that many of the cognitive deficits described, resemble those commonly seen after frontal lobe damage in man. For example, impaired performance on the Wisconsin Card Sorting test, a classic index of frontal lobe dysfunction (4) has been separately reported in patients with PD (5), HD (6) and SRO (7). Importantly however, few direct comparisons, in the same study, have been made between the cognitive deficits observed in

patients suffering from these neuro-degenerative diseases or from well documented frontal lobe damage, leaving the relationship between 'subcortical dementia' and 'frontal lobe dysfunction' in basal ganglia conditions largely unresolved.

In contrast to the extensive investigation of cognitive deficits in HD, SRO and particularly, PD, few studies have assessed the neuropsychological performance of patients with multiple system atrophy (MSA), a progressive akinetic-rigid syndrome which accounts for between 5-10% of all parkinsonians. MSA is particularly interesting since intrinsic striatal pathology (caudate and putamen) is accompanied by damage to the nigrostriatal dopamine system which is at least as severe as that seen in PD and SRO (8). Whilst patients with MSA generally have parkinsonian symptoms as a major feature, additional symptoms often include autonomic failure (Shy-Drager syndrome) or cerebellar and/or pyramidal signs (olivopontocerebellar atrophy or OPCA) (9-11). Whilst cognitive deterioration is not generally considered to be a characteristic feature of MSA (11), our own recent findings suggest that certain 'frontal-like' cognitive changes may also accompany this condition (12).

On this basis, and given the close neuropathological relationship between these basal ganglia disorders, a detailed comparison with patients with localised frontal lobe damage is of obvious clinical and theoretical interest. There are however, several problems in comparing patients from these various clinical groups. The first concerns the progressive nature of these basal ganglia disorders and the possibility that the profile of cognitive impairment may differ at various stages of the disease process. For example, several recent studies have emphasised the need to take account of the severity of clinical symptoms when assessing cognitive impairments in PD (13,14). Second, medication may play an important role in the pattern of cognitive deficits observed in these parkinsonian groups. For example, several studies have reported improved performance in certain aspects of frontal lobe function in patients with PD when L-Dopa is administered (15,16) although in others, the reverse pattern has been found (17).

One approach to these problems, which we have adopted, is to compare both medicated and non-medicated patients at various stages of PD to groups of neurosurgical patients with localised frontal lobe lesions in order to define more precisely, which frontal lobe functions are involved in PD and the extent to which this involvement is affected by such factors as disease severity and medication.

Secondly, and on the basis of these initial findings, we have been able to make informative and direct comparisons between well matched groups of patients with PD, SRO and MSA and to draw conclusions based on the pattern of cognitive deficits observed after frontal lobe damage. In both cases, the patient groups were compared on a comprehensive battery of computerised, neuropsychological tests, designed to decompose complex

cognitive functions into their constituent elements. As will become clear, this approach has advantages for understanding the nature of cognitive deficits in the clinical populations as well as facilitating cross-species comparisons between humans and non-human primates.

FRONTAL LOBE-LIKE DEFICITS IN BASAL GANGLIA DISORDERS

In recent years, sufficient neuropsychological and neuropathological evidence has accumulated to implicate a substantial role for frontal lobe dysfunction in the neuropsychological profile of patients with Parkinson's disease (6,15,18-20). In general, however, few direct comparisons have been made between patients with PD and patients with frontal lobe damage. In addition, deficits in memory and learning are also often reported in patients with PD which may be more consistent with temporal lobe dysfunction (13,21-25).

Our initial studies were designed to test the hypothesis that in PD, it is those functions which depend on the integrity of the prefrontal cortex which are most at risk. A modified version of the Tower of London test (26) was developed to compare planning ability in patients with localised frontal lobe excisions and patients with PD. In the new, computerised task the subject was required to move an arrangement of coloured balls hanging in 'socks' or 'pockets' to match a goal arrangement presented in the top half of the screen (fig. 1: I.). The test was designed to incorporate a touch sensitive screen such that a ball could be moved simply by touching it and then by touching an empty position in one of the other pockets. Task difficulty was manipulated by varying the minimum number of moves required to make the correct match between two and five moves. The proportion of perfect solutions (i.e. solved in the minimum possible number of moves) and the relative contributions of initial and subsequent 'thinking' or planning time during the execution of the solution were the main performance indices. As the time taken to complete the task was to some extent dependent on movement (i.e 'motor') time, a related 'yoked control' condition was also employed to measure motor initiation and motor execution time over an identical series of single moves. By subtracting the latencies for each move in this motor control condition from those of the planning condition, estimates of initial and subsequent 'thinking time' were derived.

