Toward a Functional Analysis of the Basal Ganglia

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Abstract

■ Parkinson patients were tested in two paradigms to test the hypothesis that the basal ganglia are involved in the shifting of attentional set. Set shifting means a respecification of the conditions that regulate responding, a process sometimes referred to as an *executive process*. In one paradigm, upon the appearance of each stimulus, subjects were instructed to respond either to its color or to its shape. In a second paradigm, subjects learned to produce short sequences of three keypresses in response to two arbitrary stimuli. Reaction times were compared for the cases where set either remained the same or changed for two successive stimuli. Parkinson patients were slow to change set compared to controls. Parkinson patients were also less able to filter the competing but irrelevant set than were control subjects. The switching deficit appears to be dopamine based; the magnitude of the shifting deficit was related to the degree to which l-dopa-based medication ameliorated patients' motor symptoms. Moreover, temporary withholding of medication, a so-called off manipulation, increased the time to switch. Using the framework of equilibrium point theory of movement, we discuss how a set switching deficit may also underlie clinical motor disturbances seen in Parkinson's disease. ■

INTRODUCTION

Because motor disability is the cardinal clinical feature of basal ganglia disease, the basal ganglia have long been thought of as part of the motor system. Neuroanatomical data over the last decade and more have indicated, however, that a number of circuits arise in frontal and other cortical regions, course through the basal ganglia, and return via the thalamus to the cortical point of origin (e.g., Alexander, DeLong, & Strick, 1986; Parent, 1990). Although some circuits arise in putative motor regions, such as the supplementary motor area, frontal eye fields, and primary motor cortex, other circuits arise from regions such as the dorsolateral prefrontal cortex, thought to subserve other functions, such as working memory (Fuster, 1985; Goldman-Rakic & Selemon, 1990). The different circuits have a remarkable similarity of detail, all involving subcircuits with net inhibitory and net excitatory influences on their cortical targets (Alexander & Crutcher, 1990). The similarity of circuitry across different cortical domains suggests that the basal ganglia provide some common function for motor and nonmotor tasks alike.

Behavioral evidence also suggests nonmotor functions for the basal ganglia. Parkinson's disease, one disorder of the basal ganglia, presents a variety of cognitive effects (for reviews see Brown & Marsden, 1990; Saint-Cyr, Taylor, & Nicholson, 1995). Patient studies (e.g., Marsden & Obeso, 1994; Owen et al., 1993; Robertson & Flowers, 1990), animal investigations (e.g., Cools, 1980), and neuroimaging studies (e.g., Corbetta, Miezen, Dobmeyer, Shulman, & Peterson, 1990) have all presented effects that can be attributed to a deficit in changing from one set that guides behavior to another set. It is this hypothesis—that the basal ganglia provide a set switching function—that is the basis of the current paper. The hypothesis is examined by analyzing performance of Parkinson patients, who have dopamine deficiency in the basal ganglia.

The switching hypothesis originated from studies involving complex tasks, such as variants of the Wisconsin Card Sorting Task (WCST). In the WCST, subjects view a succession of multidimensional stimuli. They attempt to discover the basis for classifying the stimuli into one category or another based on error feedback. Parkinson patients have difficulty with the task (e.g., Bowen, Kamienny, Burns, & Yahr, 1975). Cools, Van den Bercken, Horstink, Van Spaendonck, and Berger (1984) built on

these findings, arguing for a "shifting aptitude" deficit. They found evidence for such a deficit from tasks in three domains, verbal fluency, motor sequencing, and sorting of compound stimuli as in the WCST.

Subsequent studies have continued to examine the nature of the switching deficit in each of these domains (e.g., Brown & Marsden, 1988; Downes et al., 1989; Downes, Sharp, Costall, Sagar, & Howe, 1993; Flowers & Robertson, 1985; Owen et al., 1993; Robertson & Flowers, 1990). In most cases, the primary measures in these studies have been patterns of errors and, in classification tasks, number of trials to solution. Reaction time measures have not produced strong evidence for a general switching deficit (e.g., Brown & Marsden, 1988). Thus, a switching deficit has been inferred from differences in the probability of performing or maintaining a switch, based on the overall pattern of performance. In the present experiments we measure the time required to execute a switch. In this way we can examine not only the probability of successfully implementing a switch, but we can look for a deficit in the execution of the switch itself.

