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The Role of Learned Irrelevance in Attentional Set-Shifting Impairments in Parkinson's Disease

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In this study, the cognitive and neurochemical factors underlying learned irrelevance, one of the mechanisms thought to be responsible for attentional set-shifting deficits in Parkinson's disease (PD), were investigated. In a visual discrimination learning task, the extent to which a target dimension was irrelevant prior to an extra-dimensional shift was varied. Twenty patients with PD and 22 healthy participants performed the task twice, with patients tested on and off L-dopa. The patients made more errors than control participants in the condition in which the target dimension was completely irrelevant prior to the extradimensional shift, but not when it was partially reinforced. Moreover, L-dopa had no effect on the patients' task performance, despite improving their working memory. These results confirm that learned irrelevance is a significant factor in accounting for attentional set-shifting deficits in patients with PD, although unlike other executive impairments in this group, the phenomenon appears to be unrelated to their central dopaminergic deficit.

Keywords: dopamine, frontal lobe, basal-ganglia, executive function

Although only about 20% of patients with Parkinson's disease (PD) develop frank dementia (Brown & Marsden, 1984), less severe cognitive impairments are common even at the earliest stages of the disease (Downes et al., 1989). The pattern of these impairments is often described as predominantly executive, resembling that produced by circumscribed frontal-lobe lesions (Owen et al., 1992). *Executive processes* have been defined as cognitive mechanisms by which performance is optimized in situations requiring the simultaneous operation of a number of different processes (Baddeley, 1986). Executive functioning is required, therefore, when sequences of responses must be generated and scheduled and when novel plans of action must be formulated and carried out. The frontal lobes have long been known to play an important role in executive functioning, although the fact that the dysexecutive syndrome may be observed in patients with damage to other brain regions (e.g. Morris, Downes, & Robbins, 1990) suggests that an equivalence between the prefrontal cortex and executive functioning cannot be assumed.

Attentional set-shifting ability has been widely studied in PD, and deficits have been reported in both cognitive and motor domains (A. R. Cools, van den Bercken, Horstink, van Spaendonck, & Berger, 1984; Downes et al., 1989; Owen et al., 1992; van Spaendonck, Berger, Horstink, Buytenhuijs, & Cools, 1996). In the cognitive domain, attentional set-shifting performance has been studied most extensively with tests of visual discrimination learning (e.g. Downes et al., 1989; Owen et al., 1992). Using such tasks, a number of studies have shown that PD patients are more impaired when an attentional shift is required between two different perceptual dimensions, such as color and number (a so-called *extradimensional shift* [EDS]), than when a shift is required between two different values of the same dimension, such as blue and red (a so-called *intradimensional shift* [IDS]; Roberts, Robbins, & Everitt, 1988). This EDS-specific deficit in PD has been further delineated into two cognitively distinct processes, perseveration and learned irrelevance (Owen et al., 1993). *Perseveration* refers to an inability to disengage attention from a previously relevant dimension at the EDS stage of learning. In contrast, *learned irrelevance*, which was developed originally within the framework of classical animal learning theory, refers to the inability to attend to, or to learn about, information that has previously been shown to be irrelevant (Mackintosh, 1973). Owen et al. (1993) contrasted

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two EDS conditions that allowed perseveration (but not learned irrelevance) or learned irrelevance (but not perseveration), respectively, in groups of medicated and nonmedicated patients with PD as well as a group of patients with circumscribed frontal-lobe removals. In the perseveration condition, patients were presented at the EDS with one dimension that was already familiar and had always been relevant to the task rule during previous stages of learning and with a second dimension that was novel. They were required to shift response set to the novel dimension, ignoring the previously relevant dimension (i.e., attempt to overcome the tendency to perseverate). In the learned irrelevance condition, patients were presented at the EDS with one dimension that was already familiar but had been irrelevant during all previous stages of learning and with a second dimension that was novel. They were required to shift response set to the familiar (but previously irrelevant) dimension, ignoring the novel dimension (i.e., attempt to overcome learned irrelevance). Frontal-lobe patients made significantly more errors than control participants in the perseveration condition but performed equivalently in the learned irrelevance condition. In contrast, the medicated PD group made significantly more errors in the learned irrelevance condition but not in the perseveration condition. Finally, the nonmedicated PD group was equally and significantly impaired in both conditions. This result has two major implications for understanding the nature of attentional set-shifting deficits in PD. First, both perseveration and learned irrelevance contribute to the cognitive impairments observed in PD. Second, perseveration, but not learned irrelevance, responds to L-dopa therapy, suggesting that the former, but not the latter, is related to the central dopaminergic deficit in PD. Dopaminergic neuronal loss represents the primary neuropathology in PD and occurs predominantly in the nigrostriatal tract and, to a lesser extent, in the mesocortical pathway where neurons project from the ventral tegmental area and the medial substantia nigra pars compacta (Jellinger, 2001). Recent functional neuroimaging studies exploring the executive deficits in PD have provided supporting evidence for a role of both disruption in the nigrostriatal (Dagher, Owen, Boecker, & Brooks, 2001; Owen, Doyon, Dagher, Sadikot, & Evans, 1998) and mesocortical (R. Cools, Stefanova, Barker, Robbins, & Owen, 2002; Mattay et al., 2002) pathways.

However, the importance of learned irrelevance as a mechanism accounting for attentional set-shifting deficits in PD has been challenged (Gauntlett-Gilbert, Roberts, & Brown, 1999). Theoretically, if learned irrelevance is a core component of PD, then patients' performance should actually be improved during one type of shift not tested in the study by Owen et al. (1993), namely, when the previously irrelevant dimension remains irrelevant and a newly introduced dimension becomes relevant. Gauntlett-Gilbert et al. (1999) tested that hypothesis explicitly and showed that the performance of PD patients was actually facilitated under such circumstances. However, because the overall performance of the PD patients was still worse than that of healthy participants, Gauntlett-Gilbert et al. (1999) concluded that there is a global EDS deficit in PD that is not related specifically to learned irrelevance.

