

Mechanisms of cognitive set flexibility in Parkinson's disease

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Summary

Previous research on cognitive set shifting in patients with Parkinson's disease has often been confounded by concept formation, rule learning, working memory and/or general slowing of cognitive processes. To circumvent this problem, the present study used the task-set switching procedure in which good performance was independent of rule learning, and in which working memory load was reduced by explicitly cueing the task switches. Our results provide

strong evidence for a specific cognitive set shifting deficit in patients with mild Parkinson's disease in a non-learning context, which also cannot be explained by general slowing of cognitive processes. Moreover, the deficit was robust in a small sample of patients at the earliest stages of the disease. Finally, the impairment in task-set switching was only apparent when competing information was present, i.e. when the load on selection mechanisms was increased.

Keywords: basal ganglia; set shifting; task-set switching; selection; learning

Abbreviations: EDS = extra-dimensional set shifting; ID/ED = intra-dimensional/extra-dimensional; NART = National Adult Reading Test; RT = reaction time

Introduction

Parkinson's disease, associated with nigrostriatal dopamine depletion and, to a lesser extent, mesocorticolimbic dopamine depletion, is accompanied by cognitive impairments even in its early stages, resembling those seen in frontal lobe patients (Taylor *et al.*, 1986; Owen *et al.*, 1992). One frequently reported deficit concerns the ability to shift set, i.e. the ability to alter behaviour according to changes in dimensional relevance of stimuli (Bowen *et al.*, 1975; Lees and Smith, 1983; Cools *et al.*, 1984; Brown and Marsden, 1988*a, b*; Caltargione *et al.*, 1989; Canavan *et al.*, 1989; Downes *et al.*, 1989; Owen *et al.*, 1992, 1993*b*; van Spaendonck *et al.*, 1995; Dimitrov *et al.*, 1999; Gauntlett-Gilbert *et al.*, 1999). However, a major problem with many studies is that paradigms have been employed in which performance is dependent not only on set shifting but on many other functions as well, such as matching to sample, visuospatial learning, working memory and set formation. Therefore, these studies confounded set shifting with other abilities and apparent deficits, in fact, cannot be interpreted as stemming from shifting impairments *per se*.

For example, performance on the Wisconsin Card Sorting Test (Grant and Berg, 1948) crucially depends on concept formation in addition to set shifting, and many authors have failed to use appropriate acquisition baseline controls for

comparison with the shifting stage, or have failed to report acquisition data (e.g. Bowen *et al.*, 1975; Brown and Marsden, 1988*b*; Canavan *et al.*, 1989; see Swainson, 1998). Studies that do report the relevant baseline data produced conflicting results: whereas some report set shifting deficits (Cools *et al.*, 1984; Paolo *et al.*, 1995), others report set acquisition deficits (Taylor *et al.*, 1986; Beatty and Monson, 1990; Cooper *et al.*, 1991; Dubois and Pillon, 1997). Similarly, in studies using the intra-dimensional/extra-dimensional (ID/ED) shift paradigm (for details, see Downes *et al.*, 1989), which was designed to decompose the Wisconsin Card Sorting Test by separately investigating discrimination learning, reversal shifting, intra-dimensional and extra-dimensional shifting (EDS), a significant proportion of patients with Parkinson's disease failed to complete the early set formation stages (e.g. Downes *et al.*, 1989; Owen *et al.*, 1992). Moreover, the crucial EDS stage can be argued to represent a significantly greater challenge to learning capacities than the earlier stages. Thus, it is only at this stage that a discrimination must be made between novel, two-dimensional compound stimuli in which subjects also do not have the advantage of already attending to the relevant dimension. Therefore, the demands for new rule learning are increased at this EDS stage. Studies using the Odd-Man-Out Task (Flowers and Robertson, 1985; Richards

et al., 1993) suffer from a similar problem. In this particular paradigm, the initial correct rule is determined by the subject instead of the experimenter and, therefore, performance on a second stage in which shifting to a different rule is required depends on both rule learning and set shifting abilities. Disambiguation of learning and shifting in Parkinson's disease is particularly relevant because dorsal striatal brain circuitry has been hypothesized to underlie both functions (White, 1989; Robbins and Everitt, 1992; Knowlton *et al.*, 1996). In addition to concept formation, shifting in a rule learning context also requires working memory for the keeping 'on-line' of rejected hypotheses in the process of the trial-and-error identification of rules (see also Konishi *et al.*, 1999). Thus, in summary, whereas several studies have reported what is interpreted to be a set shifting deficit in Parkinson's disease, it is far from clear whether this deficit can be attributed to difficulties with rule learning, working memory or set shifting.

