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Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease

Adrian M. Owen,[1*] Angela C. Roberts,[1] John R. Hodges,[2] Beatrice A. Summers,[3] Charles E. Polkey[4] and Trevor W. Robbins[1]

[1]Department of Experimental Psychology, University of Cambridge, the [2]Neurology Unit, Addenbrooke's Hospital, Cambridge, the [3]Department of Neurology, Institute of Psychiatry and the [4]Neurosurgical Unit, The Maudsley Hospital, London, UK

SUMMARY

Tests which assess the ability to shift cognitive set modelled after the Wisconsin Card Sorting Test are particularly sensitive to impairments in patients with Parkinson's disease as well as in patients with frontal lobe damage. However, the underlying mechanisms responsible for the similar deficits observed in the two patient groups are not well understood and may not be identical. For example, an apparent deficit in set-shifting ability may reflect either an impairment in the ability to shift from a perceptual dimension which has previously commanded attention (i.e. 'perseveration'), or in the ability to shift to an alternative perceptual dimension which has previously been irrelevant (i.e. 'learned irrelevance').

In this study, the performance of both medicated and non-medicated patients with Parkinson's disease were compared with a group of neurosurgical patients with localized excisions of the frontal lobes on a novel task designed to assess the relative contribution of 'perseveration' and 'learned irrelevance' to impaired set-shifting ability. Patients with frontal lobe damage were worse than controls in their ability to shift attention from a previously relevant stimulus dimension. Medicated patients with Parkinson's disease were worse at shifting to a previously irrelevant dimension. In contrast to both groups, non-medicated patients with Parkinson's disease were impaired in both conditions.

These results suggest that the gross set-shifting deficits reported in both frontal lobe patients and patients with Parkinson's disease may involve fundamentally different, though related, cognitive processes, and that these may be differentially affected by medication. Specifically, L-dopa therapy may protect Parkinson's disease patients from perseveration of attention to a formerly relevant stimulus dimension.

INTRODUCTION

One of the characteristic deficits of patients with frontal lobe damage is a tendency to perseverate on the Wisconsin Card Sorting Test (WCST) (Grant and Berg, 1948). In

Correspondence to: Dr Trevor W. Robbins, Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK.

*Present address: Neuropsychology Department, Montreal Neurological Institute, 3801 University Street, Montreal, Canada, H3A 2B4.

this well-known task, patients are required to sort a pack of cards containing symbols which vary in three perceptual dimensions (colour, shape and number) according to a 'rule' based on one of those three dimensions. Frontal lobe patients frequently continue to sort cards according to a previous rule, even when the rule has been explicitly changed (e.g. from colour to shape). Using this task, Milner (1964) reported that patients with frontal lobe damage made significantly more 'perseverative' than 'non-perseverative' errors. Subsequent studies (e.g. Drewe, 1974; Nelson, 1976; Robinson *et al.*, 1980) have confirmed that perseveration on the WCST is a relatively specific indicator of frontal lobe dysfunction and usually interpret the deficit as one of impaired attentional set-shifting ability. The term 'set', used in this context, refers to a predisposition to attend selectively to a particular stimulus dimension (such as 'colour' or 'shape'), established on the basis of reinforcing feedback (i.e. 'correct' or 'incorrect' cues). In fact, the WCST also measures the ability to form a response set and to maintain it in the face of distraction from competing stimulus dimensions. Although perseveration has been a dominant feature in the description of patients with frontal damage, several recent studies have suggested that these patients have additional deficits which may affect performance in tests of sorting or concept formation similar to the WCST (Owen *et al.*, 1991; Delis *et al.*, 1992).

As might be expected from the intimate relationship that exists between the frontal cortex and the basal ganglia (Alexander *et al.*, 1986), patients with Parkinson's disease also perform poorly on the WCST, although it is not clear whether this deficit is truly 'frontal' in either behavioural or neural terms. A survey of the literature reveals that there is considerable disagreement about the extent to which the parkinsonian deficit on the WCST depends on the occurrence of perseverative errors as distinct from other types of sorting error. Indeed, several studies have shown that perseverative errors may be a less sensitive indicator of impaired performance in non-medicated patients with mild Parkinson's disease than either the number of trials required to learn the initial rule (Cooper *et al.*, 1991) or the number of 'non-perseverative' errors (Bowen *et al.*, 1975).

In order to clarify this issue, several recent studies have adopted a computerized test that specifically assesses attentional set-shifting ability (Roberts *et al.*, 1988; Downes *et al.*, 1989). Using this test, patients with frontal lobe damage, but not temporal lobe damage, have been shown to be specifically impaired in their ability to shift attention between two perceptual dimensions (i.e. at the 'extra-dimensional shift' stage) (Owen *et al.*, 1991). These results clarify and extend many of the previous reports which have shown groups of patients with frontal lobe damage to be generally impaired in tests requiring a shift of attention or response set (Rosvold and Mishkin, 1950; Milner, 1964; Drewe, 1974; Nelson, 1976; Robinson *et al.*, 1980; Cicerone *et al.*, 1983; Stuss *et al.*, 1983).

The same test of attentional set-shifting ability has also been shown to be sensitive to idiopathic Parkinson's disease, particularly when patients are non-medicated and early in the course of the disease (Downes *et al.*, 1989; Owen *et al.*, 1993). These results are consistent with previous studies which have suggested a 'frontal-like' set-shifting impairment in both medicated and non-medicated patients with Parkinson's disease (Bowen *et al.*, 1975; Lees and Smith, 1983; Pillon *et al.*, 1986; Taylor *et al.*, 1986; Canavan *et al.*, 1989). However, close inspection of the pattern of deficits observed in the patients with frontal lobe damage (Owen *et al.*, 1991) and the patients with Parkinson's disease (Downes *et al.*, 1989; Owen *et al.*, 1993), suggests that important differences may exist between the two groups in terms of the precise cognitive and neural mechanisms involved. For

example, unlike the frontal lobe patients, the patients with Parkinson's disease were impaired at shifting attention within, as well as between, perceptual dimensions (Downes *et al.*, 1989; Owen *et al.*, 1993), possibly reflecting a less specific impairment in this group (cf. Cooper *et al.*, 1991). Moreover, subjective reports from Parkinson's disease patients failing the critical extra-dimensional shift ('between stimulus dimensions') stage of the task, suggested that these patients were not simply *perseverating* to the previously relevant perceptual dimension, as one might expect of patients with frontal lobe impairment. In fact, their pattern of performance appeared to be more consistent with the adoption of rather elaborate, but misguided selection strategies. Similar observations have also been made anecdotally, for Parkinson's disease patients performing the WCST (Flowers and Robertson, 1985).