A set switching hypothesis faces two serious criticisms. First, some analytic attempts to test it have not been successful. Studies that have attempted to directly measure switching time, using a spatial-cueing paradigm based on work by Posner and Snyder (1975), have failed to find a switching deficit in Parkinson patients. In this paradigm, a cue indicates where a visual target is likely to occur. Reaction times to detect the signal on validly and invalidly cued trials are compared to reaction times following neutral cues. Reaction times following valid cues show a benefit compared to neutral cues, whereas invalid cues engender a cost. The cost often has been taken as a measure of attentional switching. Rafal, Posner, Walker, and Friedrich (1984) found no changes in either cost or benefit with variation in medication level of Parkinson patients. Subsequent investigations have found no change in cost or, if anything, a slightly reduced cost for Parkinson patients or for subjects administered a dopamine antagonist (Clark, Geffen, & Geffen, 1989; Sharpe, 1990; Wright, Burns, Geffen, & Geffen, 1990). Thus, analytic attempts to find a switching deficit either in Parkinson patients or in subjects with neurotransmitter manipulations of the basal ganglia have not been supportive of the hypothesis.

The basal ganglia could, however, be involved in set switching yet not be involved in the type of switching that occurs in a spatial cueing paradigm. Recent advances in the study of attention have suggested a network of attentional systems (Posner & Dehaene, 1994). The cueing paradigm most likely invokes neural systems involving the posterior cortex. In contrast, other attentional functions of the sort frequently called executive functions more likely have a frontal focus (e.g., Posner & DiGirolamo, in press; Stablum, Leonardi, Mazzoldi, Umilta, & Morra, 1994; Stablum, Mogentale, & Umilta, 1996). Given circuit interconnections between the frontal cortex and basal ganglia, it is possible that the basal ganglia are involved in attentional switching involving executive functions.

Executive functions are needed in situations where a conflict between possible courses of action requires an instruction to specify a basis for selection (Norman & Shallice, 1986). When shown a flower, an instruction may request either the flower's name or its color. In experimental settings, this kind of set is studied by using multidimensional stimuli or stimuli with multiple internal codes, and an instruction specifies which stimulus property or code should be attended and responded to. In a cueing paradigm, executive functions are not necessarily needed because each stimulus is associated with a single response. The cue establishes a bias or expectation regarding the stimulus, such as the position at which it will occur, but regardless of whether it appears as cued, the stimulus elicits only one possible response. This type of switching is measured by the difference in reaction times to expected and unexpected stimuli, either of which has a single relevant response. In the set switching paradigm, attentional switching is measured by the increased reaction time when instructions specifying the basis of response are altered (Allport, Styles, & Hsieh, 1994; Meiran, 1996; Rogers & Monsell, 1995). The present experiments investigate whether the basal ganglia are involved in switching instructional set.

A second criticism facing a switching hypothesis is that it has offered no account of the obvious motor problems presented with basal ganglia malfunction. It is possible that the contribution of the basal ganglia differs in the cognitive and motor domains. However, a function that generalizes across domains would be expected given the neuroanatomical similarities among the various fronto-striatal circuits. In the discussion, we consider how the shifting hypothesis could extend to the domain of movement. In particular, it appears that Parkinson's disease produces a deficit in force regulation (Stelmach & Worringham, 1988; Wing, 1988), an account in accord with observations of monkeys that have lesions of the globus pallidus (Horak & Anderson, 1984; Mink & Thach, 1991). We offer an extension of the set switching hypothesis to force regulation, providing a unified view of basal ganglia function.

In the present experiments, we test for a deficit in set switching in Parkinson patients by measuring the time required to switch set successfully. We test the generalizability of the switching function by examining both a cognitive task and a motor-based task. In the cognitive task, switching of set occurs between responding to color and responding to shape of stimuli. In the motor task, set shifting occurs between the production of one sequence of keypresses and another sequence. For each of the two domains of study—color-shape and motor

sequencing—two different experiments are conducted. The first experiment in each domain compares Parkinson patients to age-matched control subjects. The prediction is that Parkinson patients will be specifically impaired on the time to shift attention from one set to another. In these experiments, Parkinson patients are tested while under their normal levodopa medication. Of course, a purpose of the medication is to ameliorate symptoms, which it does to varying degrees in different patients. The second experiment in each domain examines a set of patients who function relatively well when medicated, and they are examined both under their usual medication regimen and when they temporarily withhold medication. The prediction is that switching deficits will become more pronounced when off medication.