To tease apart these different factors of learning, working memory and shifting, which are inherent in all tasks novel to the subject, it is necessary to utilize a set shifting task in which rule learning and working memory are minimized and the set shifting component is thus at a premium. This requirement is met by the task-set switching procedure introduced by Rogers and Monsell, in which neither feedback nor trial-and-error learning are necessary for successful performance (Rogers and Monsell, 1995). Whereas set shifts in discrimination learning tasks are essentially equivalent to the slow formation of stimulus-response bonds requiring repetitive trials following a rule change, the acquisition of task-sets is a rapid learning process and the associations between colour and naming tasks can be acquired at once. After the acquisition of task-sets in practice blocks, switches can be rapidly performed and measured under time-pressure. Moreover, in the current paradigm, task-switches are externally cued, which further reduces the load on working memory. Therefore, the task-set switching paradigm is more specific for measuring switching abilities than the ID/ED paradigm, the Wisconsin Card Sorting Test, the Odd-Man-Out Task or indeed any other rule learning paradigm.

Task-sets are defined as the dynamic configuration of stimulus-response requirements and task-set switching is the continuous selection, ordering and coordination (i.e. re-configuration) of these task-sets (Rogers and Monsell, 1995). Task-sets are operationalized as well-practised stimulus-response mappings, and subjects are required to switch continuously between two tasks A and B (letter naming and number naming). The sequence of trials generally employed (AABBAA and so on) enables the measurement of switching (i.e. A to B or B to A) against a baseline of non-switching (i.e. A to A or B to B), as captured by the computation of switch costs. Switch costs are calculated by subtracting performance (i.e. reaction times and errors) on non-switch trials from performance on switch trials.

The addition of a 'cross-talk' manipulation to the experiment enables the investigation of possible effects of

interference from competing task-sets on switching. In 'cross-talk' conditions, stimuli are associated with both the currently relevant task and the irrelevant, competing task (both a letter and a number are presented), whereas in 'no-cross-talk' conditions, stimuli are associated with the relevant task only (either a letter or a number is presented). Thus, stimuli in the 'cross-talk' condition activate the currently irrelevant task-set, and thereby greatly increase the load on response selection mechanisms associated with basal ganglia functioning (Mink, 1996).

Results from previous studies on task-set switching in patients with Parkinson's disease are conflicting. While Rogers and colleagues found patients with Parkinson's disease to exhibit normal switch costs (Rogers *et al.*, 1998), Hayes and colleagues showed an impairment in task-set switching in Parkinson's disease patients that could be improved to some extent by dopaminergic medication (Hayes *et al.*, 1998). However, baseline reaction times on non-switch trials were exceptionally high for both control subjects and patients with Parkinson's disease compared with the study by Rogers *et al.* (1998) and thus it is difficult to be sure that the increased switch costs in the study by Hayes *et al.* (1998) were not due to a general slowing of cognitive processes in Parkinson's disease. In the study by Rogers *et al.*, patients with Parkinson's disease exhibited progressively increasing switch costs in terms of errors, possibly indicating fatigue.

In the current study, we incorporated several design features in order to produce a definitive study of set shifting in Parkinson's disease. First, we employed a shorter version of the task used by Rogers and colleagues (1998), avoiding fatigue and thus increasing task sensitivity. Secondly, this shorter version allowed us to test a larger population of patients with Parkinson's disease to acquire adequate statistical power. In short, we aimed to investigate the underlying mechanism of the frequently observed, but confounded, set shifting deficit in Parkinson's disease patients by using a switch task in a non-learning context. Learning and working memory load were reduced by having subjects switch between easy and well-practised tasks that were explicitly cued on each trial. Based on previous literature associating response selection mechanisms with basal ganglia functioning (Mink, 1996; Redgrave *et al.*, 1999a), we predicted a set switching deficit in patients with Parkinson's disease that was specific to the 'cross-talk' condition.

Methods

Subjects

These studies were approved by the Cambridge Local Research Ethics committee and all subjects gave informed consent.

Patients

Forty-three Parkinson's disease patients participated in the study. All patients presented to a general neurology clinic

Table 1 Demographic and clinical characteristics of the Parkinson's disease patient group and the control group

	<i>n</i>	Sex ratio (M : F)	Age (years)	NART	Duration of disease (years)
Patients	43	31 : 12	62.1 (1.2)	118.2 (1.1)	6.9 (7.2)
Control subjects	27	18 : 9	59.4 (1.8)	116.7 (1.5)	

Data represent mean (standard deviation) values. NART = National Adult Reading Test; M = male; F = female. No significant differences were found.

and were diagnosed by a consultant neurologist (R.A.B.) as having idiopathic Parkinson's disease based on UK Parkinson's disease Brain Bank criteria and assessed using the Unified Parkinson's Disease Rating Scale (Fahn *et al.*, 1987) in the 'on' medication state. The mean (standard deviation) Hoehn and Yahr (Hoehn and Yahr, 1967) rating was 2.0 (0.6). Eleven patients showed a rating at Stage I, 21 patients at Stage II and another 11 patients at Stage III. Thirty-five patients were receiving L-dopa medication. Some of those 35 patients were also taking dopamine receptor agonists (nine patients), anticholinergic medication (four), other dopamine activity enhancers (two), monoamine-oxidase-B-inhibitors (three), antidepressants (one) and/or lithium (one). Different patients were only receiving dopamine receptor agonists (three), monoamine-oxidase-B-inhibitors (one) and/or anticholinergic medication (one) and/or antidepressants (one). Three patients were non-medicated. Demographic features of these patients are summarized in Table 1. All medicated patients were tested in the 'on' state.