Failure to shift attention between competing perceptual dimensions may reflect a deficit in cognitive mechanisms which are not directly related to perseveration of an attentional set. For example, an apparent failure to shift attentional set may arise when a subject is able to shift attention away from a previously relevant dimension (when it becomes irrelevant) but is, nevertheless, unable to refocus attention on the newly relevant dimension. This impairment may reflect the active inhibition of responding to a dimension previously made irrelevant by its random association with reinforcing feedback. In studies of associative learning mechanisms in animals, the inability to learn about previously irrelevant stimuli has been referred to as 'learned irrelevance' (Mackintosh, 1983).

These considerations suggest that deficits in tests of attentional set-shifting ability (including the WCST) such as those observed in patients with frontal lobe damage and patients with Parkinson's disease, may arise through the disruption of at least two distinct cognitive mechanisms. Thus, both the inability to release attention from a relevant perceptual dimension (perseveration), and the inability to re-engage attention to a previously irrelevant dimension ('learned irrelevance') may contribute to these deficits. This theoretical fractionation of attentional set-shifting processes into distinct mechanisms is analogous to a similar account which has led to a neural theory of spatial attention (Posner, 1980; Posner *et al.*, 1984). Posner *et al.* (1984) have shown that patients with spatial neglect following damage to the parietal lobe are specifically impaired in their ability to disengage attention from a previously relevant spatial location, rather than their ability to re-engage attention elsewhere. In contrast, patients with lesions of the thalamus have the reverse form of deficit (Posner and Petersen, 1990).

In the present study, the neuropsychological basis of attentional set-shifting deficits in patients with frontal lobe damage and patients with Parkinson's disease was investigated using a novel computerized task designed to assess the relative contribution of 'perseveration' and 'learned irrelevance' to these impairments. Two independent set-shifting tasks were designed which differed by substituting either the previously *relevant* dimension, or the previously *irrelevant* dimension, with a *novel* perceptual dimension. Therefore, in the former condition, the ability to shift attentional set from the previously relevant dimension could not be adversely affected by the presence of that dimension, thus precluding the opportunity to perseverate. Any impairment in this condition (termed the 'learned irrelevance' condition) must therefore be due to an active inhibition of responses to the previously irrelevant dimension (or '*learned irrelevance*'). Conversely, in the alternative condition, it is the *irrelevant* dimension which is replaced by the *novel* one, thereby precluding any negative biasing away from this dimension which may result from prior

learning. Failure in this condition (termed the 'perseveration' condition) must therefore reflect *perseveration* to the previously relevant stimulus dimension which is, of course, still present.

Several previous studies have suggested that attentional set-shifting deficits in Parkinson's disease may be ameliorated by medication with L-dopa (Bowen *et al.*, 1975; Downes *et al.*, 1989; Lange *et al.*, 1992). Therefore, in the present study, the effects of medication in Parkinson's disease were examined by comparing patients early in the course of the disease, and yet to receive L-dopa, with those already stabilized on dopaminergic medication.

METHOD

Subjects

Frontal lobe patients. All 18 of the frontal lobe patients included in this study had undergone unilateral or bilateral frontal lobe surgery at the Maudsley Hospital Neurosurgical Unit, London. Eleven of these patients had right-sided frontal lobe excisions among which there were four cases where a right frontal resection had been performed for the relief of pharmacologically intractable epilepsy, two cases where an aneurysm of the anterior communicating artery had been clipped, three cases where a right-sided meningioma had been removed, one case of arterio-venous malformation removal, and one case where a benign astrocytoma had been removed. Five patients had left-sided frontal lobe excisions. All had undergone unilateral resection for the relief of pharmacologically intractable epilepsy. The remaining two patients had undergone bifrontal meningioma removal.

The frontal lobe group was tested on average 4 years 10 months postoperatively (range = 3–312 months). Thirteen were on anti-convulsant medication at the time of testing and all were seen as outpatients. In Fig. 1, examples of the main lesion types are presented, based on the neurosurgeon's drawings at the time of surgery.

Parkinson's disease patients. All Parkinson's disease patients included in this study were outpatients at either the Maudsley Hospital, London, The Queen Elizabeth Hospital, King's Lynn or Addenbrooke's Hospital, Cambridge. In all cases, idiopathic Parkinson's disease was diagnosed by a consultant neurologist who also assessed the severity of clinical symptoms according to the Hoehn and Yahr rating scale (Hoehn and Yahr, 1967). In cases where medicated patients were experiencing response fluctuations, the Hoehn and Yahr rating referred to the 'on' rather than the 'off' condition.

Twenty-six of these patients were, in general, in the early stage of the disease and had not yet received any medication. In this group (non-medicated Parkinson's disease), clinical symptoms were rated either as Hoehn and Yahr stage I (15 patients), stage II (eight patients) or stage III (three patients) [mean = 1.54 (0.14)].

The remaining 23 patients were all receiving L-dopa preparations either alone, or in combination with other medication. Eleven of these patients had mild/moderate clinical symptoms and were rated as Hoehn and Yahr stage I (two patients) or stage II (nine patients). Twelve of these patients had more severe clinical symptoms and were rated as Hoehn and Yahr stage III (seven patients) or stage IV (five patients). In addition to their dopaminergic treatment, five of these patients were receiving anti-cholinergic medication at the time of testing.

