

## The neuropsychology of basal ganglia disorders: an integrative cognitive and comparative approach

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### Introduction

Over the last 30 years or so it has been realised that Parkinson's disease (PD) and other basal ganglia disorders such as Huntington's disease (HD), Steele-Richardson-Olzewski (SRO) syndrome and the recently characterised multiple system atrophy (MSA) are indeed associated with a quite well-defined profile of intellectual impairment, even in the earliest stages of the disease. The existence of dementia in the later stages of Parkinson's and Huntington's diseases has now largely been accepted (Brown and Marsden, 1988; Brandt and Bylsma, 1993), although its exact neural and neuropathological basis remains a matter for debate (see Quinn, 1993). These dementing signs could be attributed to additional pathology, distinct from the primary pathology of the nigro-striatal dopamine pathway in PD, for example, to degeneration of the basal fore-brain or locus ceruleus, or to cortical Lewy bodies (see Agid *et al.*, 1987; Quinn, 1993). In the case of Huntington's disease, it is still unclear just how much of the cognitive impairment can be attributed to striatal degeneration, as distinct from cortical atrophy (see e.g. Starkstein *et al.*, 1992).

Part of the initial reluctance to accept that PD and other conditions have their own collection of cognitive deficits may have stemmed from the prejudice that the basal ganglia are essentially structures with motor functions, notwithstanding early far-sighted theoretical speculations and findings to the contrary (e.g. Hassler, 1978; Divac, Rosvold and Szwarcbart, 1967). Part may have rested on the occasionally well-founded suspicions of confounding measurement of cognitive abilities by the complications of co-existing depression and motor dysfunction (see Marsden, 1980, 1981; and the commentaries by Cools *et al.*, 1981 and Oberg and Divac, 1981).

Increasing sophistication of neuropsychological assessment and a better understanding of functional neuroanatomy have led to a marked reappraisal of the status of cognitive deficits in basal ganglia disease. The accumulation of knowledge about the neuroanatomical organisation of the basal ganglia, largely from animal studies, has prompted new hypotheses about the nature and neural substrates of cognitive deficits in these conditions. For example, on the basis of anatomical, neurophysiological and behavioural evidence, the concept of cortico-striatal loops has evolved, which emphasises the functional inter-relationships between the neocortex and striatum (Alexander, DeLong and Strick, 1986). Of particular note is the fact that the prime target of basal ganglia outflow appears to be the frontal lobes, whether to the premotor regions such as the supplementary motor area, or to discrete regions of the prefrontal cortex, such as dorso-lateral prefrontal cortex or orbito-frontal cortex, which receive projections from different loops involving different sectors of the caudate nucleus (see Figure 3.1).

These anatomical facts are compatible with some of the earliest theories of cognitive deficits following basal ganglia malfunction that lumped them together with a diverse collection of other conditions, including hydrocephalus and multiple sclerosis, under the heading 'subcortical dementia' – to differentiate them from the more obviously 'cortical' dementia of Alzheimer's disease (Albert, Feldman and Willis, 1974; McHugh and Folstein, 1975; Cummings and Benson, 1984). The major features of subcortical dementia, of which Steele–Richardson's syndrome (i.e. progressive supranuclear palsy) was a prototypical form, included impaired mood and motivation, altered personality, specific forms of memory disturbance, slowed thinking and impaired reasoning, that were reminiscent of some of the executive deficits produced by frontal lobe damage. In the case of the basal ganglia deficits at least, the revised term 'fronto-subcortical' dementia could readily be reinterpreted as 'fronto-striatal dementia', on the basis of the new anatomical findings. However, relating specific deficits in PD to, say, its non-striatal chemical pathology, to striatal or cortical dopamine loss, or even to medication with L-dopa, has been extremely difficult, just as it has been to decide which of the cognitive features of HD are associated with striatal degeneration and which to cortical atrophy (Brandt and Bylsma, 1993). This chapter summarises the progress made in understanding the cognitive and neural nature of the cognitive deficits in basal ganglia disease, and describes our own strategy of utilising studies from non-human primates in order better to understand these deficits.

