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Dopamine dependency of cognitive switching and response repetition effects in Parkinson's patients

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Abstract

A group of people with Parkinson's disease and a group of matched controls were tested on a task involving a switch between perceptual dimensions. Patients were tested both 'on' and 'off' their normal medication cycles. Stimuli appeared in pairs for each trial, with each stimulus consisting of a color and a shape. One dimension of color and one of shape were mapped to each of two response keys. A cue was presented concurrently with each stimulus to indicate whether to respond on the basis of color or shape, following procedures developed by Hayes et al. [Hayes, A.E., Davidson, M.C., Keele, S.W., & Rafal, R.D. (1998). Toward a functional analysis of the basal ganglia. *Journal of Cognitive Neuroscience*, *10*, 178–198]. Replicating previous literature, abnormally large switch costs were observed in patients who were off their normal medication cycles. A novel finding was that patients in the 'on' state demonstrated a slight reversal of switch costs. Also novel, reaction time (RT) costs associated with switching between response keys, and interactions between response switching and task switching were influenced predominantly by on–off dopamine manipulations. It is concluded that abnormal task switching costs and response repetition effects likely reflect impairments of activation and inhibition, and both effects are dopamine-dependent.

Keywords: Parkinson's disease; Cognitive switching; Response repetition; Dopamine

1. Introduction

The basal ganglia are a subcortical complex of nuclei through which parallel circuits pass in a segregated fashion on their way from and back to the cortex via nuclei of the thalamus (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000). These circuits emanate from sensorimotor, prefrontal, temporal, parietal, cingulate, limbic, and paralimbic areas (Parent, 1990), and therefore involve both motor and non-motor regions of the brain. PD results from the degeneration of dopaminergic neurons in the substantia nigra pars compacta and a consequent loss of dopaminergic innervation of the basal ganglia (Hornykiewicz, 1973). This suggests that behaviors that rely on the integrity of basal ganglia circuitry are dopamine-dependent, as has been demonstrated for many of the cognitive and motor symptoms of PD.

1.1. Cognitive sequelae of Parkinson's disease

Although once regarded as a motor structure, given motor symptoms are most readily apparent in Parkinson's disease, recent attention has turned to possible cognitive functions of the basal ganglia. Switching from one component to the next in a movement sequence is one example of a deficit first shown in animals with dopamine depletion. For example, an early study by Cools (1980) found that the level of dopamine affected the change from one swimming sequence to another in rats attempting to escape from a tank of water. PD patients also have demonstrated impairments in switching between movements, such as that required in a complex motor sequence (Benecke, Rothwell, Dick, Day, & Marsden,

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1987b; Cools, van dem Bercken, Sahakian, & Robbins, 1984; Harrington & Haaland, 1991; Hayes, Davidson, Keele, & Rafal, 1998; Inzelberg et al., 1996, 2001; Robertson & Flowers, 1990; Roy, Saint-Cyr, Taylor, & Lang, 1993). A motor sequence might be conceptualized as a series of motor programs used to generate simple movements, such as reaching and grasping an object. The series may or may not involve a switch between different motor programs (Benecke, Rothwell, Dick, Day, & Marsden, 1987a). For example, bending the elbow after squeezing the hand would require a switch in motor programs but bending the elbow twice consecutively does not involve a switch in the program. Some evidence demonstrating both cognitive and motor switching deficits in PD patients (Cools et al., 1984) is consistent with the hypothesis that both are related to the same basic impairment, although other findings have dissociated cognitive and motor slowing in PD (Rafal, Posner, Walker, & Friedrich, 1984). This raises the question of whether deficits associated with the disease can be characterized as emanating from the same basic impairment in function.

1.2. Switching as an executive function

Research examining the role of basal ganglia operations in executive functions has gone on for some time. Moreover, some of the deficits found in PD patients appear to overlap with those demonstrated in patients with frontal lobe damage (Lange et al., 1992). Executive functions are multifaceted processes necessary for planning and executing strategies in response to changes in the environment. The Wisconsin Card Sorting Test (WCST) assesses some aspects of executive function, although performance on this task is also dependent upon other processes such as memory. The task requires a participant to figure out which strategy to use in the presence of competing strategies and then change to a different strategy when necessary (Nelson, 1976). Participants are presented with cards that contain images of geometric shapes of different dimensions (shape, color, and number of objects). Patients must sort the cards based on the correct dimension, which the patient learns from feedback given by the examiner. After 10 correct card-sorting trials, the examiner then changes the rule for sorting. For example, the scheme might change from sorting based on color to sorting based on shape. The patient has to use the error feedback from the examiner to figure out the new dimension and switch sorting strategies. PD patients have difficulty with the WCST for a number of different, but perhaps related reasons, including difficulty abstracting the sorting rule, working memory problems, and inability to filter out the irrelevant rules (Bowen, Kamienny, Burns, & Yahr, 1975; Brown & Marsden, 1988).

Based on the seminal work of Jersild (1927), a number of researchers have investigated properties of executive control in healthy adults on tasks that require a switch between different task sets or instructional cues (Allport, Styles, & Hsieh, 1994; Rogers & Monsell, 1995; Wylie & Allport, 2000). The cost of a task switch on consecutive trials, which is generally reflected in measures of reaction time (RT), is compared to similar measures on consecutive trials in which no switch is required. Some researchers have found that switch costs tend to occur only when the involved stimuli are compatible with more than one task (Jersild, 1927; Spector & Biederman, 1976). This might also apply for tasks using bivalent stimuli, in which each response key is mapped on the basis of two stimulus dimensions (e.g., shape and color) rather than only one. By this view, control processes are necessary when discriminating on the basis of which action should be executed in response to a stimulus that might induce activation to more than one relevant task (Meiran, 2000).