Exclusion criteria for the medicated Parkinson's disease patients included clinical dementia assessed using both the Mini Mental State Examination (MMSE) (Folstein *et al.*, 1975) and the Kendrick Object Learning Test (KOLT) (Kendrick, 1985). Specifically, only patients who scored above 24 out of 30 on the MMSE and 23 or above on the KOLT were included. The non-medicated group were not given the MMSE or the KOLT, although none of these patients was regarded as demented by their consultant neurologist.

Control subjects. A single group of normal control subjects (n = 25) were chosen to match the three patient groups as closely as possible with respect to age and premorbid verbal IQ, as estimated by the National Adult Reading Test (Nelson, 1982). These subjects were drawn from a large pool of control volunteers at the North East Age Research panel in Newcastle upon Tyne. Informed consent was obtained from all patients and control subjects prior to the neuropsychological testing session.

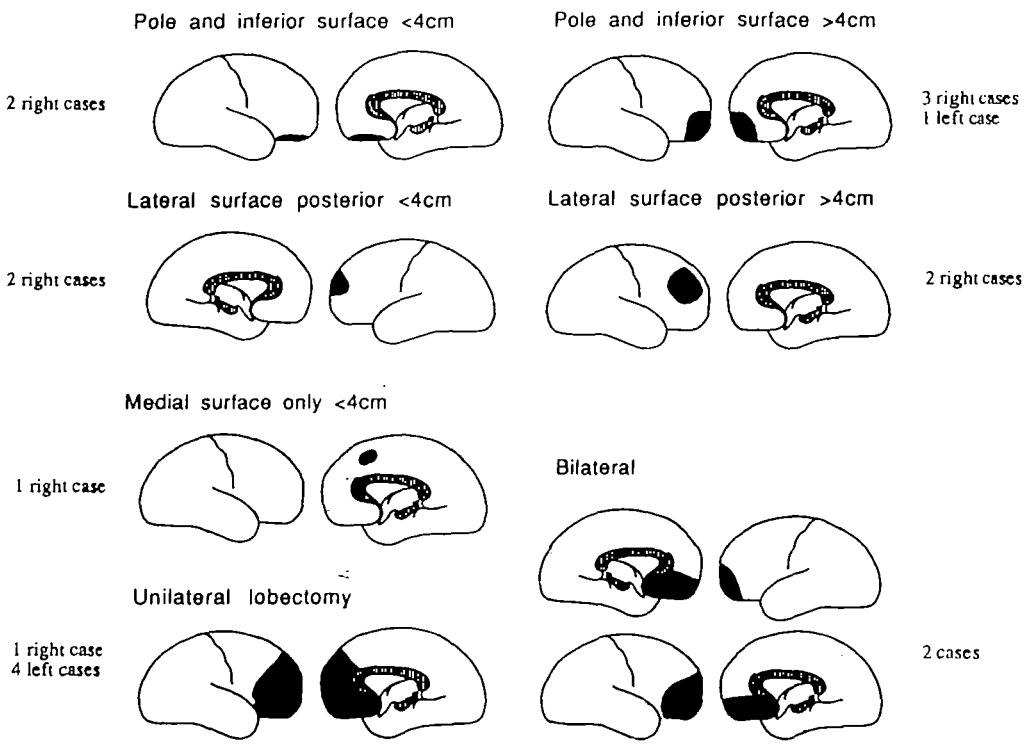

FIG. 1. Diagrams based on the neurosurgeon's drawings at the time of the operation showing the extent of the frontal lobe excision in several representative cases. The blackened areas define the lesion site.

Table 1 shows a summary of characteristics for the three patient groups and the single group of normal controls. One-way analysis of variance revealed that whilst the four groups did not differ significantly in terms of verbal IQ estimate [$F(3,88) = 2.24$, $P > 0.05$] they did differ significantly in terms of mean age [$F(3,88) = 12.6$, $P < 0.001$]. Orthonormal contrasts between the four groups confirmed that both the frontal lobe patients [t (88) = 5.75, $P < 0.001$] and the non-medicated Parkinson's disease group [t (88) = 2.64, $P < 0.05$] were significantly younger than the control subjects. Therefore, in the analysis of group differences, 'age' was treated as a covariate.

Procedure

The computerized test was essentially a substantially modified version of the CANTAB visual discrimination learning procedure which has been described previously (Downes *et al.*, 1989; Sahakian *et al.*, 1990; Owen *et al.*, 1991).

TABLE 1. SUBJECT CHARACTERISTICS

	No.	*M/F*	*Age*	*Verbal IQ (NART)*
Frontal lobe	18	9/9	48.28 (4.15)	108.3 (2.83)
Non-medicated Parkinson's disease	26	18/8	59.58 (1.99)	109.5 (1.40)
Medicated Parkinson's disease	23	15/8	65.35 (1.76)	106.4 (2.20)
Controls	25	6/19	67.64 (1.30)	113.0 (1.38)

M/F = sex; SEM are shown in parentheses.

Each subject performed in two conditions, one designed to assess perseveration to a previously relevant stimulus dimension and the other designed to assess the effect of learned irrelevance. Each condition comprised eight stages presented in the same fixed order, a simple discrimination (SD) and reversal (SDR), then a compound discrimination (CD) and reversal (CDR), then an intra-dimensional shift (IDS) and reversal (IDR) and finally, an extra-dimensional shift (EDS) and reversal (EDR) (*see* Fig. 2). Each of the two conditions lasted ~10 min. The order in which the two test conditions were presented was counterbalanced across subjects and in all cases, the conditions were separated by at least 45 min of unrelated neuropsychological tests.

Condition 1: perseveration. The subject was 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 began with a simple simultaneous discrimination for stimuli varying in only one dimension (Fig. 2). Four rectangular boxes, to the top and bottom and to the left and right of centre were presented on the screen. Two of these contained the test stimuli although the boxes used changed from trial to trial. Subjects were instructed in the following way:

'On the screen you can see two patterns. One of the patterns is "correct" and the other is "wrong" and you must point to the one which you think is correct. There is a rule which you can follow to make sure you make the correct choice every time. The computer will be keeping track of how well you are doing and when it is clear that you know the rule, then the computer will change it, but this will not happen very often. To begin with, there is nothing on the screen to tell you which of the patterns is correct so your first choice will be a simple guess. However, the computer will give you a message after each attempt to tell you whether you are right or wrong.'