The results of our initial study both confirmed and extended earlier data described by Shallice (26) in which a group of patients with 'anterior' cortical damage were shown to be impaired in the original version of the Tower of London test. Although patients with localised frontal lobe excisions were able to complete even the most difficult problems within the maximum number of moves allowed, they nevertheless required significantly more moves per problem than control subjects, matched for age and

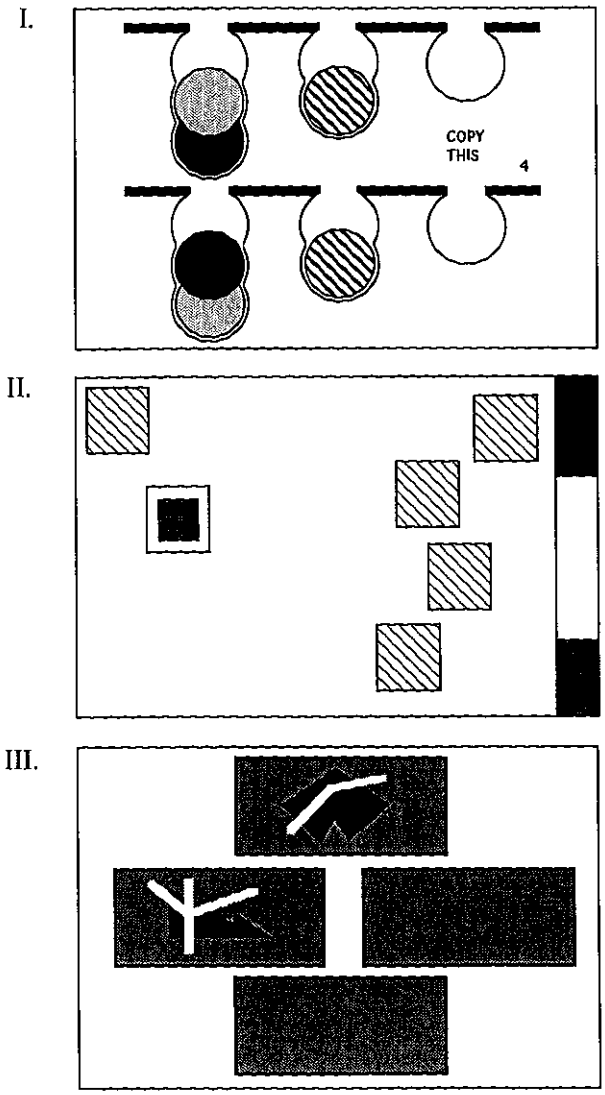

Fig. 1. Diagrammatic representation of the three computerised cognitive tests sensitive to frontal lobe damage. I. The Tower of London test. Subjects are asked to move the balls around in the bottom half of the screen to match the 'goal' arrangement presented in the top half of the screen, in this case, in four moves. II Spatial working memory. Subjects are required to 'search through' the six boxes on the screen to find 'tokens' hidden inside. III Attentional set-shifting. Two compound discriminanda, comprised of shapes and lines are presented in pairs. The subject has to learn the rule which will reliably predict reinforcement.

premorbid verbal IQ, and consequently produced fewer (perfect) minimum move solutions (27). In addition, although the two groups did not differ in the amount of time spent thinking prior to the first move (fig. 2), the frontal lobe patients spent significantly more time thinking during the execution of the problem solution. This pattern of impairment appears to be relatively specific at the cortical level since no deficits are observed in neurosurgical patients with temporal lobe damage (Owen et al, unpublished results).

A parallel study of patients with PD clearly demonstrated that L-Dopa medicated and non-medicated patients at different stages of the disease can be differentiated in terms of their performance on this test of high level planning ability (28). Thus, a 'frontal-like' impairment in solution accuracy was only evident in a group of medicated patients with severe clinical symptoms (Hoehn and Yahr stages III-IV (29)). In contrast, medicated patients with both mild (Hoehn and Yahr stages I-II) and severe symptoms were slower than controls to initiate solutions to the planning problems, but unlike the frontal lobe patients, neither group were impaired in terms of

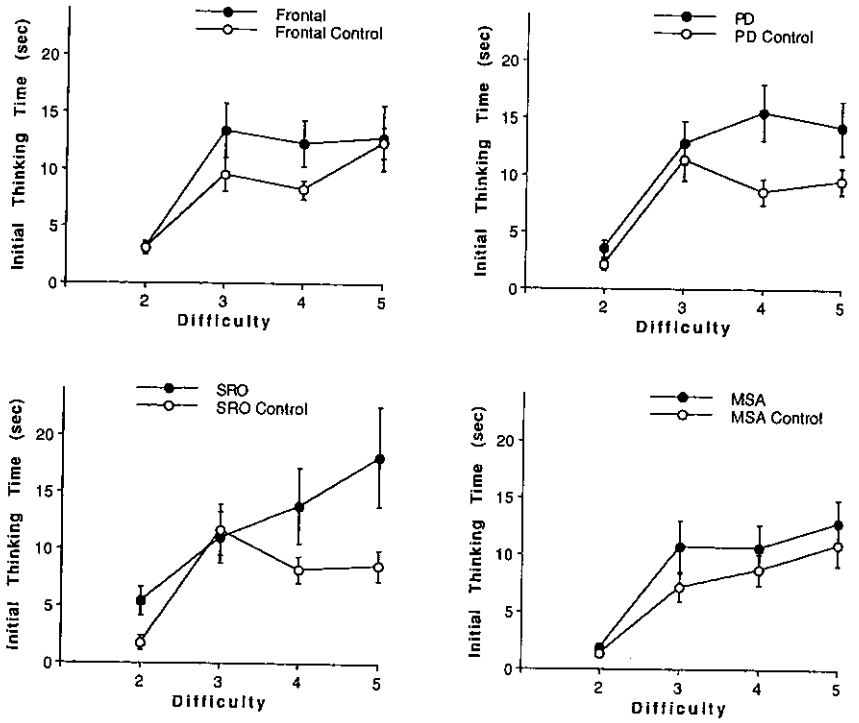

Fig. 2. Mean (s.e.m.) initial thinking time in seconds on the Tower of London test of planning for various difficulty levels. Frontal, PD, SRO and MSA groups are shown, the last three matched for degree of clinical disability.

subsequent 'thinking' time. No impairments were observed in a third group of PD patients who were non-medicated and had relatively mild clinical symptoms.