Other aspects of the learned irrelevance hypothesis also remain controversial. For example, in the original study by Owen et al. (1993), the healthy control group did not actually exhibit a significant learned irrelevance effect at all, making it impossible to unequivocally ascribe the deficit in PD patients to learned irrelevance per se. In addition, in that study, learned irrelevance was measured as a summation of errors committed at both the EDS and the reversal stage following the EDS. It has been argued recently that EDS and reversal shifts involve quite different levels of processing, the former being executed at the level of attentional set, and the latter occurring at the level of stimulus–reinforcement associations (Keri, 2003; Swainson et al., 2000). Finally, in both of the previous studies of learned irrelevance in PD (Gauntlett-Gilbert et al., 1999; Owen et al., 1993), participants were required to make a choice between the previously irrelevant dimension and a novel dimension, the assumption being that only the irrelevance factor would contribute to the shifting effect. However, several investigations have now demonstrated that patients with PD show an impaired response to novelty (Tsuchiya, Yamaguchi, & Kobayashi, 2000), suggesting that this factor may also contribute to the effects observed in studies of learned irrelevance (Lubow, 1997).

We designed the current study to address all of these issues using an entirely novel task in which we varied the extent to which a target dimension was irrelevant prior to a critical EDS from fully irrelevant (any given value of this dimension randomly co-occurred with the reinforced value of the currently relevant dimension) to partly relevant (one value of this dimension co-occurred with the reinforced value of the relevant dimension on 75% of trials preceding the EDS). Unlike the learned irrelevance procedures used previously, to prevent a contaminating effect of novelty, we did not introduce a novel dimension at the EDS stage. We hypothesised that, if prior experience of irrelevance is the basis of the learned irrelevance effect, then learned irrelevance should be attenuated in the partly relevant condition. In the first experiment, this hypothesis was tested in a large group of healthy participants.

We designed the second experiment to directly test the hypothesis that attentional set-shifting deficits in PD are related to enhanced learned irrelevance and, furthermore, that they are relatively insensitive to central dopamine levels. On the basis of previous findings, we predicted that patients with PD would be more impaired than control participants when an EDS was required to the previously fully irrelevant dimension than when an EDS was required to the previously partly relevant dimension. In addition, we tested the effect of L-dopa on learned irrelevance directly by testing the patient group both on and off their L-dopa medication. On the basis of previous findings, we predicted that manipulating dopaminergic medication to a degree sufficient to induce a significant change in an unrelated executive process (working memory) would not ameliorate the observed deficit in learned irrelevance, confirming that the impairment is unlikely to be related to the central dopaminergic loss in PD.

Experiment 1

Method

Participants

The 142 Polish-speaking healthy control participants participating in the first experiment were recruited from the Institute of Psychology at Jagiellonian University in Krakow (mean age = 35.9 years, *SD* = 23.3 years; 32 men, 110 women; all had at least 12 years of formal education). They were randomly assigned to one of two experimental groups, matched for age and gender, with each participant performing one of the two test conditions described below.

Learned Irrelevance Test

The test was modeled on the Cambridge Neurophsychological Test Automated Battery (CANTAB) ID/ED set-shifting task, which has been described in detail elsewhere (Owen, Roberts, Polkey, Sahakian, & Robbins, 1991). The original task is known to be sensitive to impairments in patients with PD (Owen et al., 1992) as well as in neurosurgical patients with excisions of the frontal cortex (Owen et al., 1991).

As in the original ID/ED set-shifting task, in the learned irrelevance test, the participants were required to learn a series of visual discriminations on the basis of feedback provided automatically by the computer after each trial (see Figure 1). The test consisted of eight stages. It began with a simple discrimination and reversal for stimuli varying in only one dimension (i.e., color). Two additional dimensions were then introduced (shape and number of items), and compound discrimination and reversal were tested. At the IDS stage and reversal, new exemplars from each of the three dimensions were presented, requiring the participants to transfer the previously learned rule to a novel set of exemplars of the same dimension (i.e., color). Finally, at the EDS and reversal, novel exemplars from each of the three dimensions were introduced again, and the participants had to shift response set to one of the alternative stimulus dimensions that had been previously irrelevant (either shape or number of elements).

However, the EDS procedure of the current task differed from the original procedure (Owen et al., 1993). To prevent a contaminating effect of novelty on learned irrelevance, in the current task, we did not introduce a novel dimension at the EDS task stage. Instead, in the current task, the participants were required to shift attentional set to a dimension that had been previously (prior to the EDS) either fully irrelevant or partly reinforced. From the compound discrimination stage of the test, the stimuli were characterized by three dimensions: color, shape, and number of items; and up to the EDS stage only one of the three dimensions (color) was relevant to the discrimination rule and consistently reinforced. At the same time, the level of task irrelevance of the other two dimensions was varied, with one dimension (either shape or number) being fully irrelevant, and the other dimension being partly reinforced. In the case of the fully irrelevant dimension, any given value of this dimension (e.g., square or circle) randomly co-occurred with the reinforced value of the currently relevant dimension (i.e., blue or red). In other words, the fully irrelevant dimension was reinforced randomly and in this sense was equivalent to the irrelevant dimension of the original CANTAB ID/ED task. In contrast, in the case of the partly relevant dimension, one value of this dimension co-occurred with the reinforced value of the currently relevant dimension on 75% of trials preceding the EDS. As a result, the partly relevant dimension predicted the reinforcement at a level that was greater than chance. At the EDS stage of the task, the participants were required to shift their attention either to the previously fully irrelevant dimension (the full irrelevance condition) or to the previously partly reinforced dimension (the partial relevance condition).