A response to either of the two boxes containing the stimuli resulted in the appropriate feedback provided automatically by the computer. The feedback for a correct response consisted of the word 'CORRECT' presented in green on the screen accompanied by a high pitched tone whilst an incorrect response elicited the word 'WRONG' presented in red accompanied by a low pitched tone. After each response, the screen cleared and a interval of 1 s occurred before the next trial.

Once the subject had learned the discrimination to a criterion of six successive correct responses, the test proceeded automatically to the next stage, although subjects were not explicitly told that any change of contingencies had occurred. For the second stage (SDR), the stimuli remained the same, although the previously incorrect choice became the correct one, i.e. the contingencies were reversed. At the third and fourth stages, a second, alternative dimension was introduced and a CD followed by a reversal were tested. To succeed, subjects had to continue to respond to the previously relevant stimuli, ignoring the presence of the new, irrelevant dimension. For this and all subsequent stages, exemplars from the two dimensions were paired on each trial in a pseudo-random way with the constraint that runs of no more than three trials with identical pairings were allowed. At the IDS and IDR stages, new exemplars were introduced from each of the two dimensions and subjects were required to transfer the previously learnt rule to a novel set of exemplars of the same stimulus dimension. This 'total change' design (i.e. new stimuli) was adopted for both the IDS and EDS stages to avoid confounds with the subject's previous experience of specific stimuli.

At the EDS and EDR stages, the previously irrelevant stimulus dimension was replaced by an entirely new stimulus dimension which immediately became relevant [i.e. shapes (relevant) and lines (irrelevant) were replaced by solidity (relevant) and shape (irrelevant), *see* Fig. 2]. Thus, in this condition, failure to shift to the new relevant dimension could not be attributed to any prior learning about this dimension since it had not been experienced previously. Failure must therefore, reflect *perseveration* to the previously relevant dimension (shapes).

At each stage of the test, a change in contingencies would occur once a subject had learnt the current rule to a criterion of six consecutive correct responses. Failure to achieve this criterion within 50 trials resulted in the premature discontinuation of that test.

Condition 2: learned irrelevance. In the 'learned irrelevance' condition, the instructions were identical to those given in the perseveration condition. Again, the subject was 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 (Fig. 2). The dimensions employed were, however, different from those used in the perseveration condition (*see below*). The test proceeded as before, through eight stages, beginning with a simple simultaneous discrimination and ending with the EDR stage. The first six stages, through to the reversal of the IDS were identical in design to the perseveration condition. However, at the EDS and EDR stages the procedure differed

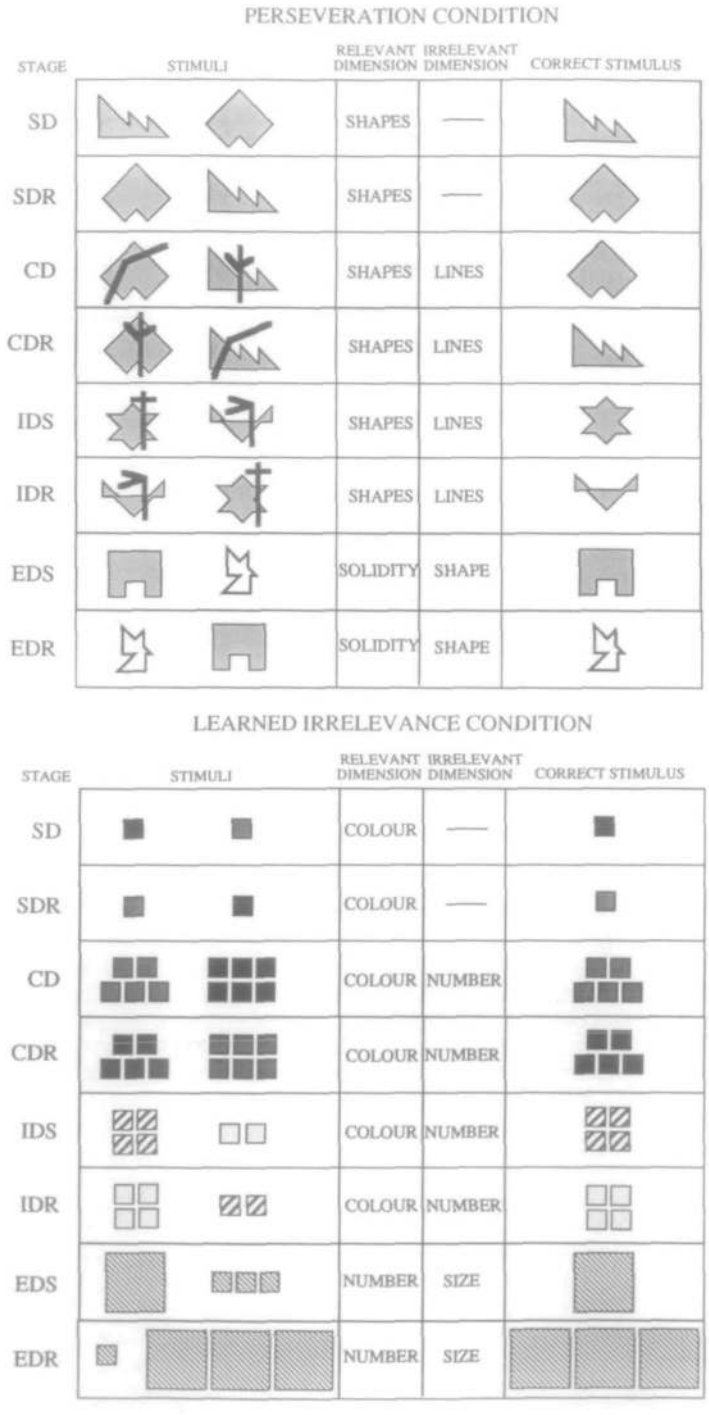

FIG. 2. Summary procedure for the intra-dimensional shift (IDS) and extra-dimensional shift (EDS) stages of the modified set-shifting task. Subjects performed twice, once in the perseveration condition and once in the learned irrelevance condition. Stimuli shown are for example only, and were counterbalanced between subjects and conditions. SD = simple discrimination; SDR = reversal of simple discrimination; CD = compound discrimination; CDR = reversal of compound discrimination; IDS = intra-dimensional shift; IDR = reversal of intra-dimensional shift; EDS = extra-dimensional shift; EDR = reversal of extra-dimensional shift.