EXPERIMENT 1: SHIFTING OF SET BETWEEN COLOR AND SHAPE

All subjects, 17 Parkinson patients on their normal medication and 13 age-matched control subjects, in training trials learned to associate two colors with two response keys and two shapes with the same two response keys. In the experimental trials, each stimulus consisted of either a single dimension alone or was bidimensional with both a shape and a color present. The word *color* or *shape* appeared simultaneously with the stimulus, indicating which dimension was relevant. Stimuli occurred in pairs; upon the response to the first stimulus of a pair, and with a 0-msec delay, the first stimulus disappeared and a second instructional word appeared simultaneously with the second stimulus. On half the occasions, the instructional word was the same as for the first stimulus of a pair; on the other half it was different, requiring a switch in set.

The primary focus of this experiment concerns the reaction time to the second stimulus as a function of whether the instruction was the same as or different from the preceding stimulus. The difference in reaction time in the two cases reflects the time for executive processes to reconfigure the relevant dimension. This difference we refer to as switching time. Because a subject is unaware prior to the response to the first member of the pair whether or not a switch will be necessary, reaction time to the first member is of little interest and is not reported here.

Independent of switching time, the paradigm also allows examination of the efficiency of filtering the irrelevant dimension once set is established. For each stimulus, the relevant dimension could appear by itself or with the irrelevant dimension also present. If present, the irrelevant dimension was either neutral, in the sense that it had no key assignment, or it could specify the conflicting key response. Slowed reaction times in the neutral or incongruent situation would be indicative of imperfect filtering of the irrelevant dimension.

Results

Switching Time

Of primary interest is the interaction between group—control subjects versus Parkinson patients—and whether the instruction on the second trial of a pair remains the same as or switches from that of the first trial of the pair. The data, averaged over medians for each subject, are shown in Table 1. Overall, Parkinson patients have slower reaction times than the controls, but in accordance with predictions, the slowing is particularly prominent in the switch condition. This interaction between subject group and switch condition is significant: $F(1, 28) = 7.70, p < 0.01$. Subtracting reaction time in the switch condition from the nonswitch condition yields a switching effect of 184 msec for patients compared to 90 msec for controls. A similar trend is shown in error rates, with the patients showing more errors, particularly in the switch condition. The interaction between subject group and switch condition for error rates is reliable by a one-tailed test: $F(1, 28) = 4.00, p < 0.03$.

Of some concern is whether the switching effect in patients differs as a function of whether in the second stimulus the irrelevant dimension was neutral, in conflict, or absent. In fact, neither the two-way interaction between switch versus nonswitch and nature of the second stimulus nor the three-way interaction adding patients versus controls approached reliability. Such lack of interaction suggests that the difference in switching time deficit in patients is robust across stimulus conditions.

A second concern involves the fact that patients are slower on average than control subjects even in the nonswitching condition. This raises the possibility that the patient deficit is not one of switching per se but simply reflects slower times in all processes that contribute to reaction time. Some perspective on this problem is gained by examining subgroups of patients.

Subgroup Variations

During the experiment session each Parkinson patient was administered a short examination adapted from the

Table 1. Reaction Time and Errors When Color-Shape Instruction Switches or Does Not in Experiment 1

	No switch	*Switch*	*Difference*
Control subjects			
Reaction Time (msec)	854	944	90
Error rate	.005	.018	.013
Parkinson patients			
Reaction time	1015	1199	184
Error rate	.034	.066	.032

motor section of the Unified Parkinsonism Rating Scale (Stern, 1988). Based on this examination, patients were divided into three subgroups. Some patients, even though medicated, remained slow of movement, retained rigidity, and showed a paucity of spontaneous subsidiary movements such as gestures in the course of speaking. These patients are labeled "hypokinetic" ($N = 6$). A second group of patients appeared relatively normal in their movements on medication. We label those "unimpaired" ($N = 5$). The third group exhibited dyskinesias as a result of medication, showing a great deal of abnormal excess movement often unrelated to current action. We call this subgroup "hyperkinetic" ($N = 6$).