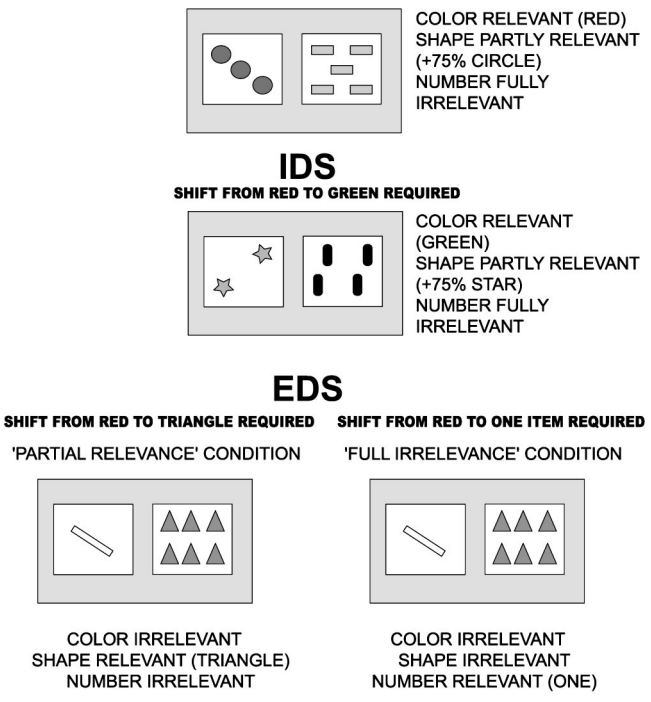

Figure 1. Learned irrelevance: Summary of the procedure for the intradimensional shift (IDS) and extradimensional shift (EDS) stages of the learned irrelevance task. Stimuli shown are for example only.

On each trial, the participants responded by pressing one of the two response keys corresponding to whether the chosen stimulus was on the left or right side of the screen. Feedback was provided after each trial. The criterion for passing from one stage to the next was 12 consecutive correct responses, and failure to achieve this criterion within 100 trials resulted in the premature discontinuation of the test. Every participant was randomly assigned to one of the test conditions, full irrelevance or partial relevance, and was required to shift response set from color either to shape or to number. The EDS target dimensions (shape or number) were counterbalanced across the test conditions. However, to make sure that conditions preceding the EDS were identical across test conditions and did not differentially affect ED shifting, we used only color as the dimension relevant prior to the EDS.

Prior to the task, the participants were provided with the following instructions:

> 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. Both correctness and speed of your responses is important.

Results

Errors to criterion were analysed at the IDS and the EDS stages of the test. Previous stages were not analyzed, as in these preliminary (preshift) trials, all of the conditions were formally identical. To assess the relationship of Shift (IDS, EDS; within-subject factor) × Test Condition (full irrelevance, partial relevance; between-subjects factor) × EDS Target Dimension (shape, number; between-subjects factor), we used a repeated measures three-way analysis of variance (ANOVA) procedure. Although the primary hypothesis concerned the two-way interaction between the shift and the test condition factors, we also assessed the effects of the EDS target dimension to explore the possibility that salience of that dimension might affect EDS performance.

The three-way ANOVA of Shift × Test Condition × EDS Target Dimension revealed a highly significant main effect of shift, $F(1, 138) = 97.53$, $p < .0001$, $\eta = 0.414$, with more errors being committed at the EDS compared with the IDS. The interaction of Shift × Test Condition was also significant, $F(1, 138) = 12.62$, $p < .001$, $\eta = 0.084$, reflecting the fact that EDS was more

difficult under the fully irrelevant condition compared with the partly relevant condition (see Figure 2). The interaction of Shift × EDS Target Dimension was also significant, $F(1, 138) = 25.15$, $p < .0001$, $\eta = 0.154$, reflecting the fact that shifting to number was more difficult than shifting to shape. However, the three-way interaction of Shift × Test Condition × EDS Target Dimension was not significant, $F(1, 138) = 2.34$, $p < .129$, suggesting that although shape was a more salient dimension than number, there was no difference in the overall dynamics of EDS shifting to shape compared with EDS shifting to number.

The results of this experiment provide evidence that learned irrelevance can affect performance of healthy participants on a rule-shift task and that this effect can be attenuated by partial relevance of the EDS target dimension experienced by participants prior to EDS. This confirms that the full irrelevance/partial relevance manipulation implemented in the IDS/EDS set-shifting task in the present study was successful and can be used to examine the relationship between PD and learned irrelevance.

Experiment 2

In the second experiment, factors underlying learned irrelevance in patients with PD were investigated with the presented learned irrelevance test. On the basis of the results of the first experiment, we predicted that patients with PD, as compared with healthy participants, would be more impaired in the full irrelevance condition than in the partial relevance condition. In addition, on the basis of the previous study of learned irrelevance in PD (Owen et al., 1993) it was hypothesised that L-dopa would not ameliorate performance deficits in PD on either test condition. To confirm that this lack of L-dopa effect was not global across all executive functions in PD, we also used a working memory task (e.g., Lewis, Cools, et al., 2003; Lewis, Slabosz, Robbins, Barker, & Owen, 2005). On the basis of previous studies (Lange et al., 1992), we predicted that deficits in working memory performance in PD would be ameliorated by L-dopa.

Method

Participants

Patients. The 20 patients with PD included in this study were all in the mild stages of the disease (mean age = 70.2 years, $SD = 6.1$ years; 12 men, 18 women). The group was drawn from a pool of the Parkinson's Disease Research Clinic at the Cambridge Centre for Brain Repair, where they had undergone careful historical review along with physical examination and neuropsychometric analysis. This included the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975); the National Adult Reading Test (NART) (Nelson, 1982) as an estimate of premorbid IQ; testing of verbal and categorical fluency FAS 60 seconds (Benton, 1983); animals 90 seconds (Goodglass, 1972); and the motor screening task, pattern and spatial recognition memory (PRM and SRM), and Tower of London planning task (TOL) from the CANTAB (Owen et al., 1992). All patients satisfied UK Parkinson's Disease Study Brain Bank criteria (Gibb & Lees, 1988). In addition to their L-dopa medication, 2 patients were taking selegiline, 2 were on anticholinergics, and another 2 were taking selective serotonin reuptake inhibitors.