Contrasting patterns of impairment on this planning task were also found in groups of patients with MSA and SRO who, in terms of their clinical disability, were most similar to the group of medicated PD patients with severe clinical symptoms described above (30). Thus, like the medicated patients with PD, the eighteen SRO patients were significantly impaired in terms of their initial thinking time (fig. 2) but not in terms of their subsequent thinking time (fig. 3) and showed a significant decrease in the number of minimum move, or 'perfect' solutions. In complete contrast, and like the patients with frontal lobe damage, the sixteen patients with MSA exhibited significantly prolonged subsequent, but not initial thinking times (figs 2 and 3) although this deficit was not accompanied by any significant impairment in performance accuracy.

Impaired performance in the Tower of London test may be considered

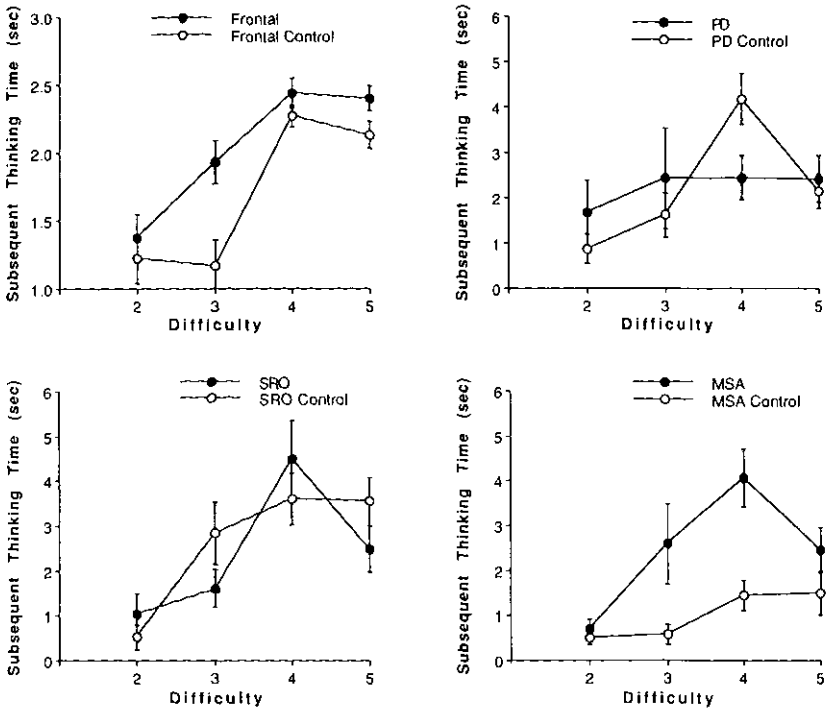

Fig. 3. Mean (s.e.m.) subsequent thinking time in seconds on the Tower of London test of planning for various difficulty levels. Frontal, PD (medicated), SRO and MSA groups are shown, the last three matched for degree of clinical disability.

in terms of the component processes required for accurate planning. For example, given the importance of attentional 'set' for efficient problem solving (see ref. 31), the ability to shift between competing possibilities may play a crucial role in the final selection of the most appropriate solution. Another possibility is that the deficits observed reflect an impairment of memory function. Accurate planning on the Tower of London test requires an active search of possible solutions, placing a significant load on spatial working memory.

In order to address these issues, two additional tests were devised to assess the relative contributions of spatial working memory and attentional set shifting ability, to the planning deficits observed in the Tower of London task.

The spatial working memory task was essentially a modification of one used by Passingham (32) to examine the effects of prefrontal cortex lesions in primates, and conceptually similar to the 'radial arm maze' which has been successfully used to assess working memory in rats (33). In our version of the task, adapted for humans, subjects were required to 'search through' a number of coloured boxes presented on the computer screen (by touching each one) in order to find blue 'tokens' which were hidden inside (fig. 1: II.). The object was to avoid those boxes in which a token had already been found. Importantly, the subjects could search through the boxes in any order they wished although the number of boxes visited before a token was found was determined by the computer. The neurosurgical patients with frontal lobe damage were significantly impaired on this task (fig. 4), making more returns to boxes ('between search' errors) in which a token had previously been found at all levels of task difficulty (27). In addition, these patients were shown to be less efficient in the use of a repetitive searching strategy, known to improve performance on this task, suggesting that at least some of their impairment in spatial working memory may arise secondarily from a more fundamental deficit in the use of organisational strategies. Our recent unpublished data suggests that this task may also be sensitive to deficits in patients with temporal lobe damage although only at the most extreme level of task difficulty (i.e. 8 boxes). Unlike frontal lobe patients, the temporal lobe group utilise a normal and effective searching strategy.