Some studies have used predictable sequences of switches (Rogers & Monsell, 1995), eliminating the necessity to present cues indicating the relevant dimension on each trial. However, if an upcoming task switch is predictable, there might also be differences in the extent to which the task configuration is prepared prior to responding (Rogers & Monsell, 1996). Thus, it is important to either manipulate the amount of response readiness on a particular task, or to cue the different tasks randomly rather than in a specified order (Meiran, 1996). One method involves presenting a cue on each trial to indicate the relevant task (or dimension) to respond to on that trial. If the cues on two successive trials are the same, then no switch is necessary. Conversely, if the two cues are different, then a switch is necessary between the first and second trials of the pair (Hayes et al., 1998; Meiran, 1996). This method, however, often confounds the switch in successive cues with the switch in operations required for the two different task sets. It might therefore be additionally important to assess switch costs when no change in cue is presented, but when the switch involves only a change from one response key to the other.

An interesting finding that has emerged from studies on healthy control subjects, is that within a series of trials of the same task, RT tends to be faster when the responses on two consecutive trials are the same, compared to when they are different, an effect referred to as response repetition. However, the magnitude of this response repetition effect tends to reduce when there is a task switch (Rogers & Monsell, 1995; Schuch & Koch, 2003). Filoteo, Rilling, and Strayer (2002) examined negative priming in healthy controls and PD patients (on their normal medication: 'on' state). Those researchers employed a task in which letter arrays appeared in specific spatial locations as prime trials followed by probe trials where distractor letters in the prime either matched or mismatched the target letter in the probe. Although the study demonstrated abnormal negative priming effects in the PD patients, which could be interpreted as a lack of normal inhibition of responding to distracting stimuli, the response repetition costs were not reliably different between the PD and control groups. Together, this pattern of findings led to the suggestion that the neurocognitive mechanisms involved in response repetition effects might be distinct from those involved in negative priming (Filoteo et al., 2002). Other recent studies have demonstrated deficits in both activation and

inhibition of responses in PD patients (Franz & Miller, 2002) and patients with Huntington's disease (Aron et al., 2003a), which leaves open the possibility that problems in activation and/or inhibition associated with basal ganglia dysfunction might translate into some of the deficits observed on cognitive tasks such as task switching and response repetition.

1.3. The influence of dopamine

A number of studies have examined cognitive performance of PD patients when on their normal medication (e.g. Cools et al., 1984; Cools, Barker, Sahakian, & Robbins, 2001b; Flowers & Robertson, 1985; Gauntlett-Gilbert, Roberts, & Brown, 1999; Richards, Cote, & Stern, 1993; Rogers et al., 1998). In addition, comparing and contrasting results of testing off and on medication establishes which of the deficits is dopamine dependent. There have been three studies reporting a significant alleviation of switching deficits in PD following L-dopa administration (Cools, Barker, Sahakian, & Robbins, 2001a; Cools, Barker, Sahakian, & Robbins, 2003; Hayes et al., 1998). These cognitive operations most likely rely on the integrity of striatal-dorsolateral prefrontal cortex circuits (Brass et al., 2003; Cools et al., 2001a, 2001b, 2003). However, contrasting effects on operations mediated by ventral frontal-striatal circuitry have been reported in PD patients following L-dopa administration, including impairments in impulsivity control (Cools et al., 2001a, 2001b, 2003). These effects are similar to those seen in non-medicated patients with first-episode Schizophrenia (Hutton et al., 2002). Determining the properties of cognitive tasks that are influenced either positively or negatively with administration of L-dopa provides a very valuable method to further define the operations of the basal ganglia circuitry, as well as the influence of dopamine innervation.

1.4. The present experiment

The present study sought to further investigate task-switching operations in PD patients, both on and off dopamine medication. The task was similar to one employed by Hayes et al. (1998). Those researchers employed an adapted version of the WCST using reaction time (RT) as a primary measure of switch costs. In their first experiment, one response key was associated with a color and a shape, and another response key was associated with a different color and shape. A neutral color and a neutral shape were also used, and neither was associated with a response key. A stimulus (a colored shape) was presented together with a word cue that indicated to subjects whether to respond on that trial to color or to shape. An elegant feature of the design was the sequential presentation of stimuli. The second of two consecutive stimulus presentations could either cue the same dimension as that cued on the first stimulus, or the second stimulus could cue the dimension that was not cued on the first stimulus. Thus, subjects would either have to maintain the same cognitive rule on consecutive trials (respond to color or respond to shape), or the rule would switch from color to shape, or vice versa. Hayes et al. were primarily interested in the differences in RT between the switch and no switch trials, as assessed by responses to the second of the two stimuli in each paired trial. They found that switch time was longer in the PD group compared to the control group. When further dividing the PD participants on the basis of their motor symptoms into three groups of hypokinetic, unimpaired, and hyperkinetic, Hayes et al. found that the largest switching cost occurred in the hypokinetic group. Although this latter finding does not provide a direct correlation between cognitive switching and motor symptoms, it implies that such a relationship might exist. Using their color-shape task, Hayes et al. were also able to perform a within-subjects test using 'on' versus 'off' medication states. They found that the switching costs were larger when patients were in their off states, indicating that dopamine plays a role in the processes utilized for cognitive switching between perceptual dimensions.