Table 1 shows a summary of characteristics for the whole patient group and for the subgroups of patients performing the two conditions of the learned irrelevance task. Compared with their on-L-dopa session, the patients exhibited significant motoric deterioration on Hoehn and Yahr (1967) staging, $t(19) = 2.1$, $p < .001$, and Unified Parkinson's Disease

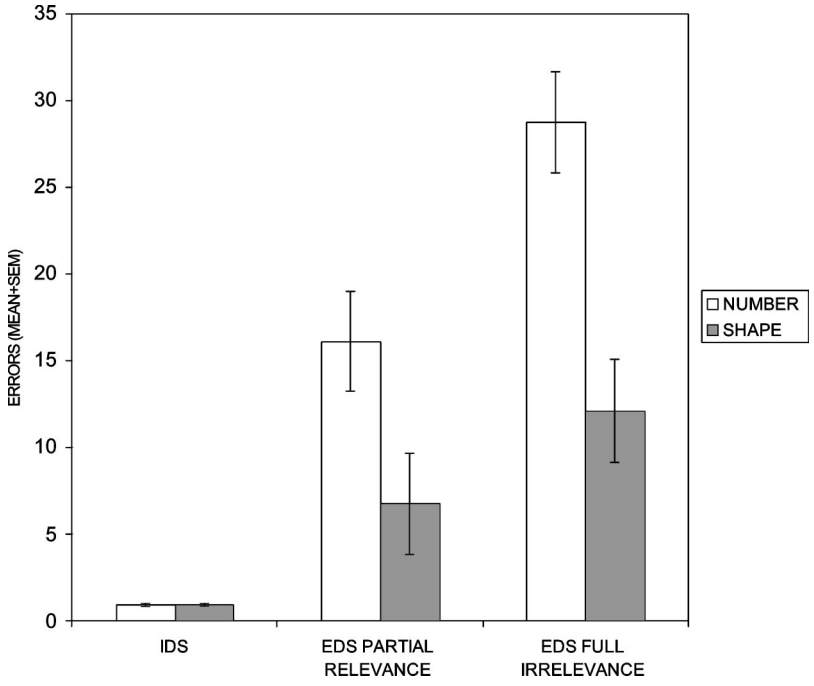

Figure 2. Learned irrelevance: Effect of irrelevance of a dimension on set-shifting performance and mean errors to criterion in relation to shift and test condition factors. Bars represent standard error of the mean. EDS = extra dimensional shift.

Table 1
Subject Demographics in Experiment 2

Variable	Patients[a]	Patients[b]		Controls[c]	
		Full irrelevance	Partial relevance	Learned irrelevance	Working memory
Age (in years)	70.20 ± 6.12	68.28 ± 7.03	72.14 ± 4.64	68.43 ± 7.9	68.30 ± 7
NART	110.25 ± 9.23	110.90 ± 12.05	109.60 ± 5.81	112.32 ± 7.41	114.40 ± 8
BDI	7.90 ± 4.20	8.30 ± 4.95	7.50 ± 3.56		
Disease duration (in years)	6.50 ± 6.00	6.60 ± 6.32	6.30 ± 6.11		
UPDRS					
On	27.00 ± 18.00	28.10 ± 21.82	25.9 ± 13.68		
Off	55.00 ± 16.00	51.80 ± 14.29	58.50 ± 17.08		
H&Y					
On	1.90 ± 0.40	1.80 ± 0.34	2.1 ± 0.32		
Off	2.70 ± 0.40	2.60 ± 0.31	2.75 ± 0.48		
MMSE	29.00 ± 1.00	29.20 ± 1.03	29.00 ± 1.05		
FAS	36.00 ± 12.00	38.10 ± 14.37	34 ± 9.40		
CF	21.00 ± 6.00	19.50 ± 2.10	22.20 ± 1.63		
Motor screening latency (in milliseconds)	1,076.00 ± 395.30	909.30 ± 299.74	1,244.20 ± 490.90		
PRM (maximum score 24)	20.50 ± 3.00	20.60 ± 3.74	20.40 ± 2.36		
SRM (maximum score 20)	15.50 ± 2.30	14.90 ± 2.92	16.00 ± 1.41		
TOL (maximum score 14)	10.30 ± 2.50	10.10 ± 2.80	10.50 ± 2.27		
L-dopa (mg)	605.30 ± 339.4	590.00 ± 229.10	620.00 ± 449.59		

Note. Values represent means ± standard deviations. NART = National Adult Reading Test (Nelson, 1982); BDI = Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); UPDRS = Unified Parkinson's Disease Rating Scale (Fahn & Elton, 1987); H&Y = Hoehn and Yahr (1967) scale; MMSE = Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975); FAS = Verbal category fluency (Benton, 1983); CF = categorical fluency (Goodglass, 1972); PRM = pattern recognition memory; SRM = spatial recognition memory; TOL = Tower of London planning task; PRM, SRM, and TOL are from the Cambridge Neuropsychology Test Automated Battery (Owen et al., 1992).
[a] $n = 20$. [b] $n = 10$. [c] $n = 22$.

Rating Scale (Fahn & Elton, 1987) ratings, $t(19) = 2.1$, $p < .001$, during their off-L-dopa medication session. There were no significant differences between the two subgroups of patients performing the two conditions of the learned irrelevance test on any recorded motor or cognitive variable (see Table 1).

Healthy participants. Two separate groups of healthy control participants performed the learned irrelevance test and the working memory test. Both control groups matched the PD group as closely as possible with respect to age and premorbid verbal IQ, as assessed by the NART (Nelson, 1982). Twenty-two healthy participants performing the learned irrelevance test were recruited from the volunteer panel at the MRC Cognition and Brain Sciences Unit (mean age = 68.4 years, $SD = 7.9$ years; 13 men, 9 women). They were randomly assigned to one of two experimental groups, matched for age, premorbid IQ, and gender, with each participant performing one of the two conditions of the learned irrelevance test. Another 19 participants were tested on the working memory task (mean age = 68.3 years, $SD = 7.0$ years; 8 men, 11 women), but only once, as previous studies in PD have shown that repeated testing has no significant effect on performance (Lewis, Cools, et al., 2003; Lewis et al., 2005). Permission for this study was obtained from the local research ethical committee, and all participants consented to participation.

Table 1 shows a summary of characteristics for the healthy control groups that performed the learned irrelevance and the working memory tasks. There were no significant differences between the whole patient group and either of the control groups with respect to age or NART (see Table 1).