in the following way. The previously relevant dimension was replaced by a completely novel dimension which was irrelevant [i.e. colour (relevant) and number (irrelevant) were replaced by number (relevant) and size (irrelevant)]. In this condition, failure to shift to the new relevant dimension (number) could not be attributed to prior learning about the previously relevant stimulus dimension (colour), since this was no longer present. Failure must, therefore, reflect learned irrelevance associated with the previously irrelevant stimulus dimension (number).

Again, at each stage in the learned irrelevance condition a change in contingencies occurred once a subject had learnt the current rule to a criterion of six consecutive correct responses. Failure to achieve this criterion within 50 trials resulted in the premature discontinuation of that test.

In each of the two conditions, three stimulus dimensions were therefore required. In total, six dimensions were chosen: colour (red, blue, yellow, white, pink), number (one, two, three, four, five, six), shapes and lines, size (large and small) and 'solidity' ('filled' and 'unfilled' shapes). Between subjects, the occurrence of four of the dimensions (lines, shapes, number and colour) was completely counterbalanced between the two conditions. Thus, every subject encountered each dimension once and only once and was never required to shift to a dimension to or from which a shift had already been made. The remaining two dimensions (solidity and size) were counterbalanced across conditions but only ever occurred at the EDS and EDR stages, since too few exemplars (i.e. two of each) were available for them to be used during the earlier stages of the task (*see* Fig. 2).

Note. Previous studies, using the original version of this computerized attentional set-shifting paradigm (Downes *et al.*, 1989; Owen *et al.*, 1991; Sahakian *et al.*, 1990) have advocated the inclusion of an additional stage, to facilitate learning, between the SDR and the CD stages in which the stimuli from the competing dimensions appear spatially separated, before being presented superimposed in the actual compound discrimination stage. In the present study, no such stage was included since for certain of the dimensions chosen (i.e shape and size, number and shape) it was not possible to present 'spatially separated' stimulus configurations.

Data analysis

In order that subjects could be effectively compared across conditions, the main index of performance was 'errors to criterion' at the IDS and EDS stages. Errors were calculated for the IDS, IDR, EDS and EDR stages of the test. Performance at earlier stages was not compared since, prior to the EDS, the two conditions did not differ in any way. A total 'ED_{errors}' error score was then computed, combining the number of errors made at the EDS and EDR stages. Similarly, total 'ID_{errors}' were calculated combining the number of errors made at the IDS and IDR stages of the test.

Given the complexity of the design, the analysis of results required the calculation of both main effects and interactions between the three critical variables, Group (frontal, non-medicated Parkinson's disease, medicated Parkinson's disease, control), Condition ('perseveration', 'learned irrelevance') and Shift (intra-dimensional, extra-dimensional). Standard tests of normality and homogeneity of variance across groups confirmed that the data were ideally suited for a parametric analysis. Therefore, a three-way analysis of variance procedure was employed to assess the relationship between Group, Condition and Shift, covarying throughout for the effects of age. Simple main effects were then calculated for each shift (ID_{errors} and ED_{errors}) and then for each of the two conditions ('perseveration' and 'learned irrelevance') again, covarying throughout for the effects of age.

Two supplementary analyses were made comparing those medicated Parkinson's disease patients who were receiving anti-cholinergic medication as well as L-dopa with those not receiving anti-cholinergic medication and comparing those frontal lobe patients on anti-convulsant medication with those not on anti-convulsants. Since no differences were observed between these patient subgroups, these results will not be reported in detail.

RESULTS

Analysis of variance revealed a significant three-way interaction between the Group (frontal, non-medicated Parkinson's disease, medicated Parkinson's disease, control), Condition ('perseveration', 'learned irrelevance') and Shift (ID, ED) factors, $F(3,88) = 2.71$, $P < 0.05$. The mean total ID_{errors} and ED_{errors}, in the perseveration and learned irrelevance conditions are presented, for the four subject groups, in Table 2.

TABLE 2. TOTAL ID_{ERRORS} AND ED_{ERRORS} IN THE PERSEVERATION AND LEARNED IRRELEVANCE TEST CONDITIONS

	Intra-dimensional shift (ID_{errors})	
	Perseveration	*Learned irrelevance*
Non-medicated patients with Parkinson's disease	2.08 (0.29)	4.62 (1.16)
Medicated patients with Parkinson's disease	3.39 (0.62)	4.43 (0.88)
Frontal	1.89 (0.28)	3.72 (0.90)
Control	2.60 (0.77)	2.96 (0.68)
	Extra-dimensional shift (ED_{errors})	
	Perseveration	*Learned irrelevance*
Non-medicated patients with Parkinson's disease	10.90 (2.50)	6.76 (1.65)
Medicated patients with Parkinson's disease	6.09 (1.43)	6.65 (1.98)
Frontal	13.60 (4.15)	3.39 (0.77)
Control	6.84 (1.42)	2.36 (0.40)

SEM are shown in parentheses.

The significant three-way interaction therefore permitted the calculation of separate two-way effects (Group×Condition) for the IDS and the EDS stages, with error terms adjusted accordingly.

At the IDS control condition, there was no overall group difference, $F(3,87) = 0.3$, no overall difference between the learned irrelevance and the perseveration conditions, $F(1,88) = 2.34$, and a non-significant interaction between the Group and Condition factors, $F(3,88) = 0.28$ (Fig. 3). Given that no significant effects were observed at the IDS, no further analyses of effects were appropriate at this stage of learning.