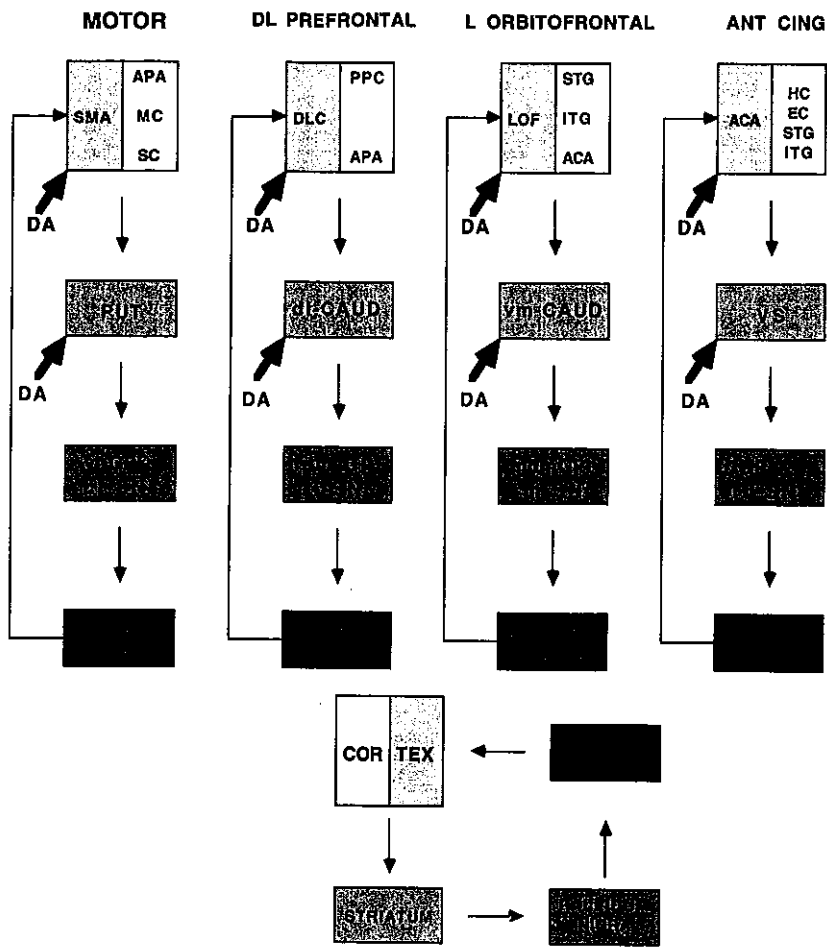


Figure 3.1. Cortico-striatal 'loops' according to the scheme of Alexander *et al.*, 1986. Note DA innervation at both the cortical and striatal levels, indicated by thick black arrows. Those cortical structures innervating the striatum are shown at the top of the diagram. The 'loop' only projects back to a restricted subset of those structures, all of which are in the frontal lobe. Abbreviations: ACA, anterior cingulate region; APA, arcuate premotor area; CAUD, caudate nucleus; DLC, dorsolateral prefrontal cortex; EC, entorhinal gyrus; GPi, internal segment of the globus pallidus; HC, hippocampus; ITG, inferior temporal gyrus; LOF, lateral orbitofrontal cortex; MC, motor cortex; MDmc, medialis dorsalis, pars magnocellularis; MD, pc, medialis dorsalis, pars parvocellularis; PPC, posterior parietal cortex; PUT, putamen; SC, somatosensory cortex; SMA, supplementary motor cortex; SNr, substantia nigra, pars reticularis; STG, superior temporal gyrus; VAmc, ventralis anterior, pars magnocellularis; VA, pc, ventralis anterior, pars parvocellularis; VL, pm, ventralis lateralis, pars medialis; VL, po, ventralis lateralis, pars oralis; VP, ventral pallidum; VS, ventral striatum; cl, caudolateral; dl-, dorsolateral; l-, lateral; ldm-, lateral dorsomedial; m-, medial; mdm-, medial dorsomedial; pm-, posteromedial; rd-, rostrorodorsal; rl-, rostromedial; rm-, rostromedial; vm-, ventromedial; vl-, ventrolateral. The bottom diagram indicates the general organisation of the cortico-striatal-pallidal-thalamic loop.

### Origins of the frontal-executive theory of cognitive deficits in basal ganglia disorders

While there is an extensive literature on visuospatial and memory deficits in PD, HD and SRO, much of this can be assimilated to the existence of a specific pattern of deficits that can be related to executive dysfunction. For example, deficits in free recall and conditional learning occur more readily than those in recognition memory (Talland, 1962; Weingartner, Burns and Lewitt, 1984; Moss *et al.*, 1986; Taylor, Saint-Cyr and Lang, 1990; see Brandt and Bylsma, 1993 for a review), and there are severe impairments in certain forms of short-term memory, exemplified especially by the Brown-Petersen test, which are often associated with 'frontal' memory deficits (Sagar *et al.*, 1988; Cooper *et al.*, 1991). Moreover, isolating specific impairments in visuospatial function from such executive requirements as planning, sequencing and attentional set-shifting has been difficult, if not impossible.

Bowen (1976) was one of the first investigators to provide specific information on 'frontal' deficits in PD from studies of the Wisconsin Card Sorting Test (WCST), a traditional means of assessing 'frontal' dysfunction. This classic study was followed by several research initiatives. The first of these was published as a paper in *Brain* in 1986 entitled 'Frontal lobe dysfunction in Parkinson's disease' (Taylor, Saint-Cyr and Lang, 1986). This paper used a number of tests with putative frontal components to test PD patients at several stages of the disease. The tests included not only the WCST, but also the 'Tower of Toronto', related to the well-known Tower of Hanoi, in order to assess planning function, as well as a number of tests of short-term memory. On the basis of results using these tests the authors asserted that the inability to elaborate efficient strategies spontaneously or use internally guided behaviours may explain recall and problem-solving deficits in PD (see also Saint-Cyr, Taylor and Lang, 1988; Taylor *et al.*, 1990). The second approach was derived from a cognitive theory that emphasised the utilisation of processing resources and the internal regulation of attention, in both of which PD patients were found to be deficient (e.g. Brown and Marsden, 1988b, 1991; Brown, 1993). The third approach capitalized on the poor performance of PD patients on the WCST first described by Bowen *et al.* (1975), even when unmedicated and early in the course of the disease (Lees and Smith, 1983; Canavan *et al.*, 1989). These deficits are generally categorised as reflecting impairments of set-formation, maintenance and, especially, set-shifting ability, and have now been observed by a number of other investigators in different forms, sometimes with test material not

directly related to the WCST (e.g. Cools *et al.*, 1984; Flowers and Robertson, 1985; Downes *et al.*, 1989; Downes *et al.*, 1993; Channon, Jones and Stephenson, 1993). A third perspective was obtained by longitudinal studies using well-established neuropsychological forms of assessment that suggested specific impairments in PD in temporal sequencing on a subtest of WAIS that can be interpreted as reflecting executive deficits (Cooper *et al.*, 1991).

Despite this emphasis on the 'frontal' hypothesis, there has been relatively little direct comparison of those cognitive deficits observed in PD with impairments present in frontal lobe damaged patients within the same study. Moreover, the specificity of deficits seen has seldom also been tested with appropriate comparisons in other relevant groups such as neurosurgical cases of temporal lobe ablation and early cases of dementia of the Alzheimer type. In the latter case, it is particularly important to focus on the performance of patients early in the course of Parkinson's disease, prior to medication. There is a similar dearth of parametric comparisons with other basal ganglia conditions, particularly Huntington's disease and the SRO syndrome (c.f. Brown and Marsden, 1988a). In the case of the former, there has been considerable interest in the comparison with organic amnesia, in the context of dissociations of different memory systems, for example for 'declarative' and 'procedural' memory (as assessed by pursuit rotor tasks or by performance on the 'procedural' aspects of Tower of Hanoi performance) (see Brandt and Bylsma, 1993). However, while it has been pointed out that the 'executive' aspects of the intellectual deficit in HD contribute importantly to everyday disability (e.g. Bamford *et al.*, 1989), there has been little formal assessment of the executive problems afflicting patients with this disease, especially early in its course. A few major clinically oriented analyses and surveys have revealed that SRO patients fail classical tests of frontal lobe function such as the Wisconsin Card Sorting Test and verbal fluency, and exhibit frontal lobe 'signs', including enhanced grasp reflexes, motor impersistence and utilisation behaviour. Two studies have shown that, when matched for age and severity of intellectual deterioration, the SRO patients perform worse than PD groups on such tests of frontal lobe dysfunction (Pillon *et al.*, 1986; Dubois *et al.*, 1988). On the other hand, one study has claimed that SRO patients are relatively intact on tests of problem-solving, a classic form of frontal lobe dysfunction (Grafman *et al.*, 1990). Clearly again there is much to be gained from a detailed neuropsychological comparison of basal ganglia disorders with patients with frontal lobe damage.