Learned Irrelevance Test

The participants were randomly assigned to one of the two test conditions, full irrelevance or partial relevance, performing the test twice under the same task condition, with the second session 2 weeks after the first one. However, to counterbalance any practice effects and the EDS target dimension effect, on one occasion an EDS to shape was required, and on the other an EDS to number was required. The patients' on- and off-L-dopa sessions were counterbalanced, and the off-medication session was performed a minimum of 12 hr post last dose of L-dopa.

Working Memory Task

The working memory test has been described in detail elsewhere (Lewis, Cools, et al., 2003; Lewis et al., 2005). The patients with PD and the healthy participants were presented with a sequence of four consonants (at 1-s intervals) to be retained in memory in the order of presentation. It was followed by a maintenance period (9–14 s), ended by a cue. The cue instructed the participants to recall the stimuli in one of three prelearned ways: (a) in the original order of presentation (a maintenance and retrieval condition), (b) in the order of the third, fourth, first, and second letters (a simple manipulation condition), or (c) in the order of the first, third, second, and fourth letters (a complex manipulation condition). Following the cue, a blank screen was presented until the participant indicated with the first key press having prepared the required answer in mind. The first button response triggered the presentation of two sets of four letters, target and foil items, and the participants were required to select the correct answer by pressing the relevant response key. The dependent variable was the number of times that the correct sequence was identified for each of the three conditions.

Results

Learned Irrelevance Test

In the learned irrelevance test, the analyses included errors to criterion committed at the IDS and EDS stages. Because no a priori predictions were made with respect to the IDS and because the

full/partial irrelevance manipulation was relevant only at the EDS stage, the IDS and EDS stages were analyzed separately. First, within the patient group alone, the hypothesis that L-dopa would have no effect on performance was tested. Accordingly, a one-way ANOVA revealed that there was no significant effect of L-dopa at the IDS, $F(1, 19) = 0.29$, $p = .599$. A two-factor ANOVA was also performed comparing performance at the EDS at the two test conditions (full irrelevance, partial relevance; between-groups factor) with and without medication (on, off L-dopa; within-group factor). This analysis revealed a significant main effect of the test condition, $F(1, 18) = 6.53$, $p < .05$, $\eta = 0.266$, no significant effect of medication, $F(1, 18) = 0.06$, $p = .810$, and no significant interaction between the two factors, $F(1, 18) = 0.05$, $p = .819$ (see Figure 3).

Because L-dopa had no effect on the PD patients' performance on the learned irrelevance test, to examine the overall effect of pathology, we calculated mean errors to criterion at the IDS and EDS stages by averaging scores on and off L-dopa. Similarly, scores for the healthy participants were averaged across the first and second sessions, and the resultant mean error scores for the two groups were compared directly.

A one-way ANOVA comparing the number of errors made by patients and healthy participants at the IDS revealed no significant difference, $F(1, 41) = 0.82$, $p = .370$. To assess performance at the EDS, we conducted a two-factor ANOVA of Pathology (PD, control) $\times$ Test Condition (full irrelevance, partial relevance). The analysis revealed a significant main effect of pathology, $F(1, 38) = 4.59$, $p = .039$, $\eta = 0.108$, with the PD patients committing more EDS errors overall than the healthy participants, and a significant main effect of test condition, $F(1, 38) = 6.62$, $p = .014$, $\eta = 0.148$, with more errors committed in the full irrelevance condition than in the partial relevance condition. The interaction between the two factors was also significant, $F(1, 38) = 4.21$, $p = .047$, $\eta = 0.100$. Simple main effects calculated separately for the two test conditions confirmed that the PD group made significantly more errors than the healthy participants in the full irrelevance condition, $F(1, 20) = 6.04$, $p = .024$, $\eta = 0.241$, but not in the partial relevance condition, $F(1, 20) = 0.01$, $p = .933$ (see Figure 4).

We conducted a supplementary analysis to compare the healthy participants tested in Experiment 1 with those tested in Experiment 2 (first session only), to determine whether there were any differences between the two control groups. A three-way ANOVA of Group (Experiment 1, Experiment 2) $\times$ Shift (IDS, EDS) $\times$ Test Condition (full irrelevance, partial relevance), revealed no significant effect of group, $F(1, 162) = 0.06$, $p = .804$. However, as would be expected from the analyses of each experiment, the effects of shift, $F(1, 162) = 48.40$, $p < .001$, $\eta = 0.230$; test condition, $F(1, 162) = 6.09$, $p = .015$, $\eta = 0.036$; and the two-way interaction of Shift $\times$ Test Condition, $F(1, 162) = 6.08$, $p = .015$, $\eta = 0.036$, were significant.

Working Memory Test

In analyzing the PD working memory data, we included session (first, second; within-group factor) as a factor of interest, as only this group was tested twice on the task. Thus, a three-way repeated measures ANOVA of Medication $\times$ Session $\times$ Condition (within-group factor) was conducted on accuracy scores (see Figure 5) in the patient group alone. This analysis revealed a significant main effect of medication (on, off L-dopa; within-group factor), $F(1, 9) = 27.74$, $p = .001$, $\eta = 0.755$; a significant main effect of condition (maintenance and retrieval, simple manipulation, complex manipulation; within-group factor), $F(1, 9) = 56.53$, $p < .0001$, $\eta = 0.863$; and no significant main effect of session (first, second), $F(1, 9) = 1.58$, $p = .240$. A significant two-way interaction of Medication $\times$ Condition was also observed, $F(1, 9) = 19.65$, $p = .002$, $\eta = 0.686$, although none of the other interaction terms approached significance. Examination of simple main effects revealed significant improvements in performance accuracy during the medicated session for those trials requiring manipulation, $F(1, 19) = 33.22$, $p < .0001$, and $F(1, 19) = 72.27$,