In another experiment, Hayes et al. examined switching time using a motor sequencing task. This task was designed so that a letter A or B was associated with a unique sequence of three keys (either 1–2–3 or 1–3–2). Subjects were presented with pairs of letters that either indicated they were to perform the same sequence twice (AA or BB), or to perform one sequence and then switch to the other (AB or BA). A clever aspect of their design was that both sequences A and B began with key 1 as the initial element. Therefore, any differences in RT due to switching between sequences could not be due to a motor component associated with striking a particular key. Again, PD patients demonstrated significantly longer RTs to the initial element in the switch trials compared to no switch trials. An 'on' versus 'off' within-subjects comparison was also performed using this task. Only six patients were tested in the off state, and although the pattern of data was in the expected direction, the critical interaction between medication level and switching cost was not significant.

The present study was an attempt to (1) extend the findings of Hayes et al. (1998) to a larger group of subjects, (2) examine switching on different levels of task sets, including between perceptually-cued dimensions and between simple symbolically-coded response keys (response repetition effects), and (3) examine on–off dopamine medication treatment comparisons on switching costs as well as on response repetitions. To accomplish these objectives, we employed the same color-shape task as by Hayes et al. (1998). A novel aspect of our experiment was that we used the same task to evaluate both cognitive switching of the type assessed by Hayes et al., and to examine response repetition effects. Our prediction was that both cognitive task-switching deficits and abnormal response repetition effects would be demonstrated in the patients, particularly when in the off-medication state. This prediction was based on the hypothesis that both forms of impairment are related to more general deficits in activation and inhibition processes (Franz & Miller, 2002), and these processes are dopamine-dependent. Cognitive switching was evaluated as the cost in RT to the second stimulus of a

pair when a switch in dimension was required on consecutive stimuli (switch from color to shape or vice versa) compared to when no switch was required. Response switching was assessed by a comparison of trials that required consecutive responses on different keys (e.g., hitting the key corresponding to one color and then the key corresponding to the other color) to trials that required consecutive responses on the same key (e.g., hitting the same key twice in succession). Extended practice was administered prior to test in an effort to eliminate transient switching costs that might be further reduced with practice.

2. Methods

2.1. Participants

Fifteen participants with a diagnosis of idiopathic Parkinson's disease, who were candidates for surgical treatment of their Parkinsonian symptoms, were included in the test phase. Potential treatments included pallidotomy or placement of deep brain stimulators in the internal segment of the globus pallidus (GPi) or subthalamic nucleus (STN). Patients with previous surgeries or significant dementia were excluded. Motor symptoms were assessed with the Hoehn and Yahr scale (Hoehn & Yahr, 1967) and according to the Unified Parkinsonism Rating Scale (Stern, 1988) by a neurologist and nurse practitioner. Table 1 shows Hoehn and Yahr, UPDRS, and disease duration of individual patients. All evaluations were conducted preoperatively and both on and off medication. The mean age for the PD group was 60.3 years. Mean education level was 14.1 years for this group. Medication protocols for all patients tested are shown in Table 2.

All but two control subjects were partners or caregivers of the patients. The remaining controls were recruited from the Davis, California community. For the control group, the mean age was 60.7 years. Their mean education level was 15.1 years.

Table 1
Patients' motor scores and disease duration (unified Parkinson's Disease Rating Scores used to compute motor scores include items #18–31)

Patient	Hoehn and Yahr	Disease duration	Total motor UPDRS
1	3	5	29
2	2.5	16	20
3	2.5	18	31
4	2	3	11
5	3	10	20
6	2.5	10	16
7	Not available	8	29
8	5	19	40
9	2.5	17	17
10	2.5	17	17
11	2.5	4	20
12	2.5	7	21
13	3	14	45
14	2.5	7	30
15	1	5	19

All patients and controls reported themselves to be right hand dominant and all were tested using the right hand, which for the patients, was the hand contralateral to their planned surgical target site. Typically, the first surgery is performed on the dominant hemisphere, but this is not always the case. However, in the present study, we included only those patients in whom the first surgical procedure was performed on the side contralateral to the dominant hand. Prior to any testing, informed consent was obtained from all participants. The behavioral protocol was approved by the Institutional Review Boards of The University of California Davis and The Kaiser Permanente Research Foundation. For performance in the "on" state, there were no changes to patients' normal medication cycles and they were considered "on" as determined by the attending neurologist (VLW). The "off" measurements for the PD group were taken after patients had been off their medication for at least 12 h.

Table 2
Patient medication protocols

Patient	Medication	Dosages (per day)
1	Sinemet CR 50/200, Sinemet 25/250	1 (4×), 1/4 (2×)
2	Sinemet CR 50/200, Sinemet 25/100, Mirapex 1.5 mg	1/2 (4×), 1/2 (4×), 1 (4×)
3	Sinemet CR 25/100, Sinemet 25/100, Mirapex 0.25 mg	All 5×
4	Amantadine 100 mg, Permex 0.25 mg	2×, 3×
5	Sinemet CR 50/200, Sinemet 25/100, Amantadine 100 mg	1.5 (1×), 2×, 2×
6	Sinemet 25/100, Mirapez 0.5 mg, Artane 2 mg, Amantadine 100 mg	1 (1×) and 1/2 (4×), 1 (1×) and 1/2 (4×), 1 (1×) and 1/2 (2×), 3×
7	Sinemet CR 50/200, Sinemet 25/100, Requip, Artane 1 mg, Levodopa	1×, 6×, 16 mg, 2×, 800 mg
8	Sinemet CR 25/100, Sinemet 25/100, Mirapex 0.75 mg	All 5×
9	Sinemet 25/100	4×
10	Sinemet 25/100, Mirapex 1 mg	2×, 1/2 (2×)
11	Sinemet CR 25/100, Sinemet 25/100	1/2 (3×), 1 (2×) and 1/2 (2×)
12	Artane 1 mg, Requip 3 mg, Selegeline 5 mg	2×, 4×, 3× weekly
13	Sinemet 25/100, Eldepryl 5 mg, Sinemet CR 50/100, Mirapex 1.25 mg	1.5 (2×) and 2 (3×), 2×, 5×, 3 (3×)
14	Sinemet 25/100, Requip 5 mg	4×, 4×
15	Eldepryl 5 mg	1×