Among the groups of patients with PD, an impairment in terms of the accuracy of performance on the spatial working memory task was observed in medicated PD patients with both mild and severe clinical symptoms. However, unlike the frontal lobe patients, neither group was impaired in terms of the strategy adopted to tackle the problem (28). Again, nonmedicated patients with PD were unimpaired on this task. Figure 4 shows the performance of a group of medicated PD patients matched for clinical disability with groups of patients with MSA or SRO.

The spatial working memory task also proved to be most sensitive to deficits in patients with MSA and SRO (fig. 4). Both groups were significantly impaired in terms of the number of returns to boxes in which a token had previously been found (30). Moreover, like the frontal lobe group, this deficit was found to relate directly to the inappropriate use of a repetitive searching strategy in the SRO patients.

The third paradigm designed to assess frontal lobe dysfunction in PD was based on similar principles to the Wisconsin Card Sorting Test (WCST), a classic index of frontal lobe dysfunction (4). Deficits on the WCST have been reported in patients with neurosurgical excisions of the frontal lobes (4,35,36) as well as in groups of patients with PD (5) and progressive supranuclear palsy (7). However, in addition to efficient set shifting, successful performance on this test requires a number of other distinct cognitive abilities not directly related to attentional set-shifting ability (for discussion, see ref. 19). These processes may not depend directly on frontal lobe mechanisms and may independently contribute to some of the deficits

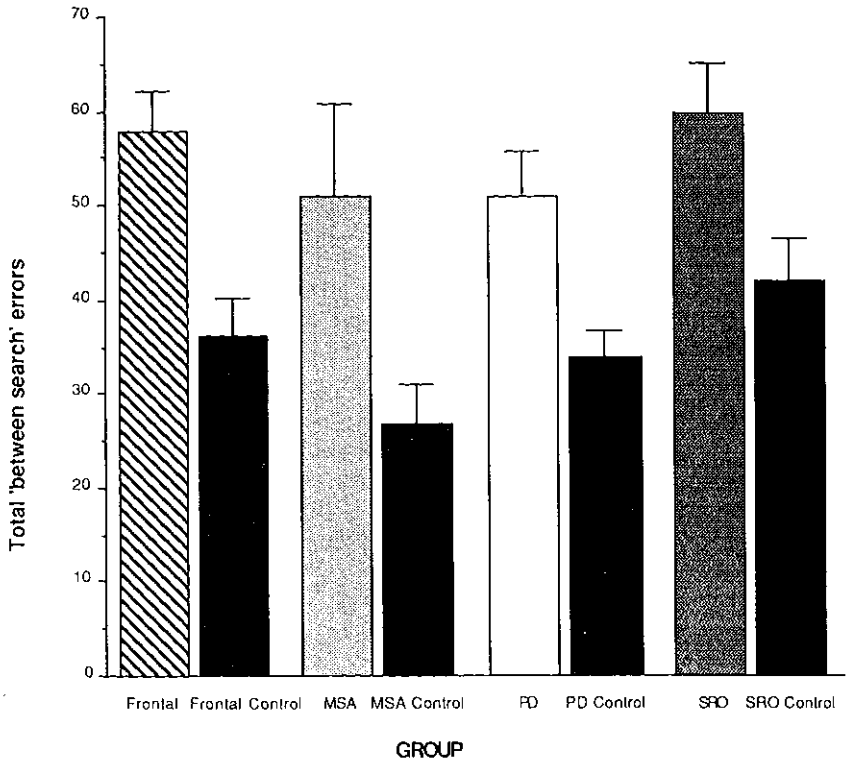

Fig. 4. Total between search errors on the spatial working memory task for frontal medicated, PD, SRO and MSA patients and their respective controls. The last three groups are matched for degree of clinical disability.

observed. For this reason, we devised a computerised test of attentional set shifting ability which helps to decompose the WCST into its constituent elements (fig. 1). The test was derived from the animal learning literature and based on the concepts of 'intra' and 'extra-dimensional' shifts. An 'intradimensional shift' (IDS) occurs when a subject is required to cease responding to one exemplar of a particular stimulus dimension (e.g. 'blue' from the dimension 'colour') and begin responding to a new exemplar of that same dimension (e.g. 'red'). An 'extra-dimensional shift' (EDS) occurs when the subject is required to switch responding to a novel exemplar of a previously irrelevant dimension (e.g. from 'red' to 'squares' from the dimension 'shape'). In this task, the subject was required to learn a series of discriminations in which one of two stimuli were correct and the other was not, using feedback provided automatically by the computer. The test was composed of nine stages presented in the same fixed order, beginning with a simple discrimination (SD) and reversal (SDR) for stimuli varying in only one dimension (i.e two white line configurations). A second, alternative dimension was then introduced (purple filled shapes) and compound discrimination (CD) and reversal (CDR) were tested. To succeed, subjects had to continue to respond to the previously relevant stimuli (i.e. white lines), ignoring the presence of the new, irrelevant dimension (shapes). At the IDS stage new exemplars were introduced from each of the two dimensions (new lines and new shapes) and subjects were required to transfer the previously learnt rule to a novel set of exemplars from the same stimulus dimension. Thus, to succeed, they had to continue to respond to one of the two exemplars from the previously relevant dimension (lines). Following another reversal of contingencies (IDR) the EDS and reversal (EDR) was presented and again, novel exemplars from each of the two dimensions were introduced. However, at this stage, the subject was required to shift 'response set' to the alternative (previously irrelevant) stimulus dimension and ignore the previously relevant dimension.