### **An integrated cognitive neuroscientific approach**

Our own approach has attempted to integrate the cognitive, neuropsychological and neurobiological approaches by using tests or collections of tests that can be theoretically decomposed into their constituent elements at a cognitive level, and which make connections with important animal neuropsychological studies. The latter serve to localise at a neural level elements of executive control that are presumably present in more elaborate forms in humans. The great advantage of animal studies is that it is possible to make highly specific neural or neurochemical interventions to isolate a fraction of the complex patterns of pathology that make difficult the analysis of basal ganglia disorders. Their main disadvantage is the difficulty of relating behavioural deficits in animals to cognitive deficits in man. Thus, it is admittedly difficult to model planning deficits in man that entail the relative evaluation of efficacy of sequences of mental responses in relation to specific goals or outcomes. However, many of the elements of planning can be defined and measured separately; for example, the working memory load, the capacity to sequence responses and to shift set on the basis of reward and the ability to respond according to conditional rules have each been addressed by primate neuropsychological studies, and are included in our own battery of tests for monkeys and human patients (CANTAB) (see Sahakian and Owen, 1992; Roberts and Sahakian 1993; Robbins *et al.*, 1994a).

### **Experimental tests of planning function**

Nevertheless, the impetus for one of our main tests for patients was born from a cognitive theory which suggested that a major aspect of executive function was attention to action, especially in novel behavioural circumstances that require planning. The 'Tower of London' test was modified by Shallice and McCarthy (Shallice, 1982) from the earlier Tower of Hanoi puzzle to stress the capacity for mental planning with only a single goal outcome specified. The usual form of the four-disc Tower of Hanoi requires the subject to sort the four discs according to their size from one vertical peg to another in a precise configuration. But this generally requires repeated trials and the subject essentially has to learn the very long effective sequences of responses on a trial and error basis more reminiscent of procedural learning routines than of mental planning, in which the subject visualises the various candidate solutions in advance before selecting the most efficacious one. This confounding between the procedural and executive aspects of problem solving can potentially confuse attempts to

isolate 'frontal' deficits, especially when the basal ganglia are often implicated in procedural aspects of memory.

Thus, modified versions of the Tower of London test were developed to compare planning ability in patients with localised frontal lobe excisions and patients with PD, SRO, MSA and, most recently, patients at different stages of HD. In one of the computerised tasks 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 (Figure 3.2a). The test incorporated 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. The degree of planning required 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 efficiency of planning, as measured by the excess moves used beyond the minimum specified, provide measures of the efficiency of planning. In two versions of the test the relative contributions of initial and subsequent 'thinking' or planning time during the execution of the solution have also been the main performance indices. As the time taken to complete the task was to some extent dependent on movement (i.e. 'motor') time, and basal ganglia damaged patients may be expected to have several disabling forms of motor impediment, 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 (Owen *et al.*, 1990) both confirmed and extended findings of Shallice (1982) using the original 'pegs and beads' version of the test that showed impairments in a group of patients with 'anterior' cortical damage. Although patients with localised frontal lobe excisions completed 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 premorbid verbal IQ, consequently producing fewer (perfect) minimum move solutions. In addition, although the two groups did not differ in the amount of time spent thinking prior to the first move (Figure 3.3), 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 for cortical frontal lesions since no deficits are observed in neurosurgical patients with temporal lobe damage (Owen *et al.*, 1995a).

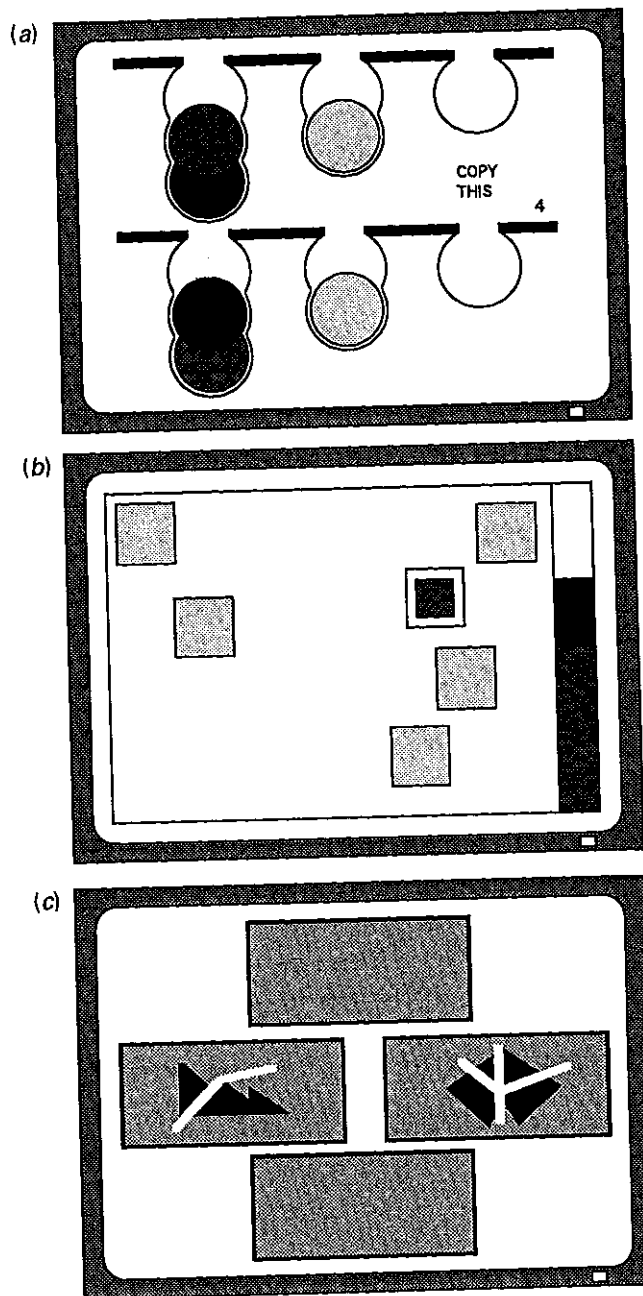


Figure 3.2. The three major computerised neuropsychological tests shown to be sensitive to frontal lobe dysfunction: (a) Tower of London; (b) Spatial Working Memory; (c) Attentional set-shifting (ID/ED test). This shows the general nature