2.2. Experimental task

Participants were seated in front of a computer screen with their right and left hands resting at the edge of the computer keyboard. The index finger of the responding hand was centered over the two adjacent response keys and the index finger of the non-responding hand was over the "ready" key. The return key was used for the "ready" key, and it was labeled with the word "ready". Each response key was labeled with both a color and a shape. One key had a black square positioned in its upper left corner and the lower right hand corner of the key was colored yellow. The other key had a black circle in its upper left corner and the lower right hand corner of the key was colored pink. These symbols and colors indicated the stimulus shape and color associated with each response key.

The stimuli were approximately centered on a computer screen and consisted of a 15 cm × 15 cm square or a 15 cm diameter circle. The colors of the stimuli were either pink or yellow and the background was white. The word cue "color" or "shape" printed in black (2 cm in height, 5 cm length) appeared just above the stimulus presentation. RT and error were recorded using Presentation, a software package designed by Neurobehavioral Systems, San Francisco, CA.

2.3. Design and procedure

There were four distinct stimuli (pink square, pink circle, yellow square, yellow circle). These stimuli were presented on the first and second stimulus positions in a completely crossed fashion to produce 16 possible sets of paired stimuli. Each of these pairs was presented with all possible combinations of cues (color–color, color–shape, shape–shape, shape–color), making 64 trial types. The trial types could be classified depending on whether there was no switch (Fig. 1A), a response switch only (switch from one response key to the other: Fig. 1B), a cognitive switch only (switch between cues but no switch between response keys: Fig. 1C), or a switch in both the response key and the cue (Fig. 1D). Fig. 1E shows the sequence of events within each trial. The number of switch and no switch trials was equal and comparable to the number of switch and no switch trials tested by Hayes et al. (1998), although our experiment differed in that Hayes et al. also included filtering control trials (and we did not), and we evaluated trials with both cue switches and response switches (and Hayes et al. did not). Consistent with Hayes et al., our participants had extended practice prior to performing the test trials, with the aim of minimizing error. All participants in the present study under-

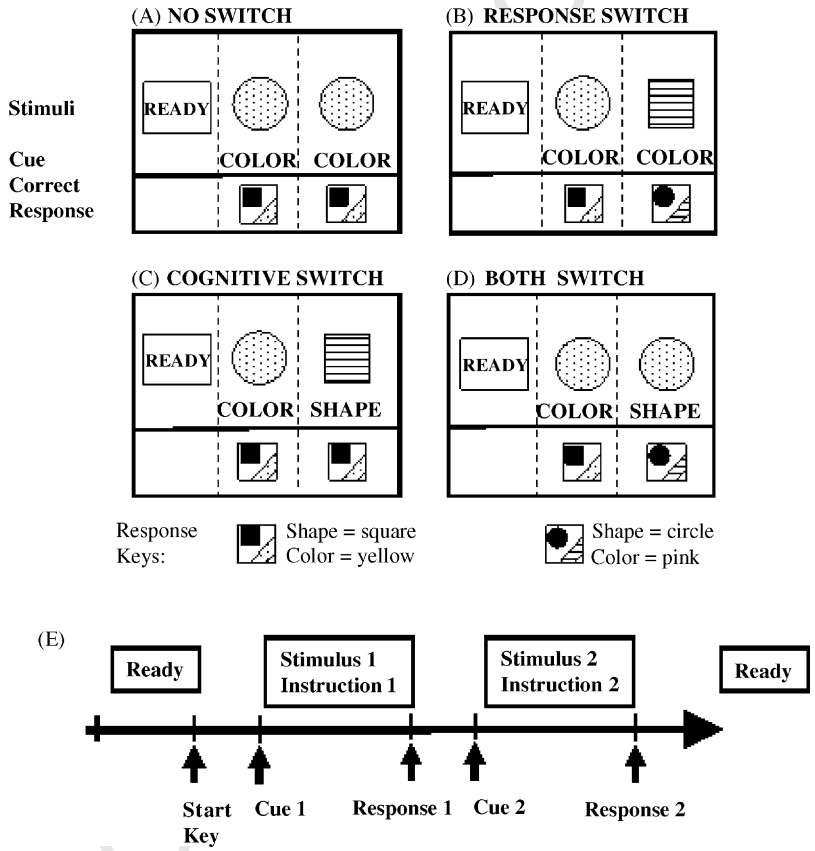

Fig. 1. Outline of task with the four different trial types, and indication of the order of events within each paired trial. Note that the stimulus and corresponding cue for Task 1 were presented when the start key ("ready") was registered, and the stimulus and corresponding cue for Task 2 were presented when the first response was registered; thus, the gaps in (E) are exaggerated so that all events are clearly depicted (see text).

went a thorough instructional session in which each type of trial was demonstrated, and the appropriate response was indicated.

Participants were instructed to respond as quickly and accurately as possible according to the dimension of the stimulus indicated by the accompanying cue. As stated above, they were first given extensive practice to learn to associate the instruction and the appropriate color or shape with the proper key, and the labels remained on the keys for the duration of the testing session.