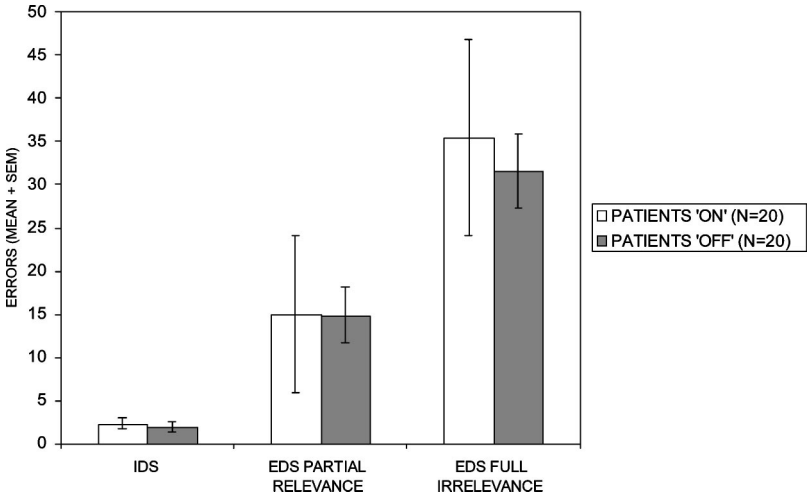

Figure 3. Learned irrelevance: Effect of L-dopa on error rate in patients with Parkinson's disease (PD). The mean number of errors for both the intradimensional shift (IDS) and the extradimensional (ED) set-shifts is shown for the patients with PD on and off L-dopa medication. Bars represent standard error of the mean.

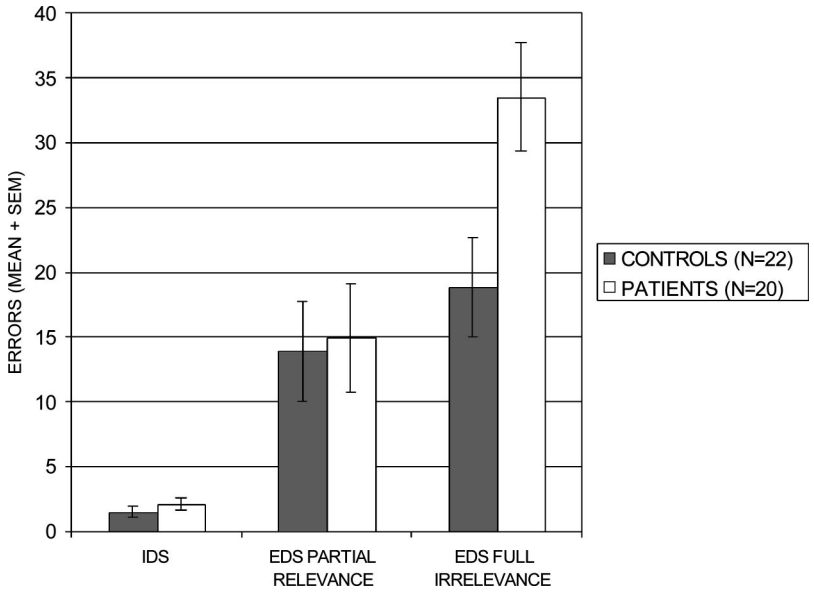

Figure 4. Learned irrelevance: Effect of Parkinson's disease (PD) pathology on error rate. The mean number of errors for the healthy participants over their two testing sessions and the patients with PD recorded on and off L-dopa medication are shown for both the intradimensional shift (IDS) and extradimensional shift (EDS). Bars represent standard error of the mean.

$p < .0001$, for simple and complex manipulation, respectively, but not in the trials that relied upon only the maintenance and retrieval of information, $F(1, 19) = 0.33$.

These results confirm that L-dopa significantly improved accuracy during the two types of manipulation trials. No significant effect was observed in those trials in which only maintenance and

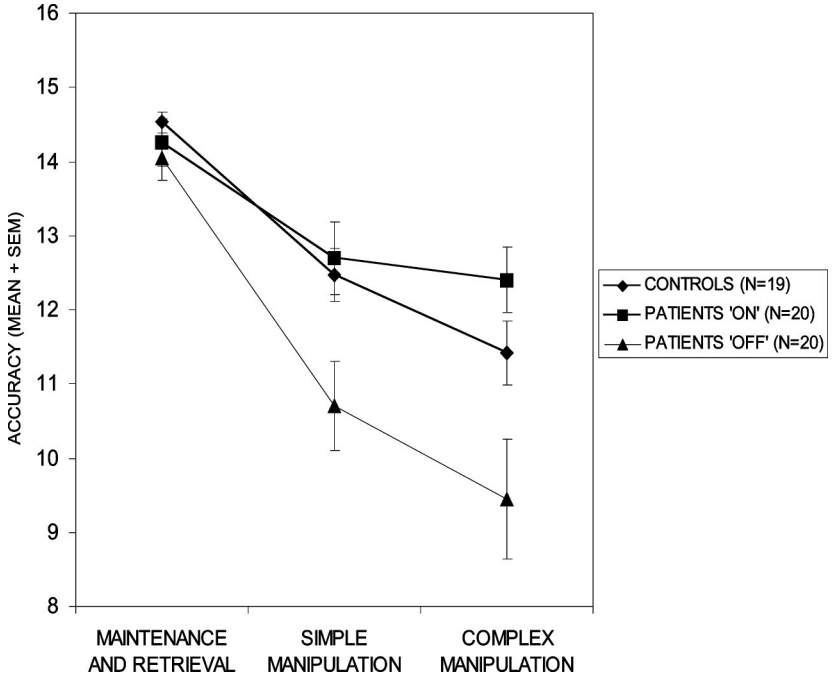

Figure 5. Working memory: Performance accuracy. The mean number of correct responses at each level of task difficulty is shown for healthy participants and patients with Parkinson's disease on and off L-dopa medication. Bars represent standard error of the mean.

retrieval was required. In addition, there were no practice effects between Sessions 1 and 2, and this factor did not interact with any of the other variables tested. To test whether patients tested off L-dopa were actually significantly impaired relative to healthy participants, accuracy in the PD patients off L-dopa was compared directly with that of the healthy participants. A two-way (pathology, condition) ANOVA revealed a significant main effect of pathology, $F(1, 37) = 6.66$, $p = .014$, $\eta = 0.153$, and a significant main effect of condition, $F(1, 37) = 74.69$, $p < .0001$, $\eta = 0.699$, although the interaction between the two factors did not reach significance, $F(1, 37) = 2.81$, $p = .10$.