Controls

Twenty-seven healthy volunteers were recruited to match the patient group in terms of age, sex ratio and premorbid verbal IQ, as estimated using the National Adult Reading Test (NART) (Nelson, 1982). Table 1 summarizes the characteristics of the two groups. One-way ANOVAs (analyses of variance) showed that the two groups did not differ in terms of age [$F(1,68) = 1.65, P = 0.2$] or premorbid verbal NART IQ [$F(1,67) = 0.96, P = 0.3$]. The chi-square test revealed no difference in sex ratio [$\chi^2(1) = 1.86, P = 0.2$].

Background neuropsychological assessments

The One-Touch Tower of London Planning Task (Owen *et al.*, 1995), a verbal fluency task (Benton, 1968), the CANTAB (CeNeS Ltd, Cambridge, UK; Robbins *et al.*, 1998) ID/ED attentional set shifting task (Downes *et al.*, 1989) and the CANTAB pattern and spatial recognition memory tasks (Sahakian *et al.*, 1988) were given to assess the background neuropsychological profile of patients and interrelationships between the different tests. For details of the test procedures, the reader is referred to the appropriate references (see above). Depression using the Beck Depression Inventory (Beck *et al.*, 1961) and dementia using the Mini-

Mental State Examination (Folstein *et al.*, 1975) were assessed to provide background data. ID/ED failure rates were analysed using the likelihood-ratio method for contingency tables (Robbins, 1977). Other data were analysed using one-way ANOVAs and are presented in Table 2. None of the patients scored less than 24 out of 30 on the Mini-Mental State Examination (cut-off score for clinical dementia), and in neither group was the mean Beck Depression Inventory score at a level indicative of a depressive illness. Overall, the neuropsychological profile of the Parkinson's disease group was consistent with the mild pattern of cognitive impairments seen in previous studies of non-demented Parkinson's disease patients (Sahakian *et al.*, 1988; Downes *et al.*, 1989; Owen *et al.*, 1992, 1995).

Task-set switching procedure (Fig. 1)

Subjects were required to switch between letter- and digit-naming tasks on every second trial. Each stimulus consisted of two closely adjacent characters presented side by side. In the letter-naming task, one of the characters was a letter (randomly presented on the left or the right of the stimulus pair) and subjects were required to name the letter as fast as possible without making a mistake. In the digit-naming task, one of the characters was a digit (randomly presented on the left or the right of the stimulus pair) and subjects were required to name the digit as fast as possible without making a mistake. The colour of the stimulus window indicated the relevant task. The design included 'cross-talk' and 'no-cross-talk' conditions. In the 'no-cross-talk' condition, the stimulus consisted of attributes, which were only associated with the relevant task. The irrelevant character was a neutral, non-alphanumeric character. In this condition, filtering of irrelevant information was not needed to perform well on the task. In the 'cross-talk' condition, the irrelevant character was again a neutral character in 33% of the trials. In 67% of the trials, the irrelevant character was associated with the competing, irrelevant (letter- or digit-naming) task. Thus, in this case, the stimulus contained both a letter and a digit. In these two-thirds of the trials, filtering of irrelevant information was needed to perform well on this task. Figure 1 is an example of a trial sequence in the 'cross-talk' condition, in which most stimuli included task-associated irrelevant characters. Subjects were told to respond as quickly as possible without making too many mistakes. When a block

Table 2 Performance of the Parkinson's disease patient group and the control group on the background tests

	ID/ED shift task % of people passing EDS stage	Tower of London mean no. correct at first attempt	Letter fluency mean no. words	Pattern recognition mean correct	Spatial recognition mean correct	MMSE mean score	BDI mean score
Patients	68	7.7 (3.7)	42.1 (1.8)	19.8 (0.4)	15.6 (0.3)	28.7 (0.2)	8.7 (1.1)
Controls	95	9.9 (1.9)	41.7 (2.2)	21.3 (0.4)	15.5 (0.4)	28.7 (0.3)	5.6 (1.1)
P-value	0.01*	0.04*	0.87	0.02*	0.94	0.92	0.06

Data represent mean (standard deviation) values. MMSE = Mini-Mental State Examination; BDI = Beck Depression Inventory; EDS = extra-dimensional set shifting. ID/ED shift task data were available for 24 patients and 21 controls; letter fluency data for 41 patients and 27 controls; BDI data for 31 patients and 27 controls and MMSE data for 43 patients and 26 controls. Tower of London data were available for 34 patients and a separate group of 16 controls. * $P < 0.05$ group difference compared with the matched control group.