A parallel study of patients with PD (Owen *et al.*, 1992) 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 planning. 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). 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 was impaired in terms of subsequent 'thinking' time. No impairments were observed in a third group of PD patients who were non-medicated and had relatively mild clinical symptoms. These results indicate that whereas a prominent test of frontal function, the Tower of London test of planning, is quite sensitive to cognitive impairment in PD, the qualitative nature of the deficits appears to be different. The slowed 'initial thinking time' seen in PD was not prominent following frontal lobe damage, and yet is consistent with the cognitive deficits of 'sub-cortical' dementia and the clinical symptom of 'bradyphrenia'. Detailed consideration of its cognitive basis is beyond our present scope (see discussion in Owen *et al.*, 1992 and Morris *et al.*, 1988). However, it seems likely that it can be related quite directly to the dopaminergic deficit in PD, as it was severely exacerbated by L-dopa withdrawal (Lange *et al.*, 1992). Only with severe clinical disability was the 'frontal' pattern of inaccurate solutions evident. Therefore, it appears that the Tower of London deficits in PD show qualitatively distinct features from those seen following frontal lobe damage, which might reflect differences in the operation of different nodes in the fronto-striatal loops (see Figure 3.1) and in their neurochemical modulation.

The comparison between frontal and PD patients has recently been extended using a version of the task that minimises the motor requirement and is amenable to activation paradigms using PET, which confirm a frontal involvement (Owen *et al.*, 1995b; Baker *et al.*, 1996). This task does not inform the subjects how many moves are required to solve the problems, requiring them to estimate this instead. This difference not only

Caption for Fig. 3.2 (*cont.*)

and presentation of the pairs of stimuli, which can be composed of any combination of elements of the two dimensions (i.e. lines and shapes). The presentation of the IDS (intra-dimensional shift) and EDS (extra-dimensional shift) stages is preceded by a series of simple tests of simple and compound discrimination learning and reversal. The subject proceeds from one stage to the next by reaching a criterion of 6/6 correct within 50 trials. See text for details, Figure 3.5 for data at the IDS and EDS stages and Figure 3.6 for data showing general performance across stages for clinical groups and controls.

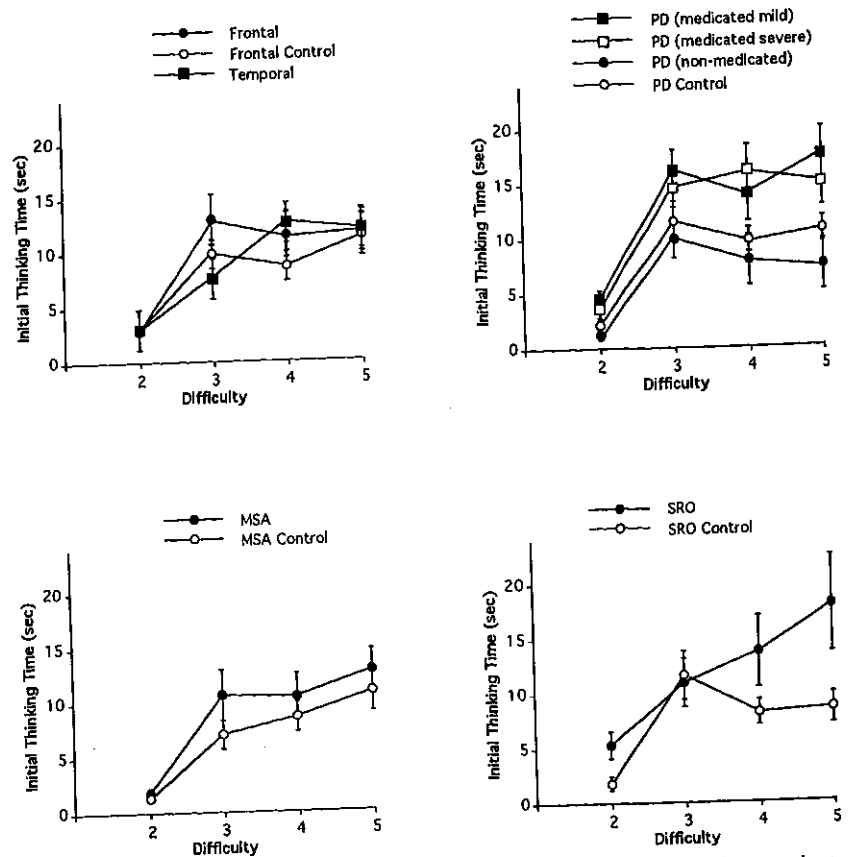


Figure 3.3. Initial thinking time on the Tower of London test for various patient groups with cortical excisions or basal ganglia degeneration, compared to age- and IQ-matched control groups. PD, Parkinson's disease; MSA, multiple system atrophy (of striato-nigral predominance); SRO, Steele-Richardson-Olzewski syndrome (see Owen *et al.*, 1991, 1992, 1995a; Robbins *et al.*, 1994b).

makes the task more difficult, but also results in a monotonic increase in thinking time as a function of the number of moves. It is significant that a deficit in unmedicated, early-in-the-course PD patients emerges under these conditions.

Contrasting patterns of impairment on the earlier planning task in which the problems are produced move by move 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 (Robbins *et al.*, 1994b). Thus, like the medicated patients with PD, the 18 SRO patients were significantly impaired in terms

of their initial thinking time (Figure 3.3) (though not in terms of their subsequent thinking time), and showed a significant decrease in the number of minimum move, or 'perfect' solutions. In contrast with the performance of PD patients, but like the patients with frontal lobe damage, the 16 patients with MSA exhibited significantly prolonged subsequent, but not initial thinking times (Figure 3.3) although this deficit was not accompanied by any significant impairment in performance accuracy.

Another pattern of disability on the same version of the Tower of London test that specifies the number of moves needed to solve the problem and requires their actual enactment, is evident from a recent comparison of performance of patients with relatively late-stage HD with dementia of Alzheimer's type, matched for overall level of dementia, as assessed by the Mini-Mental State examination (Lange *et al.*, 1995). Perhaps surprisingly, the HD patients performed significantly worse in terms of accuracy of planning, although the result is entirely consistent with the hypothesis that there are distinct patterns of deficit in dementia. However, neither group was able to attempt the most difficult problems and it could be conjectured that planning as such was impossible for both. Their partially successful performance on the easier problems might have reflected some of the more automatic features of 'planning' arising from a rapid perceptual identification of the various possibilities, analogous to the 'schema' postulated by Shallice and Norman (see Shallice, 1982), and it is this aspect of performance that appeared to be differentially disrupted in HD. Thus, again it appears that while the basal ganglia damaged patients show impairments on a 'frontal' test of cognitive function, there appear to be major *qualitative* differences in the nature of the deficits between such patients and those with frontal lobe damage that cannot easily be ascribed to the stage of the disease and general intellectual deterioration, and suggest instead that the basal ganglia fulfil quite specific functions within the context of tests of executive function.