At each stage, a change in contingencies would occur once the subject had learnt the current rule to a criterion of six consecutive correct responses. The subject was only allowed to proceed to each successive stage of the test if they reached criterion at the previous stage. This permits a very clear method of analysing and presenting the main results (see fig. 5).

The frontal lobe patients were specifically impaired in their ability to shift response set to the previously irrelevant stimulus dimension (i.e. at the EDS stage of learning) but not to shift attention to new exemplars of a previously relevant dimension (i.e. at the IDS stage of learning) (34). By comparison, in terms of the number of subjects reaching criterion, the group of patients with temporal lobe excisions were unimpaired in their ability to perform either shift.

Of the three 'frontal lobe' tasks employed, only this test of attentional setshifting ability revealed significant deficits in all three groups of patients with PD (19,28). In fact, at the earlier stages of learning prior to the extradimensional shift, deficits were if anything, worst in the non-medicated groups of patients who had relatively mild clinical symptoms. Figure 5 shows the performance decrement in a group of patients with medicated PD matched for level of clinical diasability with the MSA and SRO conditions.

This test also proved to be particularly sensitive to deficits in the groups of patients with MSA and SRO. At the extra-dimensional shift stage of learning, the impairment in the MSA group was approximately equivalent to that seen in the frontal lobe patients (fig. 5). The rather more severe deficit at this stage, in the SRO group, resembled that observed in the

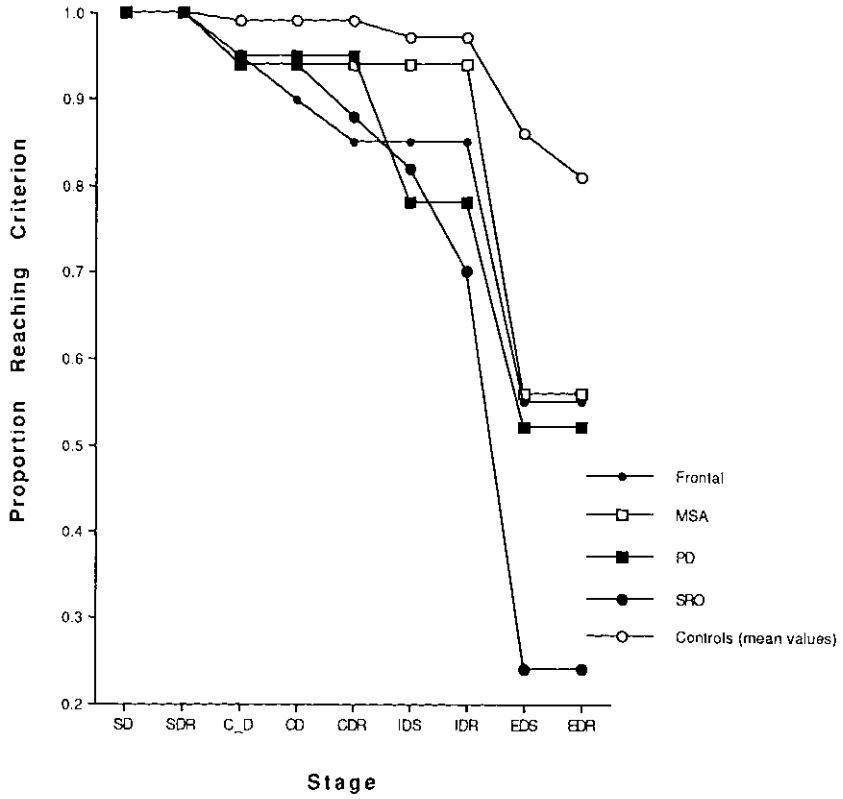

Fig. 5. Proportion of subjects successfully passing each stage of the attentional set-shifting task. For abbreviations see text. Frontal, PD (medicated), SRO and MSA patients are shown. The last three groups are matched for degree of clinical disability.

medicated PD patients with severe clinical symptoms who in fact, had a similar level of clinical disability.

The results of these studies clearly demonstrate that patients at different stages of PD can be differentiated both from each other, and from groups of patients with related parkinsonian syndromes on tests sensitive to frontal lobe damage. Both the SRO group and the MSA group were significantly impaired on all three tests of frontal lobe dysfunction although qualitative differences were observed between both groups and the frontal lobe patients. In contrast, the non-medicated PD patients with mild clinical symptoms are only impaired on one test of frontal lobe dysfunction, the attentional set-shifting task. The medicated PD patients (and in particular, those with more severe clinical symptoms) were impaired on all three tests sensitive to frontal lobe damage, although again the nature of these deficits differed in both the Tower of London planning test and in the test of spatial working memory. One obvious implication of this apparent 'progression' of cognitive impairments in the PD groups is that whilst those deficits which characterise early PD reflect a rather limited anatomical focus, more extensive regions of frontal-striatal circuitry become disrupted later in the course of the disease. Importantly however, the results may suggest a more general deterioration of cognitive abilities in the patients with severe PD including functions not usually associated with the frontal cortex.

We have recently investigated this hypothesis in the same groups of medicated and non-medicated patients at different stages of PD using a battery of computerised tests of visuo-spatial memory and learning. For comparison with the PD groups, we also assessed a group of patients with MSA (30) on these visuo-spatial memory tasks. Unfortunately, these tests, unlike the 'frontal lobe' battery, require relatively fine visual discriminations of colour and form which rendered any potential results from the SRO group, who had disturbed eye movements as a result of their neurodegenerative condition, rather difficult to interpret.