These results confirm that unmedicated patients with PD are significantly impaired at a test of working memory and that this deficit is significantly improved with L-dopa medication. In contrast, the same patients exhibit enhanced learned irrelevance when unmedicated, which was not attenuated or worsened by L-dopa.

Discussion

In this study, we devised a novel visual discrimination learning task to define more precisely the cognitive mechanisms involved in learned irrelevance in healthy participants and the role that learned irrelevance plays in the attentional set-shifting deficits observed in PD. The results of the first experiment demonstrated that learned irrelevance is dependent on the level of irrelevance of a given dimension prior to an EDS. Thus, performance in the full irrelevance condition was significantly worse than that during the partial relevance condition. To our knowledge, such an effect has not been demonstrated previously in humans, although studies of learned irrelevance in the rat have shown that experiencing a positive relationship between two events (e.g., partial relevance) can significantly attenuate the effects of learned irrelevance when the two events are subsequently randomly correlated (Nakajima, Nakajima, & Imada, 1999). Because few previous studies have investigated learned irrelevance in humans, the phenomenon is not well understood, either psychologically or in terms of the neural and/or neurochemical processes involved. In cognitive terms, the phenomenon is clearly related to latent inhibition. However, whereas learned irrelevance refers to impaired learning about an association between a conditioned stimulus and an unconditioned stimulus as a result of their uncorrelated presentations (Mackintosh, 1973), latent inhibition refers to disrupted learning following unreinforced presentations of the conditioned stimulus alone (Lubow, 1973). According to some authors, learned irrelevance may be a special case of latent inhibition, occurring as a result of preexposure of the unconditioned stimulus and conditioned stimulus (Bonardi & Hall, 1996). On the other hand, according to others, learned irrelevance is inexplicable as a simple summation of the two preexposure effects and cannot always be reduced to latent inhibition (Baker & Mackintosh, 1979; Bennett, Wills, Oakeshott, & Mackintosh, 2000; Matzel, Schachtman, & Miller, 1988). Instead, it has been argued that explicit learning occurs about the absence of a correlation between the conditioned stimulus and the unconditioned stimulus. The outcome of this process then interferes with further learning about a subsequent positive correlation.

The significance of the findings from the first experiment can best be considered in the context of the associative learning model (Mackintosh, 1975). According to this framework, changes in both the associability and the associative strength of target stimuli can be induced by the outcome of learning trials. The associability increases if the stimulus is a better predictor of the present outcome than are all other cues present on the trial. In contrast, it decreases if other cues are equally good or better predictors of the outcome. Such a decrease in associability of the previously irrelevant exemplars has a negative impact on subsequent learning in the postshift stage (see Maes, Damen, & Eling, 2004). Thus, in the current study, the relatively weak performance of the participants in the full irrelevance condition most likely reflects a stronger decrease in associability of the fully irrelevant dimension relative to the partly relevant dimension.

Changes in the associability of stimuli may also account for why significantly more errors were committed when an EDS to the dimension number was performed relative to the dimension shape (although both dimensions did produce more errors in the full irrelevance condition than in the partial relevance condition; see Figure 2). Several previous studies have suggested that stimulus saliency can affect EDS performance, modifying a difference between the IDS and the EDS in humans (Lawrence, Sahakian, Rogers, Hodges, & Robbins, 1999; Ozioko & May, 1977) and in common marmosets (Crofts et al., 2001). Because the associability of a conditioned stimulus is roughly equivalent to its saliency (or attention-drawing capacity), a less salient stimulus would therefore be expected to produce less learned irrelevance. A number of previous studies have specifically suggested that shape is a relatively salient dimension; for example, in monkeys, EDS costs have been reported for shifts from shapes to lines, but not for shifts from lines to shapes, in addition to there being a general bias toward shapes as compared with lines (Crofts et al., 2001). Similarly, in humans, attending to lines in the presence of shapes reduces the EDS when shape becomes relevant after the shift, compared with when other dimensions are involved (Lawrence et al., 1999).

The second experiment of the current study was designed to directly test the hypothesis that attentional set-shifting deficits in PD are related to enhanced learned irrelevance. The results demonstrated that, relative to healthy participants, patients with PD are impaired at the EDS only in the full irrelevance condition and not in the partial relevance condition. It is interesting, therefore, that PD patients were able to learn about the importance of the partially relevant dimension before the ED shift, even though it was not reinforced 100% of the time. In control participants, partial relevance led to a significant shifting effect (relative to IDS), albeit not as severe as that observed when a shift was required to the fully irrelevant dimension. Thus, it appears likely that in PD patients, for their learned irrelevance deficit to significantly affect behavior, the nonrelevant dimension prior to the shift really does have to be irrelevant; that is, reinforced randomly 50% of the time.

Although the results of the current study appear to confirm the importance of learned irrelevance in the attentional set-shifting deficits that accompany PD, a number of alternative explanations need to be considered. First, in previous studies of learned irrelevance (Gauntlett-Gilbert et al., 1999; Owen et al., 1993), a significant confound has been the possible effects of stimulus novelty on EDS performance. That is to say, shifts to a previously irrelevant dimension were compared with shifts to a novel dimension, to make inferences about learned irrelevance. This is important because deficits in novelty pop-out effects have been reported previously in patients with PD (Lubow, Dressler, & Kaplan, 1999;

Tsuchiya et al., 2000). In the current study, no such confound existed, as we made inferences about learned irrelevance by comparing full and partial irrelevance conditions, neither of which involved the introduction of a novel dimension.