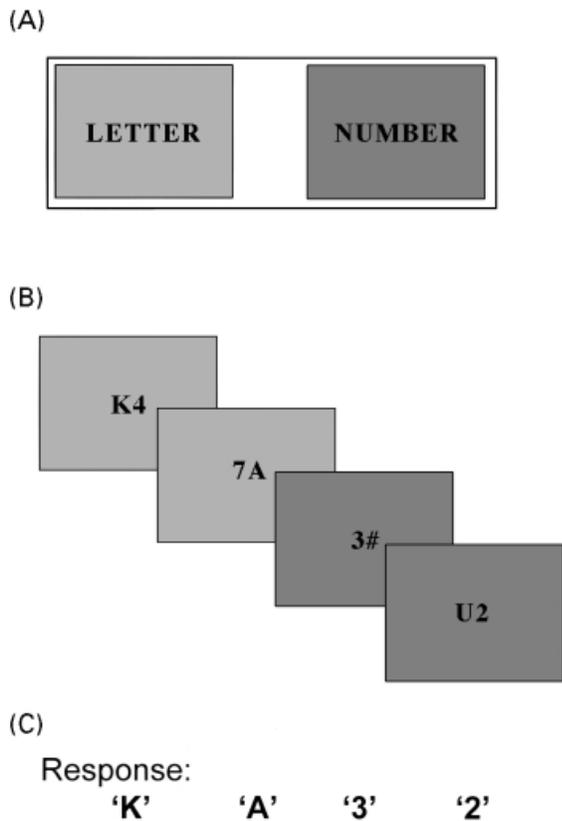


Fig. 1 Cues, stimuli and required responses are shown as used in the task-set switching paradigm. (A) The colour of the stimulus-window indicated which task (naming letters or naming digits) was to be performed by the subjects. A card with a green and a red colour-palette with the words 'letter' and 'number' was placed beneath the computer screen to help the subjects remember the colour-task associations. (B) An example of a trial-sequence in the 'cross-talk' condition is shown. In this condition 67% of trials included stimulus attributes associated with the irrelevant task (for example, 'K4'). On 33% of the trials, the irrelevant character was neutral (for example, '3#'). In the 'no-cross-talk' condition (not shown here) no stimuli included characters associated with the irrelevant competing task. (C) The required responses are shown. In this particular case the colour green (depicted here are light grey) was associated with naming letters and the colour red (dark grey) was associated with naming digits.

was completed, the word 'Ready' was displayed on the screen until the experimenter pressed the space-bar. After each block, the mean reaction time was displayed on the screen and the number of errors was given by the experimenter. A card with a green and a red colour-palette with the words 'letter' and 'number' was placed beneath the computer screen to help the subjects remember the colour-task associations (see Fig. 1A).

Design

The task started with a general training-session in which the letter- and digit-naming tasks were separately practised. This session consisted of two 24-trial letter-naming and two 24-trial digit-naming blocks. Subjects alternated between those training blocks twice. Character pairs always consisted of the relevant character and a neutral character. The general training session was followed by the actual experiment, which consisted of the two experimental conditions, 'cross-talk' and 'no-cross-talk'. The sequence of the 'cross-talk' and 'no-cross-talk' conditions was counterbalanced within the two groups. Each experimental condition, consisting of four blocks of 40 trials, was preceded by a practice session, consisting of two blocks of 40 trials. The mapping of the colour green and red with the letter- and the digit-naming tasks was also counterbalanced within the two groups.

Apparatus and stimuli

An IBM Compatible, Viglen Professional 4DX33, was used as a testing machine and the task was programmed in C and run from real-time MSDOS to ensure that responses were measured to millisecond accuracy. A small throat-microphone (RS Components 250–479) and a purpose-built voice-key, which was constructed at the Department of Experimental Psychology of the University of Cambridge, was used to record reaction times. For details of stimuli the reader is referred to the study by Rogers and colleagues (Rogers et al., 1998).

Table 3 Effect of 'cross-talk' (mean RT and mean error rates as a function of trial-type and 'cross-talk' condition)

	'Cross-talk'		'No-cross-talk'	
	RT (ms)	Errors (%)	RT (ms)	Errors (%)
Parkinson's disease patients				
Switch-trials	862.4 (37.0)	3.8 (0.4)	551.1 (13.0)	0.4 (0.1)
Non-switch-trials	802.7 (36.1)	3.5 (0.6)	526.9 (12.3)	0.2 (0.1)
Switch-costs	59.8	0.3	24.2	0.2
Control subjects				
Switch-trials	685.9 (26.6)	3.0 (0.5)	479.8 (10.1)	0.3 (0.1)
Non-switch-trials	663.3 (30.1)	1.9 (0.4)	464.8 (9.9)	0.3 (0.1)
Switch-costs	22.6	1.1	15	0.0

Data represent mean (standard error of the mean) values.