A trial began with the participant pressing the key marked "ready" in response to the "ready" signal. After the ready key was pressed, the first stimulus appeared immediately. The stimulus remained on the screen until a response key was pressed or until 3 s elapsed, whichever came first. As soon as the first response key was registered, the first stimulus and cue were replaced with the second stimulus and corresponding cue. After responding to the second stimulus, the word "ready" appeared on the screen to signal the beginning of the next trial.

Practice sessions ended when the participant produced 10 consecutive trials without error. An error was logged when an incorrect response was produced on either the first or second stimulus. If the error criterion was not satisfied by the time two blocks of trials were administered (128 trials), the participant was not included in the test phase. This criterion resulted in a clear division between participants who could and could not perform the task. The 15 participants in the PD group who were included in the test phase came from an original group of 22 in total. The seven PD participants who were eliminated from the analysis included four who did not satisfy the error criterion and therefore were not included in the test phase, and three who performed the task with the non-dominant hand. Data from the three patients who performed with the non-dominant hand did not differ in any obvious ways from data from participants who used the dominant hand (although this was a small number of participants to compare).[1] There were 19 control participants tested in total, and of the four not included in the analysis, three did not provide enough error-free trials and therefore did not proceed to the test phase, and one used his non-dominant hand. Data from the 15 participants in each group, all of whom performed the task with the dominant hand, were included in the analyses that are reported herein. Error analyses of the eliminated participants did not reveal any patterns across trial types that would be additionally informative. Error rates on the test trials ranged from 4 to 10% across individuals, with an average of approximately 8% for each group [between-group test: $F(1, 28) < 1.00$]. Errors were not differentiated on the basis of trial type, $F(3, 84) = 1.21$, $p = .312$, nor was the group × trial type interaction significant, $F(3, 84) < 1.00$. Error data will not be discussed further.

[1] Note that when we analyzed the complete set of data (including dominant and non-dominant responding hands), the reported effects became slightly larger. However, the present paper reports effects for only the 15 participants in each group who performed the task with the dominant hand, and a direct test of dominance issues will be saved for a later report.

2.4. Data reduction and statistical methods

As by Hayes et al. (1998), RT for the first stimulus of the pair was not important and was therefore not analyzed beyond our initial assessments ascertaining that all values were reasonable. Note that the type of stimulus was equally probable at time 1 (RT1) and time 2 (RT2), so effectively these two trial types were the same except for the "ready" signal that preceded the stimulus at time 1. We therefore view findings from RT2 as representative of switching behavior, as did Hayes et al., which is the primary focus of this study. The dependent variable was the median reaction time to the second stimulus of the pair.

Four primary types of analyses were performed. The first analysis employed separate mixed effects ANOVAs with the within-subjects factor of trial type (no switch, cognitive switch, response switch, and both switch) and the between-subjects variable of group (patients versus controls). These between group analyses were performed both using the Parkinson's 'on' group versus controls, and the Parkinson's 'off' group versus controls to assess primary effects of switching in each group comparison. Data were also analyzed using a 2 × 2 factorial of switch type (presence or absence of response switch × presence or absence of cognitive switch) to examine the interaction of switch type and response repetition more specifically. Simple effects ANOVAs were performed for each group on each switch type separately to assess the prediction that switch trials would be slower than non-switch trials. A final set of analyses consisted of within-subjects ANOVAs on the factors trial type × drug (on versus off), performed only on the Parkinson's group (serving as their own controls). A significance value of .05 was adopted, and those effects that were marginally significant ($.05 < p < .10$) are also reported and considered seriously given the sample size. Where violations of sphericity occurred, Greenhouse–Geisser corrections were applied.

3. Results

The averaged median RT to the second stimulus is shown for each condition in Table 3. Switching cost, or the percent increase in reaction time associated with the switching condition, is also shown in Table 3.

3.1. PD patients versus control analyses

As can be seen from the data in Fig. 2 and Table 3, PD patients in the 'on' state were not slower to respond than control subjects overall, in fact, they were slightly faster although these differences were not reliable, $F(1, 28) < 1.00$. For both the PD group in the 'on' state and the control subjects combined, there was a cost on cognitive switch trials compared

Table 3
Cognitive and response switching costs for controls and PD patients

Group	No switch (ms)	Cognitive switch (ms)	Cog switch cost (%)	Response switch (ms)	Response switch cost (%)	Both switch (ms)	Both switch cost (%)
Controls	1417 (124)	1578 (145)	11.4	1446 (97)	2.0	1514 (82)	6.8
PD patients off	1436 (124)	1761 (145)	22.7	1738 (97)	21.1	1693 (100)	17.9
PD patients on	1498 (132)	1518 (116)	1.3	1614 (85)	7.7	1564 (72)	4.4

Times listed are averaged median reaction times to the second stimulus ($n = 15$ PD patients and 15 controls). Switching cost is the percent increase in reaction time associated with each respective switch condition. Standard errors are shown in parenthesis.

to no switch trials, $F(1, 28) = 5.62$, $p = .025$. Furthermore, the data presented in Table 3 and Fig. 2 suggest that the PD group in the 'on' state actually outperformed the control group on the cognitive switch task, particularly on same response trials. This interaction of cognitive switch and group was nearly significant, $F(1, 28) = 3.58$, $p = .07$. In contrast to the effects on cognitive switching, response switch trials were not reliably different from the no switch trials for either the controls or the PD-on group, nor did the cognitive switch × response switch interaction reach statistical significance for the two groups combined ($p > .05$).