In contrast, at the EDS stage of learning there were highly significant differences between the three patient groups and the controls in terms of their relative performance in the 'learned irrelevance' and the 'perseveration' conditions. Thus, there was a highly significant interaction between the Group and Condition factors, $F(3,88) = 4.89$, $P < 0.001$ (Fig. 4) and significant main effects of both Group $F(3,87) = 12.39$, $P < 0.001$ and Condition $F(1,88) = 23.3$, $P < 0.001$. The significant interaction effect permitted the calculation of separate simple main effects for ED_{errors}, in the two test conditions, with error terms adjusted accordingly. A restricted set of six planned comparisons, selected a priori, were then made between each of the patient groups and the controls in the 'perseveration' and 'learned irrelevance' conditions. One-way analysis of variance revealed that the frontal lobe patients differed significantly from the controls in the 'perseveration' condition, $F(1,42) = 12.28$, $P < 0.001$, but not in the learned irrelevance condition, $F(1,42) = 0.27$. In contrast, the medicated Parkinson's disease group differed significantly from the controls in the 'learned irrelevance' condition, $F(1,46) = 5.5$, $P < 0.05$, but not in the perseveration condition, $F(1,46) = 0.16$. The non-medicated Parkinson's disease patients differed from the controls in both the 'perseveration' condition, $F(1,50) = 5.28$, $P < 0.05$, and the 'learned irrelevance' condition, $F(1,49) = 6.15$, $P < 0.05$.

Mean response latencies for the IDS and the EDS stages were analysed in precisely

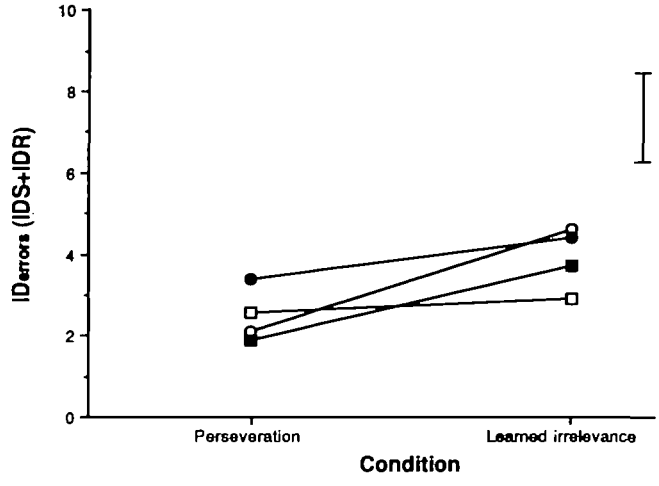

FIG. 3. The intra-dimensional shift (IDS): the mean total (ID_{errors}) errors to criterion for the perseveration and learned irrelevance conditions. The bar represents one standard error of the difference between the means. This is an appropriate index of variation for computing *post hoc* tests of significance between the mean values of the groups and is calculated according to the formulae provided by Cochran and Cox (1957). Open circles = non-medicated Parkinson's disease patients; closed circles = medicated Parkinson's disease patients; closed squares = patients who had undergone frontal lobe excisions; open squares = control group.

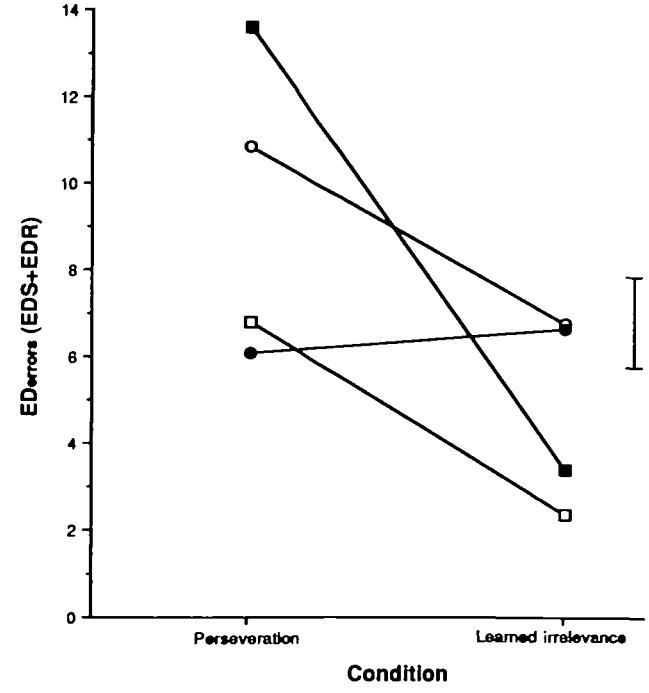

FIG. 4. The extra-dimensional shift (EDS): the mean total (ED_{errors}) errors to criterion for the perseveration and learned irrelevance conditions. The bar represent one standard error of the difference between the means. For symbols, *see* legend to Fig. 3.

the same way as the error scores described above. There were no significant effects of Group, Condition or Stage of learning.

These results confirm that, at the EDS stage of learning, different patterns of deficit were observed in the three patient groups. Specifically, whilst the frontal lobe patients exhibited increased 'perseveration' with normal levels of 'learned irrelevance', the reverse pattern was observed in the medicated patients with Parkinson's disease. In contrast, the non-medicated Parkinson's disease patients were significantly, and equally impaired in both conditions.

The effects of laterality of lesion in the frontal lobe group

The effect of laterality in the frontal lobe group was investigated by comparing the number of errors at the EDS and EDR stages of learning in the five left-sided cases and the 11 right-sided cases in the two test conditions. Although there was a tendency for the right-sided patients to make more errors than the left-sided patients in the perseveration condition [16.0 (6.7) and 8.4 (5.2), respectively] but not in the learned irrelevance condition [3.18 (0.9) and 4.0 (2.3), respectively] small cell sizes and large variance within the subgroups precluded any formal statistical interpretation of this result.