Data analysis

The first four trials of each block and all unreliable trials (e.g. when the voice key was triggered by any noise not related to a naming response, such as lip-pops) were excluded from all analyses. Reaction times (RTs) faster than 200 ms, RTs slower than 5000 ms and three trials following an error were excluded from the RT analyses. However, detailed inspection of the data showed that RTs from controls never exceeded 2000 ms, while RTs from patients never exceeded 3000 ms. Proportions of errors were arcsin-transformed (Howell, 1997) ($2\arcsin\sqrt{x}$). Greenhouse–Geisser corrections were applied when the sphericity assumption was violated.

Mean RTs and proportions of errors were analysed using a repeated measures ANOVA, with the between-subject factor group and three within-subject factors: switch (switch trials versus non-switch trials), task (letter-naming versus digit-naming) and 'cross-talk' (the 'cross-talk' condition versus the 'no-cross-talk' condition). Details of further ANOVAs are described in the results section (see also Rogers *et al.*, 1998).

Results

RT data

RT data as a function of switch and 'cross-talk' are presented in Table 3. Overall, patients responded more slowly than control subjects [main effect of group: $F(1,68) = 11.97$, $P < 0.001$]. Moreover, consistent with our prediction, Parkinson's disease patients exhibited increased switch costs relative to controls [a significant switch \times group interaction: $F(1,68) = 5.23$, $P = 0.025$]. The mean proportionate increase in RT in switch trials over non-switch trials was 6.6% in patients, while the mean proportionate increase in RT was only 3.7% in control subjects. Patients also responded more slowly in the 'cross-talk' condition than in the 'no-cross-talk' condition relative to controls [group \times 'cross-talk' interaction: $F(1,68) = 5.44$, $P = 0.023$]. Although the group \times switch \times 'cross-talk' three-way interaction only tended towards significance [$F(1,68) = 2.6$, $P = 0.1$], inspection of the data (see Table 3) clearly suggests differences in switch costs between the two conditions.

Moreover, we had *a priori* hypothesized that the switching deficit would be specific to the 'cross-talk' condition, which allowed us to perform simple interaction effect analyses. These analyses confirmed that the group \times switch interaction was significant in the 'cross-talk' condition [$F(1,68) = 7.7$, $P = 0.007$], but not in the 'no-cross-talk' condition [$F(1,68) = 0.47$, $P = 0.49$]. Thus, patients with Parkinson's disease exhibited increased switch costs compared with control subjects, but only in the 'cross-talk' condition, in which the currently irrelevant task was activated.

Error data

Percentages of errors and error switch costs are presented separately for the 'cross-talk' condition and the 'no-cross-talk' condition as a function of group in Table 3. Over all conditions, patients made significantly more errors than controls [$F(1,68) = 4.76$, $P = 0.033$]. Moreover, patients made more errors in the 'cross-talk' condition than in the 'no-cross-talk' condition relative to controls [group \times 'cross-talk' interaction: $F(1,68) = 4.53$, $P = 0.037$]. However, there was no significant difference between patients and controls as a function of switch [$F(1,68) = 0.05$, $P = 0.83$] or switch \times 'cross-talk' [$F(1,68) = 0.37$, $P = 0.55$].

Supplementary analyses

In an additional analysis the effects of practice were examined across the six switching blocks (two practice blocks and four experimental blocks). In both groups, overall RTs and switch costs reduced significantly over the course of six blocks, as is evident from a significant block main effect [$F(5,325) = 47.9$, $P < 0.001$] and a significant switch \times block interaction [$F(5,325) = 2.95$, $P = 0.03$]. However, practice effects were similar in patients and controls in terms of overall RTs, errors and switch costs. In a second analysis the 40 trials of each block were broken up into five intervals and the effects of 'fatigue' within a block of trials was examined. Performance gradually deteriorated within blocks in terms of overall RTs [$F(4,272) = 21.9$, $P < 0.001$], but not in terms of switch costs [$F(4, 272) = 1.3$, $P = 0.3$]. Although the RT increase

within a block of trials was more pronounced for patients than for controls [a significant trial-interval \times group interaction: $F(4,272) = 7.1, P < 0.001$], patients did not exhibit greater progressive increases in switch costs over the course of a block. No group effects were found for errors.