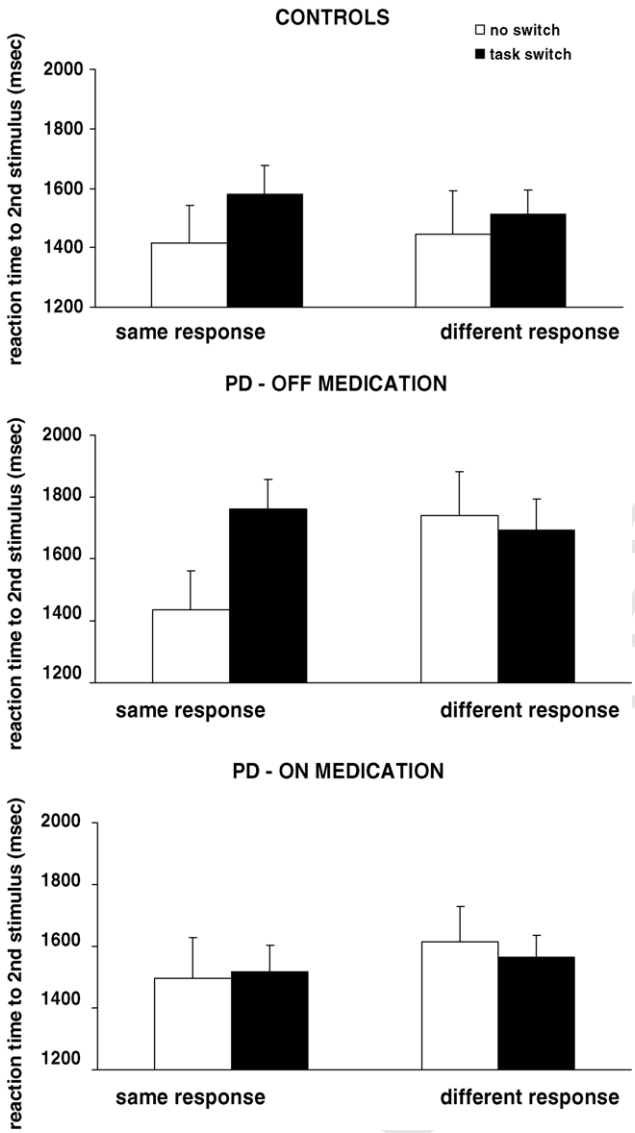

Fig. 2. Mean response times for the response repetition × task switching interaction for the control, PD-off, and PD-on groups.

The main effect of trial type was highly significant in the analysis of Parkinson's patients in the 'off' state compared to control subjects, $F(3, 84) = 3.90$, $p = .01$. Additional analyses revealed a highly significant difference between the no switch trials and the cognitive switch trials across the two groups combined, $F(1, 28) = 9.13$, $p = .005$. However, this effect reached statistical levels of significance for the PD group alone, but did not reach significance for the control group, respectively, $F(1, 14) = 6.22$, $p = .026$ (PD-off group), and $F(1, 14) = 2.92$, $p = .11$ (control group).

The response switching cost differed for the control group and the PD-off group, $F(1, 28) = 5.16$, $p = .03$, due primarily to a highly significant effect in the comparison of no switch trials to response switch trials in the PD group, $F(1, 14) = 11.57$, $p = .004$. Further analysis of the response switch × cognitive switch interaction in the control group versus PD-off comparison revealed a significant two-way interaction for the two groups combined, $F(1, 28) = 5.936$, $p = .02$. As can be seen in Fig. 2, task switch costs are larger in the same response compared to different response trials for both the controls and the PD-off groups. Given the interaction was not significant for the controls versus PD-on comparison, it is parsimonious to conclude that the response-repetition effects emerge primarily due to the depletion of dopamine in the PD-off group, as will become more obvious in the following results section.

3.2. PD patients 'on' versus 'off' states

The 'on' versus 'off' medication comparison for the PD group was highly significant when all trial types were considered together, $F(3, 42) = 4.78$, $p = .006$. As can be seen by comparing the PD-off versus PD-on data presented in Table 3, all switch types (response switch, cognitive switch, and both switch) were influenced by medication state. The interaction between on–off states and trial type was marginally significant when all trial types were considered, $F(3, 42) = 2.514$, $p = .07$. When analyzed as a 2×2 factorial of response switch × cognitive switch, a highly-significant interaction of switch type was found across the on and off states combined, $F(1, 14) = 16.32$, $p = .001$. This effect further interacted with

the on versus off manipulation, $F(1, 14) = 3.39$, $p = .08$. As can be seen by viewing Fig. 2, when in the 'off' state, PD patients show severe slowing on cognitive switches compared to when in the 'on' state, but only when responses were the same on consecutive trials. When responses were different on consecutive trials, a slightly reversed switch cost was found.

4. Discussion

The results from this study support the hypothesis that cognitive switching is impaired in patients with Parkinson's disease. In addition, the present findings support the conclusion from earlier work, that switching deficits are ameliorated significantly by L-dopa administration (Cools et al., 2001a, 2003; Hayes et al., 1998).

These findings replicate those of Hayes et al. (1998) on which the present task was based, with the PD group in the 'off' state producing large cognitive switch costs, and the control group producing similar, albeit smaller, cognitive switch costs. The present results also extend findings of switching deficits to the simple response switch trials that were not assessed in the study by Hayes et al. (1998). Simple response switch costs were largest in the PD-off group, which suggests a role of dopamine in mediating the movement slowing associated with these effects.

The slight reversal in cognitive switch costs observed in the PD patients in the on-medication state provides a novel and interesting data point in the context of task switching. The increased levels of dopamine in the on-medication state might actually result in too high a level of response activation (see Franz & Miller, 2002), thereby not only eliminating but actually reversing the expected costs in task switching. Whether or not this converges with evidence demonstrating a heightened level of impulsivity (Cools et al., 2003) similar to that found in unmedicated patients with first-episode schizophrenia (Hutton et al., 2002) remains open to additional investigation. It therefore remains possible that under some circumstances, L-dopa administration produces contrasting influences on cognitive variables associated with task switching as well.