Pattern recognition memory was assessed by presenting subjects with a series of twelve coloured patterns, presented one at a time in the centre of the computer screen. After all twelve patterns, the subject was presented with twelve pairs of stimuli and, for each pair, was asked to indicate which pattern had been seen before. The test was then repeated a second time with new patterns. In an analogous test of spatial recognition memory, the subject was presented with a series of five white boxes located in different positions on the screen. After all five boxes, the subject was presented with five pairs of boxes and, for each pair, was asked to identify which of the two 'locations' had been seen before. The test was repeated three times with unique stimuli.

Our preliminary results suggest that performance on these tests of pattern and spatial recognition memory is more impaired following temporal lobectomy than following excisions of the frontal cortex (Owen et al, in

preparation). Moreover, whilst none of the three groups of patients with PD were impaired on the test of pattern recognition memory, in the spatial recognition memory task, deficits were clearly evident in the medicated patients with more severe clinical symptoms. In contrast, no impairments were observed in patients with MSA in either task (12).

A computerised simultaneous and delayed matching to sample paradigm was also employed to assess visual pattern recognition memory over a randomised series of 0, 4 and 12 second delays. Subjects were presented with a 'target' stimulus in the centre of the screen and were then asked to select the same pattern from among three distractor stimuli either simultaneously, or after a variable delay. Although all three groups of PD patients performed well in the simultaneous matching condition, impairments were observed in the medicated patients with severe clinical symptoms as soon as a short (0-12 second) delay was introduced. Our preliminary results with neurosurgical patients suggest a similar pattern of impairment following temporal lobectomy but not following frontal lobe excisions (Owen et al, in preparation). Paradoxically, the MSA group was significantly impaired in the simultaneous condition, but performed at control levels across delays (12).

In the final test, which required both visual pattern and visuo-spatial memory, subjects were required to remember and then learn the locations of up to eight different visual patterns on the screen. Task performance was assessed in terms of the number of patterns correctly placed after just one presentation (memory score) and the number of trials required to learn the locations of all the patterns (learning score). Our recent results suggest that performance on this test is affected by both frontal lobe damage and by lesions of the temporal lobe structures. Among the three PD groups, learning and memory deficits were only observed in those medicated patients with more severe clinical symptoms (37). Deficits were also observed in the MSA patients although unusually, these were only evident at the easiest, and not the hardest levels of task difficulty (12).

Table 1 summarises the results from this series of comparative series of studies of patients with PD and neurosurgical patients with localised frontal lobe damage. Where data are available, results are also given for patients with MSA and SRO.

THE PROGRESSION OF COGNITIVE DEFICITS IN PD

Taken together, the results of these studies have considerable significance for the staging of cognitive decline in patients with PD. There is an apparent increase in severity and a broadening of cognitive impairments as patients show increasing clinical disability. Because of the controlled nature and design of these tests, these deficits cannot simply be explained in terms of motor dysfunction. More likely, it appears that the cognitive impairments

Table 1.

	FRONTAL	NMED PD	MED PD (mild)	MED PD (severe)	MSA	SRO
SPATIAL WORKING MEMORY ('BETWEEN SEARCH' ERRORS)	✗	✓	✗	✗	✗	✗
MINIMUM MOVE SOLUTIONS (TOWER OF LONDON)	✗	✓	✓	✗	✓	✗
INITIAL THINKING TIME (TOWER OF LONDON)	✓	✓	✗	✗	✓	✗
SUBSEQUENT THINKING TIME (TOWER OF LONDON)	✗	✓	✓	✓	✗	✓
ATTENTIONAL SET SHIFTING	✗	✗	✗	✗	✗	✗
PATTERN RECOGNITION	✓	✓	✓	✓	✓	—
SPATIAL RECOGNITION	✓	✓	✓	✗	✓	—
DELAYED MATCHING TO SAMPLE	✓	✓	✓	✗	✓	—

✓ = UNIMPAIRED ✗ = IMPAIRED

progress in parallel with the motor deficits which characterise PD and may reflect differing forms of neuropathological involvement. The nonmedicated patients were impaired on only one task, the 'frontal lobe' test of attentional set-shifting ability and this may suggest a limited anatomical focus for the cognitive impairments occurring early in the course of PD. Importantly, this relatively specific deficit is not simply a function of test sensitivity since patients with mild dementia of the Alzheimer type successfully complete the task despite showing deficits in all the tests of visual memory function described above (38-40).

The medicated patients with mild clinical symptoms were impaired on all three tests of frontal lobe function, although the nature of these impairments was not identical to the deficits observed in patients with frontal lobe damage. This pattern contrasts markedly with the complete lack of deficits observed in this PD group in the four tests of visuo-spatial memory and learning. It may be argued that some of these 'frontal-like' deficits may be attributable to various aspects of medication since L-Dopa has previously been shown to affect cognitive performance in patients with PD (17). However, it is unlikely that dopaminergic medication disrupts performance on these tasks since we have recently demonstrated a marked deterioration of performance on all three tests of frontal lobe function following

controlled withdrawal of L-Dopa in patients with PD (16). Importantly, L-Dopa withdrawal had no effect on the visuo-spatial memory tests of pattern and spatial recognition memory, simultaneous and delayed matching to sample and visuo-spatial conditional associative learning.