#### **Fractionation of component cognitive abilities**

The above analysis shows that impaired performance in the Tower of London test may be profitably considered further in terms of the component processes required for accurate planning. For example, given the importance of attentional 'set' for efficient problem solving, the ability to shift between competing possibilities may play a crucial role in the final selection of the most appropriate solution. Consistent with this possibility, Wallesch, Karnath and Zimmerman (1992) found that the performance of

Parkinson's disease patients in a 'covered' maze, presented on a computer screen was markedly disrupted by problems of response shifting; the nature of this deficit contrasted rather sharply with that of patients with frontal lobe excisions, as we would have predicted on the basis of our analysis of the Tower of London task. Cronin-Golomb, Corkin and Growdon (1994) have recently also argued this point in the case of a rather different form of problem solving in patients with PD.

Another possibility is that the planning 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 fact, a recent large-scale analysis of Tower of London performance has confirmed that the test loads significantly with tests of spatial working memory in factor analyses, which reveal an unprecedentedly high degree of intercorrelation for tests of frontal lobe function (Owen *et al.*, 1992; Robbins *et al.*, 1997).

#### *(i) Spatial working memory*

The spatial working memory task is essentially a modification of one used by Passingham to examine the effects of dorsolateral prefrontal cortex lesions in primates (Passingham, 1985) and conceptually similar to the 'radial arm maze', which has been successfully used to assess the role of the hippocampus in working memory in rats (Olton, Becker and Handelman, 1979). The test is open-ended in the sense that the subject is free to produce his or her own 'self-ordered' sequences of responses.

In our version of the task, adapted for humans, subjects were required to 'search through' a number of red boxes presented on the computer screen (by touching each one) in order to find blue 'tokens' that were hidden inside (Figure 3.2b). 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 (Figure 3.4), making more returns to boxes ('between search' errors) in which a token had previously been found, at all levels of task difficulty as determined by the number of boxes employed (2, 3, 4, 6 or 8). In addition, these patients were shown to be less proficient in the use of a searching strategy known to improve performance on this task. This strategy retraced previous 'routes' while 'editing' them to exclude previously successful locations. This strategic impairment suggested that at least some of the frontal impairment in spatial

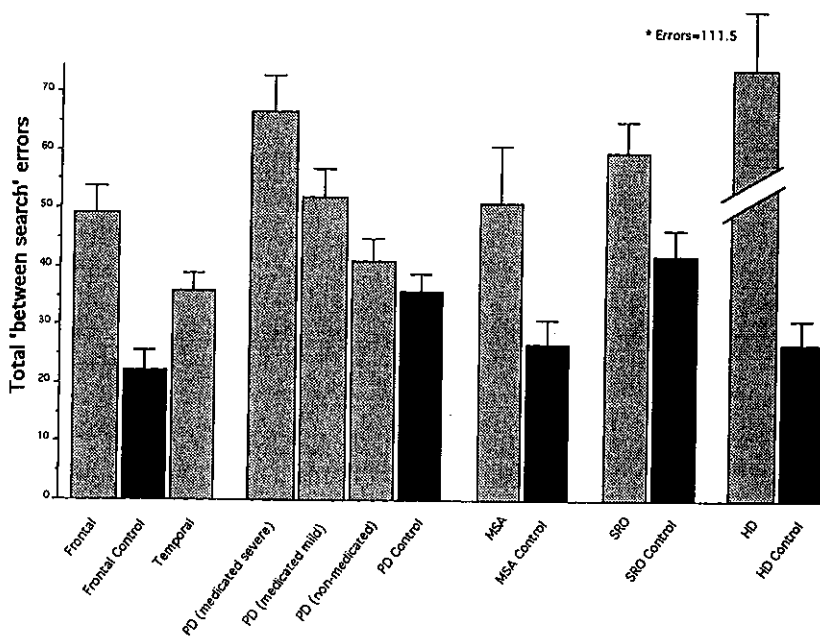


Figure 3.4. Performance on the spatial working memory test, as measured by between search errors. PD, Parkinson's disease; HD, Huntington's disease; MSA multiple system atrophy (of striato-nigral predominance); SRO, Steele-Richardson-Olzewski syndrome. Data taken from Owen *et al.*, 1992, 1995a; Robbins *et al.*, 1994. The HD group were relatively late in the course of disease (see Lange *et al.*, 1995).

working memory arises secondarily from a more fundamental deficit in the use of organisational strategies. 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 the frontal lobe patients, however, the temporal lobe group utilises a normal and effective searching strategy (Owen *et al.*, 1995a). This test therefore has fundamental mnemonic requirements that interact powerfully with strategic factors, thus requiring the co-ordination of posterior cortical capacities with the executive functions of more anterior zones. As such, the task provides an intriguing challenge for patients with basal ganglia deficits who could be expected to be impaired on the basis either of deficient processing of information carried by temporal lobe afferents to the basal ganglia or by connections to the frontal lobes.

We have found that tests sensitive to temporal, but not frontal lobe damage, such as the capacity to recognise briefly presented patterns, are only sensitive to deficit in PD with severe clinical disability, who are presumably late in the course of the disease. When these deficits in pattern

recognition occur, they are also not exacerbated by L-dopa withdrawal (Lange *et al.*, 1992). These observations suggest that the nature of the profile of cognitive deficits in PD is quite distinct from that of Alzheimer's disease, and that tests sensitive to frontal lobe damage are generally also sensitive to deficits in relatively early-in-the-course PD, although the nature of these deficits may not be identical.

In support of the view that patients with basal ganglia disease have a qualitatively distinct cognitive profile of deficits to those of Alzheimer's disease, it has been shown recently that patients with advanced HD are certainly much more severely impaired on the spatial working memory task than those with DAT; indeed the HD group deficit is as great as any we have observed following frontal lesions (Lange *et al.*, 1995 – see Figure 3.4). It seems likely that it results from a combination of memory and strategic deficits. Among 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. Non-medicated patients with PD were unimpaired on this task (Owen *et al.*, 1992), but medicated PD patients with either mild or severe clinical disability showed significant impairment.