DISCUSSION

The results of this study reveal distinct patterns of cognitive impairment in patients with frontal lobe damage, non-medicated patients with Parkinson's disease and medicated Parkinson's disease patients with more severe clinical symptoms. At the IDS stage of learning, which served as control condition for general learning and perceptual deficits, the performance of the three patient groups did not differ significantly from the controls in either of the test conditions (i.e. 'perseveration' or 'learned irrelevance'). In contrast, the critical EDS stages of learning revealed distinct patterns of impairment among the three patient groups. Specifically, frontal lobe patients made more errors than control subjects in the 'perseveration' condition but performed identically to controls in the 'learned irrelevance' condition. Conversely, the medicated Parkinson's disease group made more errors in the 'learned irrelevance' condition but performed similarly to controls in the 'perseveration' condition. Finally, the non-medicated Parkinson's disease patients were equally impaired in both conditions.

The results of this study unequivocally confirm previous suggestions that the behaviour of frontal lobe patients in tests requiring shifts of attentional 'set' may indeed be described as *perseverative* (Milner, 1963; Drewe, 1974; Nelson, 1976; Robinson *et al.*, 1980; Cicerone *et al.*, 1983). Although normal control subjects made slightly more than twice the number of errors at the EDS stages of the 'perseveration' condition than at the same stages of the 'learned irrelevance' condition, by comparison, frontal lobe patients made more than four times as many errors. The behaviour of frontal lobe patients on tests such as the WCST is often described as perseverative on the basis of the increased numbers of 'perseverative' relative to 'non-perseverative' errors made by these patients. Although this classification is a useful description of the behaviour and obviously suggests an underlying perseverative tendency, the present analysis makes it clear that attentional set-shifting can also be disrupted by factors not directly related to perseveration. Nevertheless, our results indicate that attentional set-shifting deficits in patients with frontal

lobe damage do indeed reflect an increased tendency to perseverate in their responses to a previously relevant perceptual dimension.

It is important to point out that the deficit in frontal lobe patients observed in this study, represents a relatively complex form of perseveration, akin to the 'stuck in set', rather than either the 'recurrent' form or the 'continuous' form of perseveration described by Sandson and Albert (1984, 1987). Since the subjects were required to shift attention between stimulus dimensions, rather than merely between different exemplars of the same stimulus dimension, the deficit in frontal lobe patients presumably reflects a relatively high level disturbance in the inhibitory mechanisms of selective attention as opposed to an impairment in the reversal of a specific stimulus–response habit. This distinction between different levels of inhibitory control over response output is important because of related data which suggests that the frontal cortex is involved in both forms of perseveration. For example, at the level of reversing stimulus–reward associations, orbitofrontal lesions produce perseverative impairments in extinction and reversal learning in monkeys (Mishkin, 1964). In terms of perseveration at the higher level of control, Passingham (1972) examined the effects of prefrontal lesions on a series of discriminations which apparently required monkeys to shift attention between various stimulus properties. Deficits were found, although a precise interpretation of the results is not possible since identical stimuli were retained throughout the series of attentional shifts. Of more direct relevance to the current study, Roberts *et al.* (1991, 1992) have shown differential effects of cholinergic and dopaminergic deafferentation of the prefrontal cortex on these two forms of inhibitory control in marmosets. Specifically, cholinergic deafferentation of the prefrontal cortex led to impaired reversal learning in marmosets, but produced no deficit in extra-dimensional set-shifting ability (Roberts *et al.*, 1991), whereas dopaminergic deafferentation led to enhanced EDS performance, with no effect on reversal learning (Roberts *et al.*, 1992).

There is relatively little information available for linking these results to studies of attentional set-shifting in man. Milner (1964) has argued that damage to the dorsolateral prefrontal cortex is the crucial factor in producing perseverative errors on the WCST. However, in the present study, no obvious relationship was observed between the precise location of the frontal lobe excision and the degree of perseveration in these patients, although it is possible that more precise imaging of these ablations would clarify whether such a relationship actually exists. Whilst this issue remains open, a recent study utilizing PET has shown that conditions requiring selective attention produce activation in circuitry including the lateral orbitofrontal cortex, the caudate nucleus and the globus pallidus, rather than the dorsolateral prefrontal regions, which are activated instead, under conditions of divided attention (Corbetta *et al.*, 1991).

A very different pattern of deficits from that of frontal lobe patients was observed in patients with Parkinson's disease, who, compared with controls, exhibited both perseveration and a failure to respond appropriately to a previously irrelevant dimension ('learned irrelevance'). This dual failure does not simply reflect a non-specific disruption of attentional set-shifting ability for the following reasons. First, in the medicated Parkinson's disease group, impairments were only observed in the 'learned irrelevance' condition. These patients did not perseverate, suggesting further that they have deficits in tests of attentional set-shifting ability which are not necessarily attributable to a dysfunctioning of circuitry involving the prefrontal cortex. Secondly, in the non-medicated Parkinson's disease group, the pattern of deficits observed suggests that such patients may also exhibit a separate

'frontal-like' perseverative tendency which is not apparent in the medicated group with more severe clinical symptoms. This somewhat surprising difference between the two groups of Parkinson's disease patients strongly suggests that L-dopa medication selectively ameliorates the deficit in the 'perseveration' condition, but does not affect performance in the 'learned irrelevance' condition. This result substantiates previous findings in Parkinson's disease patients which have suggested that L-dopa selectively improves cognitive deficits that are associated with frontal lobe dysfunction (e.g. Lange *et al.*, 1992). It also suggests that perseveration of attentional set occurs as a consequence of damage to the striatal dopaminergic projections, although possible effects of L-dopa on non-striatal mechanisms cannot be ruled out. For example, Parkinson's disease patients also exhibit dopamine loss in the prefrontal cortex (Scatton *et al.*, 1983) which could contribute to perseverative behaviour in this group. However, in monkeys, prefrontal dopamine depletion leads to enhanced, rather than impaired, ED set-shifting, with an associated up-regulation of striatal dopaminergic function in the same animals (Roberts *et al.*, 1992). These considerations, together with the PET studies of Corbetta *et al.* (1991) described above, certainly implicate dopamine dependent functions of the striatum in certain of the inhibitory control mechanisms that contribute to selective attention.