A novel finding was the interaction of response switching × task switching that was largest in the PD-off group. The relation between dopamine and inhibitory processes is not yet understood, although dopamine is implicated in processes of inhibition, given the on- versus off-medication differences found in a number of studies using tasks that require some form of inhibition (see Section 1). One hypothesis suggested by Rogers and Monsell (1995) is that response repetition reflects a generalized inhibition that occurs on all activity belonging to a task which just received a response. The abolition of response repetition effects in the PD-on state compared to the PD-off state in the present study supports this account. Effects of response repetition have also been reported to be similar in PD patients (on normal medication) and healthy controls using other types of paradigms (Filoteo et al., 2002).

Earlier studies on the cognitive effects of PD have clearly shown that these patients are impaired on tasks involving extradimensional switching especially after interruption of dopamine medication, although there remains some debate as to whether this form of switch deficit is due to an inability to inhibit a cognitive set that is no longer necessary, or to an inability to activate a new set (Gauntlett-Gilbert et al., 1999; Owen et al., 1993). Notwithstanding this ongoing debate, there is agreement across studies that deficits in extradimensional switching are a characteristic of Parkinson's disease. Less is known about whether PD patients are impaired on switch tasks where no switch between perceptual dimensions is necessary. Our analysis of response switch trials sheds some light on this issue, given our pure response switch trials did not involve a switch in the cued perceptual dimension. As indicated above, it is clear from our findings that both cognitive and response switching appear to be dopamine dependent, given that the switch costs in the patients were exacerbated in the off-medication state. In addition, the response repetition × task switching effects were clearly different in the PD group when off their normal medication than when on regular medication, again bolstering the claim that dopamine levels influence response repetition effects. Given the primary effect responsible for this interaction is the lack of a task switching cost on the repeated (same) response trials in the PD group in the on medication state (see Fig. 2), we can cautiously suggest that administration of L-dopa ('on' state) results in a disinhibition of the normal inhibitory processes that affect task switches on repeated response trials. In a similar vein, the loss of dopamine due to PD exacerbates task-switching costs on repeated response trials beyond the level seen in normal controls. In addition, the very slight task switch cost seen in different response trials for the controls is actually reversed for the PD group (both in the on and off states), again suggesting a lack of normal inhibition on responses.

An issue that should be mentioned is the possibility that congruity between the stimulus dimensions and the responses (in which the stimulus has elements associated with both possible responses) might differentially influence responses in the two groups (e.g., Aron et al., 2003b). Although the present study did not specifically focus on congruity effects, congruent and incongruent trials were equally probable and varied randomly with each type of switch trial. Reanalysis of our data with respect to this factor did not reveal any clear effects that would differentiate the PD and control groups.

In summary, the present findings replicate and extend those of earlier studies in that PD patients are impaired on switching tasks, particularly when off their normal medication cycles. When regular dopamine medication was interrupted temporarily, the patients suffered much worse switching deficits on both the cognitive switching task (replicating earlier studies), and the simple version of response switching. In addition, the interaction of response switching and cognitive switching revealed significant response repetition effects, particularly for PD patients in the off-medication state. Stud-

ies using other tasks that implicate inhibitory processes have demonstrated evidence in support of abnormal response inhibition in PD (e.g., Filoteo et al., 2002; Franz & Miller, 2002) and Huntington's disease (Aron et al., 2003a) patients. It is therefore possible that general deficits in activation and inhibition that are associated with Parkinson's disease and depleted levels of dopamine, underlie both response switching and cognitive switching deficits in the patients. In sum, the present findings support the conclusion that switching operations are dopamine-dependent and rely on the integrity of the basal ganglia.

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References

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, *9*, 357–381.

Allport, A., Styles, E. A., & Hsieh, S. (1994). Shifting intentional set: Exploring the dynamic control of tasks. In C. Umilta & M. Moscovitch (Eds.), *Attention and Performance XV* (pp. 421–452). Cambridge, MA: MIT Press.

Aron, A. R., Schlaghecken, F., Fletcher, P. C., Bullmore, E. T., Eimer, M., Barker, R., et al. (2003). Inhibition of subliminally primed responses is mediated by the caudate and thalamus: Evidence from functional MRI and Huntington's disease. *Brain*, *126*, 713–723.

Aron, A. R., Watkins, L., Sahakian, B. J., Monsell, S., Barker, R. A., & Robbins, T. W. (2003). Task-set switching deficits in early-stage Huntington's disease: Implications for basal ganglia function. *Journal of Cognitive Neuroscience*, *15*, 629–642.

Benecke, R., Rothwell, J. C., Dick, J. P., Day, B. L., & Marsden, C. D. (1987a). Disturbance of sequential movements in patients with Parkinson's disease. *Brain*, *110*, 361–379.

Benecke, R., Rothwell, J. C., Dick, J. P., Day, B. L., & Marsden, C. D. (1987b). Simple and complex movements off and on treatment in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *50*, 296–303.

Bowen, F. P., Kamienny, R. S., Burns, M. M., & Yahr, M. D. (1975). Parkinsonism: Effects of levodopa treatment on concept formation. *Neurology*, *25*, 701–704.

Brass, M., Ruge, H., Meiran, N., Rubin, O., Koch, I., Zysset, S., et al. (2003). When the same response has different meanings: Recoding the response meaning in the lateral prefrontal cortex. *NeuroImage*, *20*, 1026–1031.

Brown, R. G., & Marsden, C. D. (1988). An investigation of the phenomenon of "set" in Parkinson's disease. *Movement Disorders*, *3*, 152–161.