The spatial working memory task also proved to be most sensitive to deficits in patients with MSA and SRO (Figure 3.4). Both groups were significantly impaired in terms of the number of returns to boxes in which a token had previously been found. 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 (though not in the MSA) patients (Robbins *et al.*, 1994b).

This form of self-ordered spatial working memory test is known to depend on the integrity of prefrontal lobe function in monkeys, but has not been studied specifically in terms of neurochemical mechanisms within the frontal cortex or via its connections with the basal ganglia. Much better understood is the simpler delayed response task, a test of short-term spatial memory that can be made using either limb movements or delayed saccades (c.f. Goldman-Rakic, 1990). The delayed response task similarly depends on the dorsolateral prefrontal cortex, on the basis of behavioural, electrophysiological and metabolic evidence (Goldman-Rakic, 1990). Some evidence also argues for a role for dopamine D1 receptors (Goldman-Rakic, 1992) and adrenergic alpha-2 receptors (the latter in aged primates, Arnsten, Cai and Goldman-Rakic, 1988). In terms of the basal ganglia,

classical studies found that radiofrequency lesions aimed at that region of the head of the caudate nucleus in monkeys that is known to be part of the 'dorsolateral prefrontal cortex loop' in purely anatomical terms (see Figure 3.1) impaired the ability to perform the task, though not as severely as damage to the prefrontal cortex itself (Battig, Rosvold and Mishkin, 1960, 1962). Recent studies have shown that MPTP-treated monkeys resulting in profound striatal dopamine depletion exhibit delayed response deficits (Schneider and Kovelowski, 1990). Therefore, there is a clear anatomical substrate for this type of task that makes it susceptible to striatal, as well as frontal lobe damage. There is considerable evidence for a contribution to inefficient spatial working memory performance in PD, as our study of the effects of controlled L-dopa withdrawal in a small group of patients with marked clinical disability showed a significant further deterioration of performance (Lange *et al.*, 1992). However, the locus of this effect (i.e. frontal or striatal) remains unknown.

### (ii) Attentional set-shifting

The third paradigm designed to assess frontal lobe dysfunction in PD was based on similar principles to the Wisconsin Card Sorting Test (WCST), the classic index of frontal lobe dysfunction (Milner, 1963) used in so many of the previous studies of basal ganglia patients. 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 Downes *et al.*, 1989). These processes may not depend directly on frontal lobe mechanisms and may independently contribute to some of the deficits observed. For this reason, we devised a computerised test of attentional set-shifting ability, which helps to decompose the WCST into its constituent elements (Figure 3.2c). The test was derived from the animal learning literature and based on the concepts of 'intra' and 'extra-dimensional' shifts. An 'intra-dimensional 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 begins 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 the colour 'red' to 'squares' from the dimension 'shape'). In fact, we used shifts between shapes and superimposed lines (Figure 3.2c). If the subject commits more errors when attempting the EDS compared with the IDS, then it can be inferred that he was employing

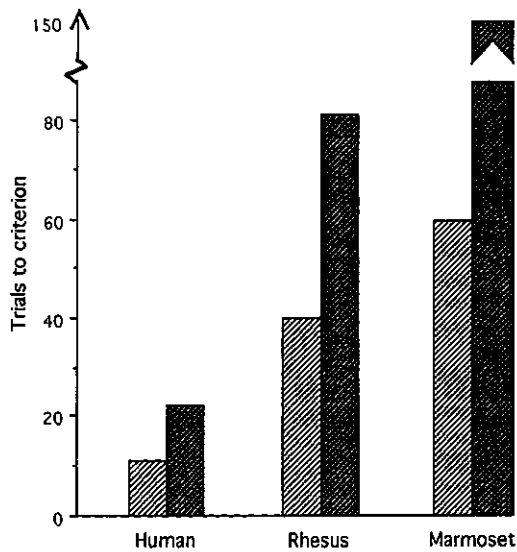
selective attentional processes in solving the task, rather than a somewhat inefficient learning strategy that requires list-learning of different configurations of the test stimuli (see Roberts, Robbins and Everitt, 1988). This pattern of superior IDS performance is found in a variety of species ranging from humans, rhesus monkeys (personal communication from L. Gold and G.F. Koob) and marmosets (see Figure 3.5) to the rat. Thus, this paradigm successfully passes the test of cross-species behavioural homology. There are also neural homologies between monkeys and man in that the EDS component of the test is selectively impaired in both man (Owen *et al.*, 1991) and marmoset (Dias, Roberts and Robbins, 1996) following frontal lobe excisions in neurosurgical cases and excitotoxic lesions, respectively (see Figure 3.5). Current research is seeking to define more clearly those 'cortico-striatal loops' mediating performance in marmosets.

For both monkeys and man, the IDS/EDS test necessarily involves training on a number of more elementary stages (see Downes *et al.*, 1989). For example, initially the subject is required to learn a series of discriminations in which one of two stimuli was 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 intra-dimensional shift (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 extra-dimensional shift (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 he or she reached criteria at the previous stage. This permits a



a). Attentional set-shifting ability in monkeys and man



b). Attentional set-shifting ability following damage to the prefrontal cortex

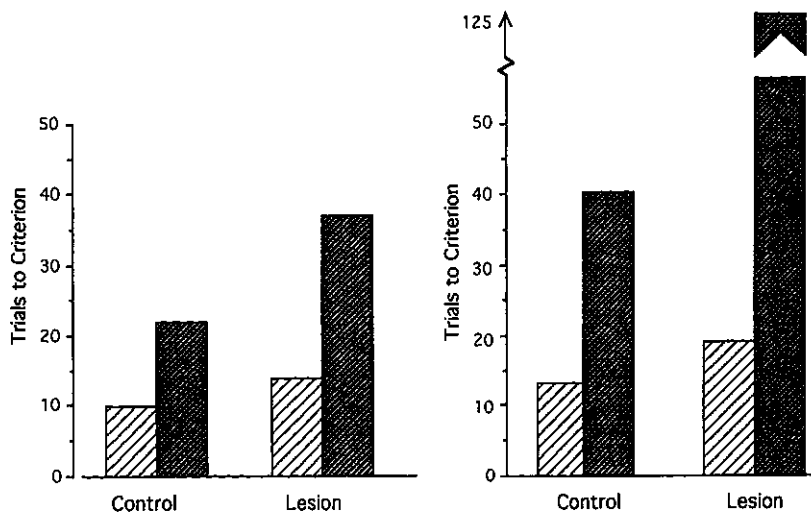


Figure 3.5. Light cross-hatching is IDS (intra-dimensional shift); dark shading EDS (extra-dimensional shift). (a) Behavioural homology: comparison of man, rhesus monkey and marmoset on trials to criterion for the intra- and extra-dimensional shift stages. Note in all three stages the superiority of IDS over EDS performance, indicating selective attention to the different dimensions. (b) Neural homology: similar effects of frontal lesions in marmoset and man selectively to impair EDS, but not IDS, performance (from Roberts *et al.*, 1997, with permission).

clear and simple method of analysing and presenting the main results (see Figure 3.6).