Effect of general cognitive slowing

To investigate whether the significantly increased switch costs in patients could be a consequence of general slowing, a subgroup of patients with the mildest clinical disability ($n = 9$; Hoehn and Yahr score = 1.0; matched on age, sex ratio and NART IQ) was analysed. These mild patients were selected because it was expected that they had the lowest baseline RTs. Two of the 11 mildest patients were excluded because they were non-medicated and were therefore expected to have increases in baseline RTs as a result of less well-controlled motor symptoms similar to more severe patients. Baseline non-switch RTs in the 'cross-talk' condition did not differ between the selected patient group and the control group (see Fig. 2). However, consistent with our prediction, simple interaction effect analyses revealed that mild medicated Parkinson's disease patients exhibited increased switch costs in the 'cross-talk' condition [$F(1,34) = 9.6, P = 0.004$], but not in the 'no-cross-talk' condition [$F(1,34) = 0.3, P = 0.6$].

Effect of depression

A final analysis was conducted to investigate whether the increased switch costs in patients could be a consequence of the increased scores in Parkinson's disease patients on the Beck Depression Inventory. For this purpose, only those subjects (20 patients and 22 controls) were selected who scored 9 or lower on the Beck Depression Inventory (which is the cut-off score for mild depression). Patients still exhibited significantly increased switch costs compared with controls, and again only in the 'cross-talk' condition [$F(1,40) = 10.4, P = 0.003$] and not in the 'no-cross-talk' condition [$F(1,40) = 0.59, P = 0.59$].

Correlations of task-set switching with background tests

Pearson or, where appropriate, Spearman's product moment correlation coefficients were calculated between switch costs, mean RTs and background task variables on the group as a whole. A small but predicted significant correlation was found between switch costs and the number of errors at the EDS stage in the ID/ED shift paradigm in the predicted direction [$r(45) = 0.3, P = 0.047$]. There were no significant correlations between the Tower of London task and task-set switching or ID/ED shifting. Switch costs correlated neither with mean reaction times nor with the overall difference in reaction times between the 'cross-talk' and the 'no-cross-talk' conditions. No other significant correlations were found. Of particular importance was the lack of correlation of the

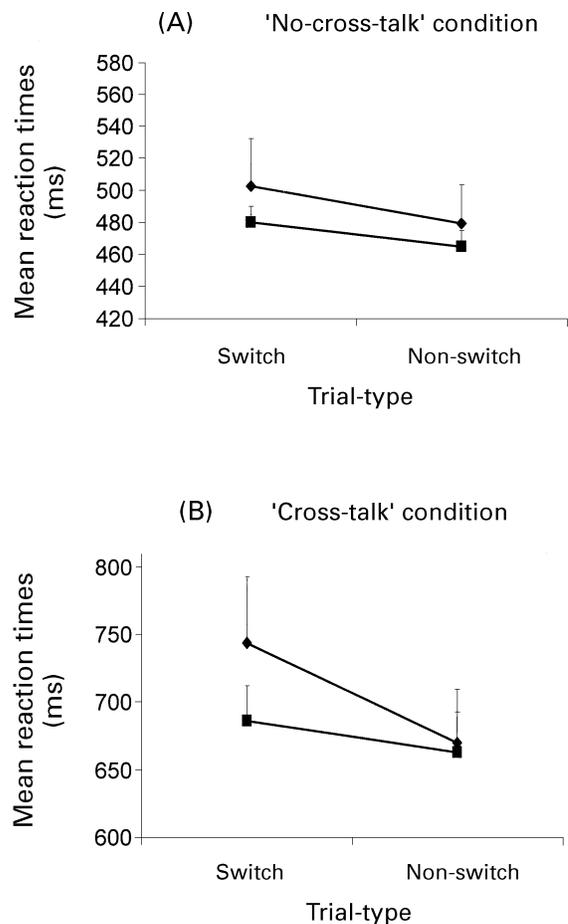


Fig. 2 Mean and standard error of the mean reaction times (in milliseconds) of the medicated subgroup of Parkinson's disease patients with mildest clinical disability obtained from the task-set switching procedure are shown as a function of trial type (on the x-axis) and group (as separate lines) for the 'no-cross-talk' condition (A) and the 'cross-talk' condition (B) separately. The medicated Parkinson's disease patients with mildest clinical disability (filled diamonds) exhibited equal baseline reaction times on non-switch trials and showed significantly increased switch-costs compared with control subjects (filled squares). Simple interaction analyses revealed that mild medicated patients exhibited increased switch costs in the 'cross-talk' condition [$F(1,34) = 9.6, P = 0.004$], but not in the 'no-cross-talk' condition [$F(1,34) = 0.3, P = 0.6$]. Error bars represent standard errors.

Beck Depression Inventory scores with switch costs [$r(58) = 0.18, P = 0.18$] suggesting that the small group difference in Beck Depression Inventory scores cannot account for the set shifting deficit in Parkinson's disease.