Second, as the previously relevant dimension was still present at the EDS stage, it is possible that differences between the PD patients and the healthy participants are attributable to perseveration, rather than to learned irrelevance. However, at least three factors argue against this explanation. First, Maes et al. (2004) recently demonstrated that in a task in which both learned irrelevance and perseveration errors were possible, the former makes a disproportionate contribution to the overall score relative to the latter. Second, in the current study, the previously relevant dimension was present in both the full irrelevance condition and the partial relevance condition; perseveration would therefore be expected to affect these two conditions equally, yet the PD patients were impaired only in the full irrelevance condition. Finally, previous studies have demonstrated that perseveration is susceptible to dopaminergic medication (Owen et al., 1993), yet L-dopa withdrawal had no effect on performance on this task, suggesting again that perseveration is not a significant factor in accounting for the PD deficit.

Third, an alternative explanation for some of the findings in the current study is that patients with PD may exhibit a general, nonspecific problem with cognitive resources (e.g. Brown and Marsden, 1988), so that more difficult tasks will always be performed more poorly, irrespective of the nature of that difficulty manipulation. If that were the case, it could be argued that the disproportionate effect in the full irrelevance condition in patients with PD reflects this nonspecific impairment of cognitive resources, rather than a specific susceptibility to learned irrelevance per se. However, examination of the working memory data renders this interpretation highly unlikely. Thus, manipulating difficulty in that task (between the simple and the complex manipulation conditions) did not produce a corresponding decrement in task performance, suggesting that these patients do not have a general problem with cognitive resources. In addition, the fact that L-dopa improved working memory performance but had no effect on learned irrelevance suggests that the core processes associated with these tasks are largely independent and do not stem from the same general difficulty factor.

A final point to consider is that the difference between the partial and full irrelevance conditions appears to be larger for the younger participants in the first experiment than for the older control group who were compared with the PD patients in the second experiment. It is important to point out, however, that the older control group performed the learned irrelevance task twice, whereas the younger participants performed it only once. Although no significant practice effects were observed, post-hoc examination of the data from the two sessions did confirm a reduced difference between the full and the partial irrelevance conditions during the second session for the older control group. It seems likely that this reflects interference from the first to the second session in this group, given that different stimulus dimensions were used at the EDS stage on each occasion. In contrast, in the PD group, the difference between the full and the partial irrelevance conditions was clearly evident during both sessions.

Deficits in working memory have been frequently reported in patients with PD (Gotham, Brown, & Marsden, 1986; Owen et al., 1992), although few studies have directly related subcomponents of working memory to dopamine depletion in these patients (Cooper et al., 1992; Costa et al., 2003; Lange et al., 1992). In the current study, L-dopa selectively improved manipulation within working memory relative to other cognitive processes such as maintenance and retrieval. This result concurs fully with a recent functional MRI study of PD patients performing exactly the same working memory task that was used in the current investigation (Lewis, Dove, Robbins, Barker, & Owen, 2004). In that study, selective impairments in manipulation were associated with reduced activity in the ventrolateral and dorsolateral prefrontal cortices and the striatum. It is widely accepted that the prefrontal cortex plays a critical role in aspects of working memory (Fuster, 1997; Goldman-Rakic, 1987; Smith & Jonides, 1999), and a number of neuroimaging studies in healthy control participants have suggested that the manipulation of information within working memory preferentially involves the mid-dorsolateral prefrontal cortex (Owen, 2000; Owen et al., 1999; Owen, Evans, & Petrides, 1996). The ventrolateral frontal cortex is also frequently activated in such tasks but is thought to be specifically involved in more basic mnemonic functions, including encoding and retrieval (Owen, 2000; Owen et al., 1996, 1999). Taken together, the results of the current study, and the fMRI study by Lewis, Dove, Robbins, Barker, and Owen (2003), suggest that the selective influence of dopamine depletion on manipulation of information within working memory rather than retrieval may be related to dysfunction of circuitry involving the mid-dorsolateral and/or the mid-ventrolateral frontal cortices.

The question that remains, therefore, is whether a plausible neural and/or neurochemical account can be formulated for the learned irrelevance effects in PD. Unfortunately, relevant data from other clinical groups is sparse, although the fact that patients with circumscribed excisions of the frontal cortex are unaffected on learned irrelevance tasks suggests mechanisms other than those that are traditionally considered to be executive. Although patients with schizophrenia have been shown recently to be significantly affected on a test of learned irrelevance, the pattern of impairments suggests a reduced rather than an enhanced effect (Young et al., 2005). Thus, among first-episode schizophrenic patients, cue–target associations to (irrelevant) preexposed cues were as fast as those to novel cues (see also Gal et al., 2005), exactly the opposite pattern that would be predicted in PD on the basis of the current findings. Although such evidence may suggest a role for dopamine in learned irrelevance, the direct manipulation of dopamine levels through medication conducted in the current study more strongly suggests otherwise. In fact, the lack of effect of L-dopa and of frontal-lobe damage (Owen et al., 1993) on learned irrelevance in patients with PD suggests that neither the dopaminergic mechanisms of the striatum nor the prefrontal cortex mediate this process. In monkeys, prefrontal dopamine depletion impairs spatial working memory but has no significant effect on extradimensional set-shifting performance (Roberts et al., 1994), a result that is broadly consistent with those of the current study. Nondopaminergic forms of pathology, including noradrenergic, serotoninergic and cholinergic deafferentation of the cortex, also occur in PD (Agid, Javoy-Agid, & Ruberg, 1987) and may play a significant role in learned irrelevance, although this possibility will require further investigation. Similarly, cortical Lewy bodies, which may

occur even in the early stages of PD, may play a contributory role (Byrne, Lennox, Lowe, & Godwin-Austin, 1989; Gibb, Luthert, Janota, & Lantos, 1989).

In summary, this study sheds new light on the nature of learned irrelevance effects in PD which has direct relevance to a broad literature on executive deficits in this patient group. For example, numerous studies of executive function in PD over the last 20 years have shown that attentional set-shifting tasks are both highly sensitive to early stage disease (e.g., Downes et al., 1989; Owen et al., 1992) and (in early stage at least) moderately selective (e.g., deficits are not seen in early Alzheimer's disease; see Sahakian et al., 1990). Our results, together with those of related studies, suggest that some of those findings may more specifically reflect learned irrelevance, which appears to be neither dependent on the frontal lobe (e.g., Owen et al., 1993) nor affected by dopamine and, therefore, may not be executive at all.

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