The medicated patients with more severe clinical symptoms were also impaired on all three tests of frontal lobe dysfunction although in each case, the cognitive deficit was somewhat more severe than in the patients with more mild clinical disability. In addition, widespread impairments were observed in these patients in the tests of visuo-spatial memory which appear to rely more heavily on temporal, rather than frontal lobe structures. It is important to note that in the series of studies described here, all the PD patients included were clinically diagnosed as non-demented and were screened for dementia using both the Mini Mental State Examination (41) and the Kendrick Object Learning Test (42). In addition, the three groups of patients with PD could not be distinguished in terms of their performance on the test of pattern recognition memory, although significant deficits have been observed on this task in patients with mild and moderate dementia of the Alzheimer type (39,40). Clearly then, the emergence of widespread visual memory impairments in patients with severe PD does not simply reflect the neuropsychological manifestation of clinical dementia, as defined by standard clinical instruments. Similarly, whilst depression has been implicated in the cognitive profile of patients with PD (43), in the present series of studies, indices of depression correlated only with measures of motor, and not measures of cognitive performance.

In summary, examination of table 1 suggests that in PD, the late emergence of deficits in tests of delayed matching to sample and spatial recognition memory may reflect a relative sparing of functions associated with temporal lobe structures early in the course of the disease. This contrasts markedly with the relatively poor performance of these same PD patients in tests sensitive to frontal, but not temporal lobe damage. The results therefore suggest, that the cognitive deficits associated with PD emerge and subsequently progress according to a defined sequence which begins with frontal type deficits and only later includes more posterior cortical functions. This contrasts with the reverse pattern observed in dementia of the Alzheimer type (38,39,44) which corresponds to the typical progression of neuropathological signs in the cortex of these patients (44,45).

Although it has been possible to define a specific pattern of cognitive deterioration in patients with PD, the precise neurochemical nature or neural substrates of this progression remains a matter of some debate. One possibility, supported by recent anatomical and neuropathological evidence suggests that the sequence may be linked to what is known about the likely spatio-temporal progression of dopamine depletion within the striatum in relation to the terminal distribution of its cortical afferents. In particular,

several recent studies have demonstrated that although both the temporal and frontal cortices project strongly to the head of the caudate nucleus, inferotemporal cortex (area TE) tends mainly to innervate more posterior regions within this structure whilst the prefrontal cortex tends to innervate more rostral areas (46-48). In PD, dopamine depletion is significantly greater in the most rostral extent of the head of the caudate compared to its caudal limits (49) suggesting perhaps, that the more rostral regions are subjected to greater disruption by the disease and probably at an earlier stage of its progression. This may concur with the present findings that tests of visuo-spatial recognition memory, which are more sensitive indicators of temporal lobe dysfunction than frontal lobe dysfunction, are relatively preserved early in the course of PD. However, two alternative hypotheses should considered. First, it is possible that the deficits of visual memory and learning that accompany severe PD might be related to non-dopaminergic (and hence, probably non-striatal) forms of pathology, for example in the cortical deafferentiation of noradrenergic, cholinergic and serotoninergic neurotransmitter systems (50). Cortical Lewy bodies which are most evident later in the course of PD, may also be implicated (51,52). Our finding that L-Dopa withdrawal did not affect performance on tests of visuo-spatial memory and learning (16) certainly suggests that one or more of these alternative forms of pathology may be responsible for those deficits which emerge only late in the course of PD.

Second, whilst the caudate nucleus remains the most obvious neural candidate for those 'frontal' cognitive impairments which are significantly affected by L-Dopa withdrawal, these effects may also be mediated by damage to the mesocortical dopamine projections in PD (20). However, in marmosets, prefrontal dopamine depletion leads to enhanced performance at the extra-dimensional shift stage when tested on an identical attentional setshifting paradigm to that used in the patient experiments described above. This apparent improvement in function most likely reflects the associated up-regulation of striatal dopaminergic function observed in the same animals (53). These results certainly implicate the dopamine dependent functions of the striatum in the relatively specific deficits in attentional set-shifting ability observed early in the course of PD.

THE COMPARATIVE NEUROPSYCHOLOGY OF PD, MSA AND SRO

Table 1 demonstrates that groups of patients with different basal ganglia conditions may be clearly differentiated in terms of their performance on tests known to be sensitive to frontal lobe damage in man. The patient groups with MSA, SRO and PD (severe) were well matched in terms of their clinical disability according to the Hoehn and Yahr rating scale. However, cognitively, minor qualitative differences were found between the groups in terms of their neuropsychological test performance.