Summary

The main results were as follows. (i) Patients with Parkinson's disease exhibited significantly increased switch costs compared with control subjects, but only in the 'cross-talk' condition, in which inhibition of competing information was necessary. (ii) Over the course of six blocks, patients and

controls exhibited similar practice effects in terms of RTs and time switch costs. (iii) Over the course of single blocks patients showed significantly greater increases in terms of overall RTs, but not in terms of switch costs, compared with controls.

Discussion

The present study provides the first evidence for a cognitive set shifting deficit in patients with mild Parkinson's disease, uncontaminated by impairments in concept formation, rule learning, working memory or general slowing of cognitive processes. The impairment was robust even in a small sample of patients at the earliest stage of the disease. Moreover, the data show that the shifting deficit is only present when stimuli activate the currently inappropriate task, as in the 'cross-talk' condition.

In contrast to previous studies in which rule learning tasks were used (see Introduction), the present study isolates shifting from learning by using the task-set switching procedure, in which subjects were required to continuously and rapidly switch between easy stimulus-response mappings that were already well practised beforehand. We argue that the working memory load, in the sense of keeping multiple task-sets 'on-line' at the same time, was reduced by using what was, relatively speaking, an explicitly cued procedure, which did not depend on trial and error feedback. Therefore, learning and memory difficulties are unlikely to account for our results. In addition to the nature of the task, the clear-cut pattern of findings renders an explanation in terms of memory problems even more implausible. First, switch costs did not correlate with performance on the One-Touch Tower of London Planning Task, for which working memory is required (Owen *et al.*, 1995). Secondly, additional analyses showed that patients and controls did not differ in terms of practice effects, confirming that the switching deficit is independent of any deficits in procedural learning or memory.

The possibility that the increased switch costs were a consequence of generally increased RTs can also be dismissed for the following reasons. (i) A supplementary analysis of the subgroup of Parkinson's disease patients with the mildest clinical disability whose baseline RTs were not increased compared with those of controls showed that they exhibited significantly increased switch costs, again only in the 'cross-talk' condition. This analysis indicates that the additional overall slowing seen (and expected) in patients who have more severe motor symptoms cannot fully explain the increased switch costs. (ii) There was no correlation between switch costs and overall mean reaction time. (iii) Detailed analyses revealed that the slowing of RT was specific to certain ('cross-talk') conditions. (iv) Patients and controls exhibited different proportional switch costs, which were calculated as a percentage of the corresponding baseline non-switch RTs (Salthouse, 1985).

Finally, it is unlikely that group differences on some of the other background measures, including the Beck Depression Inventory, can account for the impairment in task-set

switching because no significant correlations were found between switch costs and these background measures. A supplementary analysis confirmed that the increased switch costs cannot be explained by depression in Parkinson's disease patients. We also excluded patients with MMSE (Mini-Mental State Examination) scores in the dementing range and employed a group with relatively mild clinical disability whose performance on background tests (Table 2) was largely consistent with previous work (Sahakian *et al.*, 1988; Owen *et al.*, 1992, 1993a). As expected, a small but significant correlation was found between switch costs as measured with the task-set switching procedure and the number of errors at the EDS stage of the ID/ED task.

The present results help to resolve contrasting findings from two previous studies on task-set switching in Parkinson's disease patients (Hayes *et al.*, 1998; Rogers *et al.*, 1998). Rogers and colleagues found that Parkinson's disease patients exhibited progressive increases in the error costs associated with switching as a function of time on task, but overall there was no evidence of a switching deficit in terms of RTs or errors. In contrast, in the present study no such progressively increasing switch costs were observed. These findings may indicate that the present shortened version of the task succeeded in avoiding fatigue, which may have reduced the sensitivity of the previous study (Rogers *et al.*, 1998). Our results are partly consistent with the study by Hayes and colleagues in which Parkinson's disease patients were shown to exhibit significantly increased switch costs in a related switching paradigm (Hayes *et al.*, 1998). However, because the group \times switch interaction in our study cannot be explained by general slowing (as outlined above), the current results provide much stronger evidence for a switching deficit than those in the study by Hayes and colleagues, in which baseline RTs of patients were increased compared with those of controls (see Introduction). Moreover, while switch costs were not affected by the presence of irrelevant information in Hayes and colleagues' study, the present study indicates that switch costs were only significantly increased when currently irrelevant information was present. Generally prolonged RTs on switch trials may have masked a higher order switch \times 'interference' interaction in Hayes and colleagues' study.