Cools, A. R. (1980). Role of neostriatal dopaminergic activity in sequencing and selecting behavioural strategies: Facilitation of processes involved in selecting the best strategy in a stressful situation. *Behavioural Brain Research*, *1*, 361–368.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001a). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral Cortex*, *11*, 1136–1143.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001b). Mechanisms of cognitive set flexibility in Parkinon's disease. *Brain*, *124*, 2503–2512.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). L-dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*, *41*, 1431–1441.

Cools, A. R., van den Bercken, J. H., Horstink, M. W., van Spaendonck, K. P., & Berger, H. J. (1984). Cognitive and motor shifting aptitude disorder in Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry*, *47*, 443–453.

Filoteo, J. V., Rilling, L. M., & Strayer, D. L. (2002). Negative priming in patients with Parkinson's disease: Evidence for a role of the striatum in inhibitory attentional processes. *Neuropsychology*, *16*, 230–241.

Flowers, K. A., & Robertson, C. (1985). The effect of Parkinson's disease on the ability to maintain a mental set. *Journal of Neurology, Neurosurgery and Psychiatry*, *48*, 517–529.

Franz, E. A., & Miller, J. (2002). Effects of response readiness on reaction time and force output in people with Parkinson's disease. *Brain*, *125*, 1733–1750.

Gauntlett-Gilbert, J., Roberts, R. C., & Brown, V. J. (1999). Mechanisms underlying attentional set-shifting in Parkinson's disease. *Neuropsychologia*, *37*, 605–616.

Harrington, D. L., & Haaland, K. Y. (1991). Sequencing in Parkinson's disease. *Brain*, *114*, 99–115.

Hayes, A. E., Davidson, M. C., Keele, S. W., & Rafal, R. D. (1998). Toward a functional analysis of the basal ganglia. *Journal of Cognitive Neuroscience*, *10*, 178–198.

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression and mortality. *Neurology*, *17*, 427–442.

Hornykiewicz, O. (1973). Parkinson's disease. From brain homogenates to treatment. *Fed. Proc. Am. Soc. Exp. Biol.*, *32*, 183–190.

Hutton, S. B., Murphy, F. C., Joyce, E. M., Rogers, R. D., Cuthbert, I., Barnes, T. R., et al. (2002). Decision making deficits in patients with first-episode and chronic schizophrenia. *Schizophrophrenia Research*, *55*, 249–257.

Inzelberg, R., Plotnik, M., Flash, T., Schechtman, E., Shahar, I., & Korczyn, A. D. (1996). Switching abilities in Parkinson's disease. *Advances in Neurology*, *69*, 361–369.

Inzelberg, R., Plotnik, M., Flash, T., Schechtman, E., Shahar, I., & Korczyn, A. D. (2001). Mental and motor switching in Parkinson's disease. *Journal of Motor Behavior*, *33*, 377–385.

Jersild, A. T. (1927). Mental set and shift. *Archives of Psychology*, 89.

Lange, K. W., Robbins, T. W., Marsden, C. D., James, M., Owen, A. M., & Paul, G. M. (1992). L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. *Psychopharmacology (Berl)*, *107*, 394–404.

Meiran, N. (1996). The reconfiguration of processing mode prior to task performance. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *22*, 1423–1442.

Meiran, N. (2000). Modeling cognitive control in task-switching. *Psychological Research*, *63*, 234–249.

Middleton, F. A., & Strick, P. L. (2000). Basal ganglia output and cognition: Evidence from anatomical, behavioral, and clinical studies. *Brain and Cognition*, *42*, 183–200.

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal love defects. *Cortex*, *12*, 313–324.

Owen, A. M., Roberts, A. C., Hodges, J. R., Summers, B. A., Polkey, C. E., & Robbins, T. W. (1993). Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain*, *116*, 1159–1175.

Parent, A. (1990). Extrinsic connections of the basal ganglia. *Trends in Neurosciences*, *13*(7), 254–258.

Rafal, R. D., Posner, M. I., Walker, J. A., & Friedrich, F. J. (1984). Cognition and the basal ganglia. Separating mental and motor components of performance in Parkinson's disease. *Brain*, *107*, 1083–1094.

Richards, M., Cote, L. J., & Stern, Y. (1993). Executive function in Parkinson's disease: Set-shifting or set-maintenance? *Clinical and Experimental Neuropsychology*, *15*, 266–279.

Robertson, C., & Flowers, K. A. (1990). Motor set in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *53*, 583–592.

Rogers, R. D., & Monsell, S. (1995). The cost of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General*, *124*, 207–231.

Rogers, R. D., Sahakian, B. J., Hodges, J. R., Polkey, C. E., Kennard, C., & Robbins, T. W. (1998). Dissociating executive mechanisms of task control following frontal lobe damage and Parkinson's disease. *Brain*, *121*, 815–842.

Roy, E. A., Saint-Cyr, J., Taylor, A., & Lang, A. (1993). Movement sequencing disorders in Parkinson's disease. *International Journal of Neuroscience*, *73*, 183–194.

Schuch, S., & Koch, I. (2003). The role of response selection for inhibition of task sets in task shifting. *Journal of Experimental Psychology: Human Perception and Performance*, *29*, 92–105.

Spector, A., & Biederman, I. (1976). Mental set and shift revisited. *American Journal of Psychology*, *89*, 669–679.

Stern, M. B. (1988). *The comprehensive management of Parkinson's disease*. New York: PMA Publishing Corp.

Wylie, G., & Allport, A. (2000). Task switching and the measurement of "switch costs". *Psychological Research*, *63*, 212–233.