Thus, as mentioned above, 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). This deficit was neurally specific in that a 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 set-shifting ability revealed significant deficits in *all three* groups of patients with PD, including the never-medicated group. In fact, at the earlier stages of learning prior to the extra-dimensional shift, deficits were, if anything, worst in the non-medicated groups of patients who had relatively mild clinical symptoms (see Figure 3.6).

This test was also particularly sensitive to deficits in the groups of patients with MSA and SRO (Robbins *et al.*, 1994b). 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 (Figure 3.6). The rather more severe deficit at this stage, in the SRO group, resembled that observed in the medicated PD patients with severe clinical symptoms who, in fact, had a similar level of clinical disability. In recent work we have shown that patients early in the course of HD are also susceptible to failure at the EDS stage (Lawrence *et al.*, 1996), although HD patients later in the course fail even at the simple reversal stage, because of a failure to inhibit perseverative responding to the previously reinforced stimulus (see Figure 3.6). The latter deficit was greater than in patients with dementia of the Alzheimer type (DAT) (Lange *et al.*, 1995). Indeed, patients with mild, probable Alzheimer's disease, who exhibit significant memory deficits are no worse than age- and IQ-matched controls at negotiating the ID/ED test (Sahakian *et al.*, 1990 - see Figure 3.6). This is a very significant finding, as it implies that the deficits in attentional set formation and shifting in patients with basal ganglia disorders have some specificity. An obvious hypothesis is that, unlike DAT, these conditions have a profile of cognitive deficits that is reminiscent of frontal lobe dysfunction. By contrast, the deficits present in early DAT resemble those produced by posterior cortical, especially temporal lobe, damage.

However, our own incidental observations, as well as anecdotal reports from the literature, led us to consider once again that the deficit in the ID/ED test following frontal lobe damage and basal ganglia disorders may

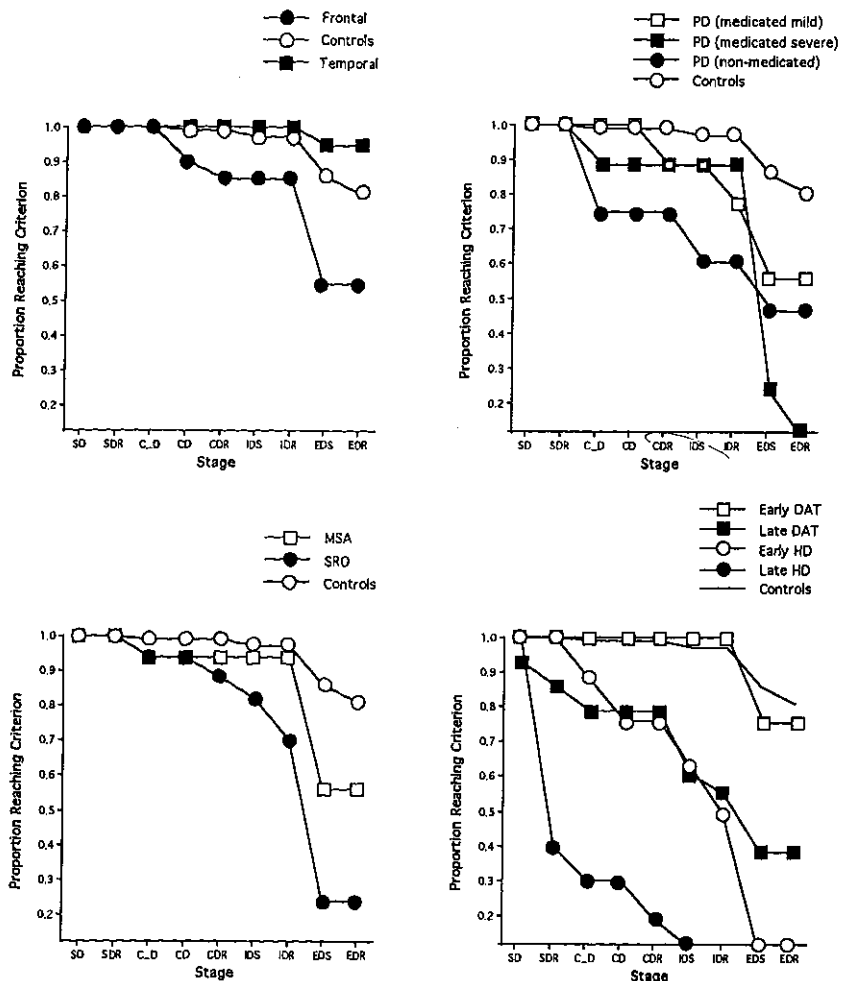


Figure 3.6. Performance on the attentional set-shifting paradigm, assessed in terms of the proportion of subjects reaching each stage of the test. SD, simple discrimination; SDR, simple reversal; C\_D, compound discrimination, spatially discontinuous elements; CD, compound discrimination; CDR, compound discrimination reversal; IDS, intra-dimensional shift; IDR, intra-dimensional reversal; EDS, extra-dimensional shift; EDR, extra-dimensional reversal. Other abbreviations as for Figure 3.3. DAT, dementia of Alzheimer type. Data taken from Owen *et al.*, 1991, 1992; Robbins *et al.*, 1992, 1994b; Sahakian *et al.*, 1990; Lange *et al.*, 1995.

reflect qualitatively distinct forms of impairment. One possibility is that frontal patients 'perseverate' as described by Milner and others, by failing to disengage their responses from the previously reinforced dimensions, whereas patients with basal ganglia disease fail the shifting task for other reasons. Flowers and Robertson (1985), for example, report how PD patients do not so much perseverate on the WCST as apparently 'lose their way' when a shift is required, by adopting esoteric but inappropriate response strategies. More specifically, we hypothesised that they are impaired because they are reluctant to respond to a stimulus dimension that has never previously been reinforced. An analogous phenomenon in the animal learning literature is called 'learned irrelevance' (Mackintosh, 1983). Therefore, we sought to disconfound these two potential forms of deficit in a novel form of the set-shifting task in which a novel dimension was substituted either for the previously reinforced, or for the previously non-reinforced, dimension at the EDS stage (Owen *et al.*, 1993). In the former case the patient is required to shift to the previously non-reinforced dimension, so any deficit cannot be attributed to perseveration, and must reflect impairments in processing previously non-reinforced stimuli ('learned irrelevance'). In the latter case, it is the non-reinforced dimension that is removed, so any deficit must be attributed to a perseverative tendency, which presumably reflects an inability of the subject to become emancipated from old stimulus-response habits learned on the basis of non-reinforcement. We tested a group of patients with frontal lobe lesions, as well as patients with PD either early in the course and therefore unmedicated, or later in the course and medicated with L-dopa preparations. Each patient received both conditions at different stages in a single test session, in a counterbalanced manner.