Several authors have argued that Parkinson's disease patients have difficulties with set shifting, but only when internal generation or guidance by 'internal control' is necessary, additionally implying a dependence on working memory mechanisms (Cools *et al.*, 1984; Taylor *et al.*, 1986; Brown and Marsden, 1988a). The present results show that the deficit can also be present when task switches are externally guided, as was the case here with the explicitly cued task-set switching procedure, which drastically reduced working memory load. Rather than being dependent on 'internal control', our results suggest that the shifting deficit is dependent on interference from competing task-sets. Patients only exhibited increased switch costs in the 'cross-talk' condition, in which stimuli primed such previously relevant,

but currently distracting, task-sets. This indicates that the switching deficit is due to impairments in selection mechanisms, necessary for disengaging from a previous task-set and engaging a new task-set in the face of distraction. Our finding that 'cross-talk' produced non-selective deficits on both non-switch and switch trials (in terms of errors) suggests an additional general susceptibility to interference from competition on the current trial (i.e. increased distractibility). This latter finding can be related to previously reported impairments on Stroop (Brown and Marsden, 1991; Henik *et al.*, 1993; Stam *et al.*, 1993; Dujardin *et al.*, 1999), selective attention (Sharpe, 1990; Wright *et al.*, 1990; Filoteo *et al.*, 1994; Maddox *et al.*, 1996) and rule learning tasks (Flowers and Robertson, 1985; Partiot *et al.*, 1996).

The role of dopamine and frontostriatal circuitry in task-set switching

Recent patient and brain imaging studies have related task-set switching to functioning of the (left) frontal lobes (Stablum *et al.*, 1994; Meyer *et al.*, 1998; Rogers *et al.*, 1998; Mecklinger *et al.*, 1999; Dove *et al.*, 2000; Sohn *et al.*, 2000). For example, using a shorter version of the current paradigm, Rogers and colleagues showed that patients with left, but not right, frontal lobe damage exhibited significantly increased switch costs compared with control subjects (Rogers *et al.*, 1998). As was the case in our Parkinson's disease group, the increased switch costs were particularly pronounced in the 'cross-talk' condition. The current results demonstrate that Parkinson's disease, primarily affecting dopamine levels in the striatum, also impairs task-set switching. Thus, these data suggest that the frontal lobes are not uniquely involved in task-set switching, but rather, disrupted interactions between the striatum and the frontal cortex may underlie the switching deficit. This hypothesis is substantiated by recent results from our laboratory, indicating that patients with Huntington's disease, a disease causing neurodegenerative damage of the striatum, also exhibit relatively increased switch costs (L. Watkins, T. W. Robbins, B. J. Sahakian, unpublished data). Moreover, both the withdrawal of dopaminergic medication in Parkinson's disease patients (Cools *et al.*, 2001) and the administration of the dopamine D2 receptor antagonist sulpiride to healthy volunteers (F. Manes, M. Mehta, T. W. Robbins, B. J. Sahakian, unpublished data) were shown to have specific detrimental effects on switching between well-established task-sets. These data add weight to the current finding that Parkinson's disease patients exhibit a specific task-set switching deficit.

The finding that the switching deficit was only present when stimuli primed the competing task-set is consistent with the proposal that the basal ganglia play a crucial role in the selection and inhibition of competing cognitive and motor programmes (Barker, 1988; Mink and Thach, 1993; Mink, 1996; Redgrave *et al.*, 1999a, b). For example, Mink's (1996) hypothesis states that competing motor mechanisms are inhibited by subthalamic nucleus activation, leading to

increased impact of tonically active inhibitory output of basal ganglia on thalamocortical areas and the brainstem. On the other hand, focused, context-dependent inhibitory output from the striatum selectively decreases activity in the globus pallidus, leading to disinhibition of the desired thalamocortical and brainstem programmes. The existence of large corticostriatal projections that subservise mainly cognitive functions (Alexander *et al.*, 1986) indicates that the basal ganglia could play such a 'focusing' role in cognition (Redgrave *et al.*, 1999b). Dopamine has been suggested to facilitate this 'focusing' function by gating or disinhibiting task-relevant, and inhibiting task-irrelevant, corticostriatal projections (Gerfen, 1992; Cohen and Servan-Schreiber, 1993; Mirenowicz and Schultz, 1996; Braver and Cohen, 2000), and has been implicated in both behavioural and cognitive switching (Cools, 1980; Robbins and Sahakian, 1983; Collins *et al.*, 2000). A dysfunctioning 'focusing' mechanism in Parkinson's disease could account both for the specific shifting deficit that is only present when stimuli prime the competing task (as in the 'cross-talk' condition) and the non-specific interference effect in terms of errors.

Conclusion

The present study provides evidence that patients with Parkinson's disease exhibit a specific deficit in externally guided set shifting, uncontaminated by concept formation, learning, working memory or general slowing of cognitive processes. The impairment in task-set switching was only apparent when irrelevant information was present that primed the competing task-set. Moreover, Parkinson's disease patients were generally more susceptible to interference than controls in terms of errors. These findings are consistent with current selection and inhibition models of the basal ganglia. Overall, these data suggest that disturbed interactions between the frontal cortex and the striatum may underlie failures of 'cognitive control', not only in novel, but also in familiar contexts.

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