The pattern of cognitive impairment in patients with MSA was, if anything, more similar to the pattern observed in patients with localised frontal lobe damage than to the matched group of medicated PD patients with severe clinical symptoms. Thus, like the frontal lobe group, the MSA patients exhibited a significant increase in subsequent thinking time, but not initial thinking time in the Tower of London test of planning although this impairment was not accompanied by a 'frontal-like' deficit in performance accuracy. On the spatial working memory task, the MSA patients made significantly more 'between search errors' to a similar degree as the frontal lobe group although they did not show the same impairment in strategy observed in that group. In addition, in the attentional set-shifting paradigm, the performance of the MSA patients was both qualitatively and quantitatively similar to the frontal lobe group. Finally, there was no evidence of impaired performance on tests of pattern and spatial recognition memory which appear to be more sensitive to temporal than frontal lobe lesions (Owen et al, in preparation). Importantly, deficits in the pattern recognition task were observed in the matched group of PD patients and both recognition memory tests have previously been shown to be sensitive to early dementia of the Alzheimer type (39). The MSA group did show minor impairments in the other tests of visuo-spatial memory and learning, although these deficits were quite distinct qualitatively, from those seen either in medicated patients with severe PD or in patients with Alzheimer's disease (39). None of the major cognitive deficits in the MSA group were significantly correlated with disease duration or Hoehn and Yahr ratings of disease severity and only three of the sixteen patients in this group had significant premorbid (estimated) versus current verbal IQ discrepancies. Taken together, these results are in complete agreement with the clinical impression that MSA is not characterised by a progressive dementing condition (11,54,55).

Compared to the MSA group, the performance of patients with SRO was rather more similar to the group of medicated PD patients with severe clinical symptoms. Thus, like the PD group, the SRO patients exhibited a significant increase in initial thinking time, but not subsequent thinking time in the Tower of London test of planning and this impairment was accompanied by a 'frontal-like' deficit in performance accuracy. It is possible that the lengthened initial thinking time observed in these two conditions reflects the clinical concept of bradyphrenia, as slowing of thought processes have been considered to be a prominent feature of both PD, and particularly SRO and we have discussed this possibility in some detail elsewhere (28,56). Our results strongly suggest that when sensorimotor disabilities are controlled for, in matched groups of patients with PD and SRO, there is no quantitative difference in this 'thinking time' impairment. The SRO patients also made significantly more 'between search errors' on the spatial working memory task and, like frontal lobe patients, this deficit

was found to relate directly to the inappropriate use of a repetitive searching strategy. Finally, in the attentional set-shifting paradigm, the performance of this patient group was if anything, more severe than that seen in the matched group of medicated patients with PD. This result is particularly important because it cannot be attributed to disturbed eye movements in the SRO group as the stimulus dimensions for the discrimination of the compound stimuli were superimposed and the time factor was not relevant to performance. In general, these results from the patients with SRO support the findings of other investigators (57,58) although there are some differences of detail and interpretation.

In summary, all three of the basal ganglia conditions assessed in this series of studies exhibited deficits on tests of frontal lobe dysfunction. This gross similarity in cognitive performance contrasts with the obvious clinical differences associated with these disorders but may indicate a common, fundamental syndrome of cognitive dysfunction. The PD patients with severe clinical disability also showed significant impairments on several of the 'nonfrontal' tests of visuo-spatial memory and learning although there was little consistent evidence of such deficits in MSA. This clearly suggests that the cognitive deficits in PD are broader in nature than those in MSA, when patients are matched for the degree of clinical disability. Importantly, in either condition, the pattern of cognitive impairment does not simply reflect a global deterioration of intellectual function since quite different patterns are observed in patients with dementia of the Alzheimer type. For example, the attentional set-shifting task which has proved so sensitive to deficits in all three basal ganglia disorders is relatively insensitive to impairment early in the course of Alzheimer's disease (39). This clearly suggests that this capacity is compromised relatively specifically, in patients with frontal or basal ganglia dysfunction and may therefore be dependent on the integrity of the functional neural loops which connect the basal ganglia with the frontal cortex (59). Moreover, the fact that there were subtle qualitative differences between the patterns of deficit observed in the frontal lobe and basal ganglia groups raises the possibility that the cognitive sequelae of frontal lobe damage or striatal dysfunction may be differentiated using the same tests. For example, whilst the spatial working memory impairment observed in the patients with PD and MSA could not be related directly to the inappropriate use of a particular searching strategy, deficits in the use of such a strategy were found in both the SRO patients and the frontal lobe group. This clearly suggests that the contributions of both mnemonic and 'executive' factors may be differentiated using this task and more importantly, that they may be differentially affected in basal ganglia conditions.

Certain analogies may be drawn between the pattern of cognitive deficits observed in these three basal ganglia conditions and the syndrome of 'subcortical dementia'. This syndrome is said to subsume the cognitive and

behavioral deficits shown by patients with pathology of the basal ganglia and other subcortical structures and is quite distinct from the 'cortical' dementia observed for example, in patients with Alzheimer's disease. Our results certainly support the distinction between the cognitive profile of patients with PD, SRO and MSA on one hand and early Alzheimer's disease on the other. However, given the obvious similarity between the cognitive performance of these basal ganglia disorders and the group of patients with localised frontal lobe damage, 'fronto-striatal' syndrome may be a more appropriate term.

In conclusion, this approach of drawing comparisons between neurosurgical populations and patients with PD and other basal ganglia disorders has been a profitable one in terms of establishing the likely neural and neurochemical substrates of cognitive impairment in these neurodegenerative conditions. In addition however, the distinctions drawn between these disorders are possibly useful in establishing separable contributions of the prefrontal cortex and the striatum to performance on 'frontal lobe' tests and in turn, may help to unravel the functional significance of each of these systems in the co-ordinated operation of cortico-striatal circuitry (59).

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