The results for frontal patients were clear-cut, with considerable evidence for perseveration, but no deficits in the 'learned irrelevance' condition. Therefore, frontal patients were able to shift when the previously reinforced dimension was removed, even when required to respond to previously irrelevant stimuli. These were, however, unable to shift responses when a previously reinforced dimension was present. It is of interest that a similar, though yet more pronounced perseverative tendency has been demonstrated in a group of chronic schizophrenics (Elliott *et al.*, 1995).

In the group of medicated PD patients completely the opposite pattern of results was obtained. These patients showed no perseverative tendency but made more errors in the 'learned irrelevance' condition, suggesting that the normal reluctance to respond to a never-reinforced dimension had been exacerbated in those patients. However, while these data are consistent with

the hypothesis that PD patients exhibit qualitatively distinct problems compared with patients with frontal lobe damage, the interpretation is complicated by the performance of the never-medicated PD patients. These early-in-the-course patients showed *equivalent* deficits in the learned irrelevance and perseveration conditions. Thus, the cross-sectional comparison with the later-in-the-course medicated PD patients would seem to indicate that the effect of medication with L-dopa and related preparations was to reduce perseveration – that aspect of the deficit resembling the effects of frontal lobe damage. However, from these results, it is not possible to say with any confidence what the neural substrates of the ‘learned irrelevance’ deficit might be. Comparisons with HD might be informative, given the nature of the striatal pathology in this disorder. Preliminary evidence (A. Lawrence, B.J. Sahakian and T.W. Robbins, unpublished observations) suggest that early HD patients have problems in both the learned irrelevance and perseveration components of the task.

#### **Extrapolating from animals to humans (and vice versa)**

While the advent of sophisticated neuroimaging techniques provides a way for us to begin to pinpoint the neural underpinnings of some of the deficits described above, and to relate them to the functioning of discrete cortico-striatal loops, it is obvious that studying patients with multiple forms of pathology is not the ideal means of achieving this. An alternative approach is to lesion selectively the brain in experimental animals, but this approach may be limited by the capacity to relate any functional deficits to the cognitive impairments seen in humans. This problem of extrapolation can be circumvented to a degree by employing similar cognitive tests. We have found this most feasible in the case of the attentional set-shifting paradigm described above, which is based on animal learning theory, and where it is possible to use stimuli more or less identical to those employed in the clinic.

Following on from the demonstration that, as in man, damage to the frontal cortex impairs extra-dimensional shift performance, we have also used the neurotoxin 6-OHDA infused into the trajectory of the mesocortical dopamine projections in the marmoset, to test the hypothesis that depletion of frontal cortical DA may be responsible for the set-shifting deficit in patients with PD (Roberts *et al.*, 1994). To our surprise, however, far from being impaired in this task, marmosets with substantial prefrontal DA depletion, actually showed *improved* performance over sham-operated controls. This observation clearly argues against the premise that this particular form of cognitive deficit in PD results from prefrontal DA loss

(although it should be noted that there were deficits in performance of the delayed response task in these marmosets). Following a previous hypothesis that there is a reciprocal balance in the regulation of cortical and subcortical DA systems, we also made direct measurements of the functional status of the subcortical DA systems in these monkeys by measuring striatal extracellular DA concentrations following a potassium pulse, and found them to be enhanced. Therefore, it is possible that the improved shifting performance results from an up-regulation of the striatal DA system, consistent with the hypothesis that the deficit in PD reflects striatal DA loss, and its remediation by L-dopa is caused by an up-regulation of striatal dopamine function. This hypothesis can of course be tested efficaciously by producing experimental depletion of striatal DA using 6-OHDA, and this is currently under investigation.

Further convergence of evidence between these studies of the effects of DA depletion in marmosets and patients with PD is provided by a recent study (Leenders, 1993) that has tried to relate the degree of DA loss in the frontal cortex and striatum to the WCST deficit in patients with PD, by determining the extent to which the magnitude of the deficit correlated with the extent of 6-L-[<sup>18</sup>F]-dopa binding in the striatum and mesial frontal cortex in these patients. In this study a significant inverse relationship between binding in the frontal cortex (as measured by  $K_D$ ) and perseverative behaviour on the WCST was found. Although this is a counter-intuitive finding, it is in keeping with the results of our animal studies. It is anticipated that future attempts to bridge the gap between clinical and basic studies of cognitive deficits in patients with basal ganglia disorders will be reinforced by this cross-fertilisation of approaches that allows us to determine the nature of the underlying cognitive processes, and how they are normally subserved by defined interactions between the cortex, striatum and their innervation by chemically defined neurotransmitter systems of subcortical origin.

### Summary

An approach has been outlined for testing the hypothesis that the cognitive deficits in patients with basal ganglia diseases resemble those executive deficits that follow frontal lobe damage, and are the product of disruptions of functioning of highly organised cortico-striatal anatomical 'loops', which appear to operate in a segregated and parallel manner. This approach makes detailed comparisons of performance following basal ganglia disease, with other informative groups, including DAT, and patients

with neurosurgical excisions of the temporal lobe, and most importantly, the frontal lobes themselves. It also allows the possibility of direct comparisons with the effects of selective lesions in monkeys, thus allowing inferences to be made about the causal role of underlying pathology in the human neurodegenerative diseases. The main findings are that certain tests of frontal lobe function are very sensitive to deficits in diseases such as PD, HD, MSA and SRO. In PD, some of these deficits are apparently responsive to L-dopa therapy. However, the nature of the deficits in these conditions often differs qualitatively from those produced by frontal lobe damage, and this suggests that the tests are helping to define the functions of striatal nodes in the cortico-striatal loops, as well as of the prefrontal cortex itself.

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