The mild perseverative tendency observed in the non-medicated Parkinson's disease patients suggests deficits in some of the inhibitory mechanisms that normally allow attention to be released onto other salient dimensions. However, the parallel deficit in the 'learned irrelevance' condition suggests that other inhibitory mechanisms of attention may be overactive in Parkinson's disease, although little is known about the neural substrates of such processes. The lack of effect of L-dopa and of frontal lobe damage suggests that neither the dopaminergic mechanisms of the striatum, nor the prefrontal cortex itself, mediate these processes. It remains possible, however, that the deficit in 'learned irrelevance' is striatal in nature and is improved by L-dopa medication, but that this relative improvement is masked by the effects of disease progression. There is, as yet, little relevant evidence in experimental animals, although the presence of a range of non-striatal forms of pathology in Parkinson's disease, including noradrenergic, cholinergic and serotonergic deafferentation of the cortex (Agid *et al.*, 1987) suggests that impaired 'learned irrelevance' may arise from one or more of these alternative forms of pathology. Cortical Lewy bodies may also be implicated in Parkinson's disease (Byrne *et al.*, 1989; Gibb *et al.*, 1989), although these are most evident late in the course of Parkinson's disease, and the learned irrelevance deficit was clearly observed in unmedicated patients early in the course of the disease, as well as in those with more severe clinical symptoms.

The present results bear importantly on previous theories concerned with the nature of cognitive deficits in Parkinson's disease, and with the functions of the striatum itself, based on the concept of 'set' (Buchwald *et al.*, 1975; Bowen, 1976; and the 'shifting aptitude' of Cools *et al.*, 1984). In some cases, more emphasis has been placed on the problems that Parkinson's disease patients have in maintaining, as well as shifting, set. For example, in ambiguous situations where more than one 'rule' has previously been used to guide behaviour, Parkinson's disease patients exhibit difficulties in the consistent use of one particular rule (Talland, 1962; Flowers and Robertson, 1985; Robertson and Flowers, 1990). Indeed, similar problems in forming and maintaining sets have been shown in previous studies using tasks related to the present paradigm (Downes *et al.*, 1989; Owen *et al.*, 1993). However, the present study was specifically designed to

investigate the mechanisms involved in shifting attentional set although in the patients with Parkinson's disease, no consistent impairment was observed up to and including the IDS stage, suggesting that these patients had no difficulties in forming and maintaining sets based on this stimulus material.

In previous discussions of specific set-shifting deficits in Parkinson's disease, Brown and Marsden (1988) have argued that Parkinson's disease patients are only impaired when they have to rely on internal control for the regulation of behaviour, rather than on external cues. The issue of internal versus external control over set-shifting is not addressed by the present study, because shifting in both the 'perseveration' and the 'learned irrelevance' conditions was governed by previous experience, either of positive feedback for the previously relevant dimension, or of negative feedback for the previously irrelevant one. However, the results clearly demonstrate that these different forms of internal regulation of attention may both contribute to the set-shifting impairment in Parkinson's disease.

The present experiments have concentrated on set-shifting ability governed by distinctive visual features, such as shape, but have not considered possible spatial determinants of attention. Thus, in terms of the present results, it is of interest that Posner *et al.* (1984) have argued that covert orienting of spatial attention in the visual field involves three putative mental operations: (i) disengagement from a current focus of attention; (ii) movement across the visual field; (iii) engagement on a target. Failure at the 'disengagement' stage would lead to perseveration in favour of that particular stimulus, a pattern of behaviour analogous to that seen in the frontal lobe patients in the present study. Using a task designed to assess the speed of orientation of attention to spatial locations, Rafal *et al.* (1984) showed that manipulation of medication with L-dopa for Parkinson's disease patients had no effect on the spatial orienting of attention. However, several other recent studies have reported deficits in spatial orienting in Parkinson's disease (Wright *et al.*, 1990; Yamada *et al.*, 1990). The former study reported that under certain conditions, Parkinson's disease patients showed faster orienting to an exogenously summoned target, an effect resembling that produced by treatment with drugs affecting catecholaminergic function (Clark *et al.*, 1989). The latter study reported impairments in covert shifts of attention only in more disabled Parkinson's disease patients. These results confirm that, in Parkinson's disease, there are multiple deficits in spatial attention which may occur in parallel to the impairments in attentional set-shifting described in this paper and which may depend upon analogous mechanisms.

The paradigm presented in this paper represents a novel approach to understanding the types of mechanisms that contribute to set-shifting deficits in clinical populations. Its utility may be seen from the dissociable pattern of deficits observed in the frontal lobe patients and in the patients with medicated Parkinson's disease, which makes it most unlikely that the results can be understood in terms of such general constructs as motivational inertia in either group. The demonstration of 'true' perseveration in the frontal group underlines the normal role of the prefrontal cortex in suppressing automatic tendencies and thus allowing new goal-directed actions to be expressed. The fact that unmedicated patients with Parkinson's disease also exhibit perseveration compared with controls raises the question as to whether this behaviour too can be further fractionated into component processes. For example, it is possible that striatal dopaminergic mechanisms operate to facilitate switching by affecting contention scheduling of response tendencies in the basal ganglia, possibly via such mechanisms as lateral inhibition (Shallice, 1988; Robbins and

Sahakian, 1983). Conversely, such switching may also be affected by 'top-down' mechanisms that operate to resolve conflicts between previously dominant and new responses via the agency of attentional resources to the basal ganglia provided by the prefrontal cortex itself (Shallice, 1988). This issue can be addressed by a combination of empirical and modelling studies (e.g. Dehaene and Changeux, 1991) and may lead us to understand the distinctive roles played by the frontal cortex and the striatum in the operation of fronto-striatal functional 'loops' (Alexander *et al.*, 1986).

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