The reaction times for the second stimulus of stimuli pairs in the nonswitch and switch conditions are shown in Table 2, broken down by subgroup. The grouping of the Parkinson patients by motor symptoms is validated by the finding that compared to controls, reaction times were greatly slowed in the hypokinetic subjects, slowed less so in the unimpaired subjects, and slowed only marginally in the hyperkinetic subjects. This main effect of subgroup, however, is not significant in an analysis of variance of the patients classified by subgroup, perhaps because the number of patients in each subgroup is rather small. There is also no significant interaction between subgroup classification and switch condition.

Compared to the Parkinson group as a whole, the unimpaired Parkinson patients are not as different from control subjects in the nonswitch condition—999 msec versus 854 msec. Comparison of the switching times in those two groups is therefore of special interest. The switching effect for the controls is 90 msec, whereas that for the unimpaired Parkinson patients is 200 msec, a difference of 110 msec between the two groups. This group by switching condition interaction is reliable: $F(1, 16) = 4.62$, $p < 0.025$ by a one-tailed test. The fact that the increase in switching time compared to controls for these selected patients is itself nearly as large as the baseline increase makes it very unlikely that the switching time deficit can be attributed solely to slower reaction times in all phases. Moreover, the fact that switching time deficits are nearly the same in the hypokinetic and unimpaired Parkinson patients, despite large differences in baseline reaction time, further indicates that the switching time deficit is partially independent of changes in reaction time per se.

Table 2. Reaction Time by Patient Subgrouping When Color-Shape Instruction Switches or Does Not in Experiment 1

	No switch	*Switch*	*Difference*
Control subjects	854	944	90
Parkinson patients			
Hypokinetic	1168	1386	218
Unimpaired	999	1199	200
Hyperkinetic	876	1011	135

Switching time in the hyperkinetic patients was little different from that of the control subjects. Such results suggest that medication levels that are sufficient to produce dyskinesias alleviate switching time deficits. This issue is further examined in a second experiment that manipulated medication, but before turning to that, let us consider filtering.

The Efficiency of Filtering

The presence of an irrelevant dimension that sometimes specifies a conflicting response requires attentional set to select the relevant dimension. Once set is established, one may ask how effectively the irrelevant dimension is filtered. Two different comparisons can be made. One compares reaction times when the two dimensions conflict to a neutral condition in which the presented feature of the irrelevant dimension has no response assignment. The other compares the incongruent condition to the absence of an irrelevant dimension.

Figure 1 shows reaction times and errors for these comparisons. Regarding reaction times, there is a significant interaction between subject group and the nature of the stimulus: $F(2, 56) = 3.14$, $p = 0.05$. The addition of an irrelevant dimension, whether incongruent or neutral, increases reaction time to a greater extent for Parkinson patients than for controls. Such a result suggests that any filtering difficulty in patients is of a particular type. The presence of an irrelevant dimension slows processing regardless of whether the irrelevant dimension specifies a response in conflict with that of the relevant dimension. Unfortunately, this conclusion is complicated by two factors. One is that baseline reaction times and errors in the condition with no irrelevant dimension are very different for the patients and controls. Patients' high baseline error rates especially make the results difficult to interpret because there is no consensus on how error rates should be scaled. To appreciate the scaling problem, one might note that if the error probabilities were converted to z scores, the interaction between subject group and stimulus type disappears. In turn, uncertainty regarding error interpretation influences the interpretation of reaction times.

The problem of baseline reaction times is somewhat clarified when the patients are subdivided into the subgroups of hypokinetic, unimpaired, and hyperkinetic. Figure 2 shows that the baseline reaction times for the condition of relevant dimension alone are less markedly different between the unimpaired patients and the control subjects (933 vs. 815 msec). Nonetheless, the effect of incongruent stimuli is much more marked for the unimpaired patients than for the controls. Reaction time increases by 305 msec over the single-dimension base-

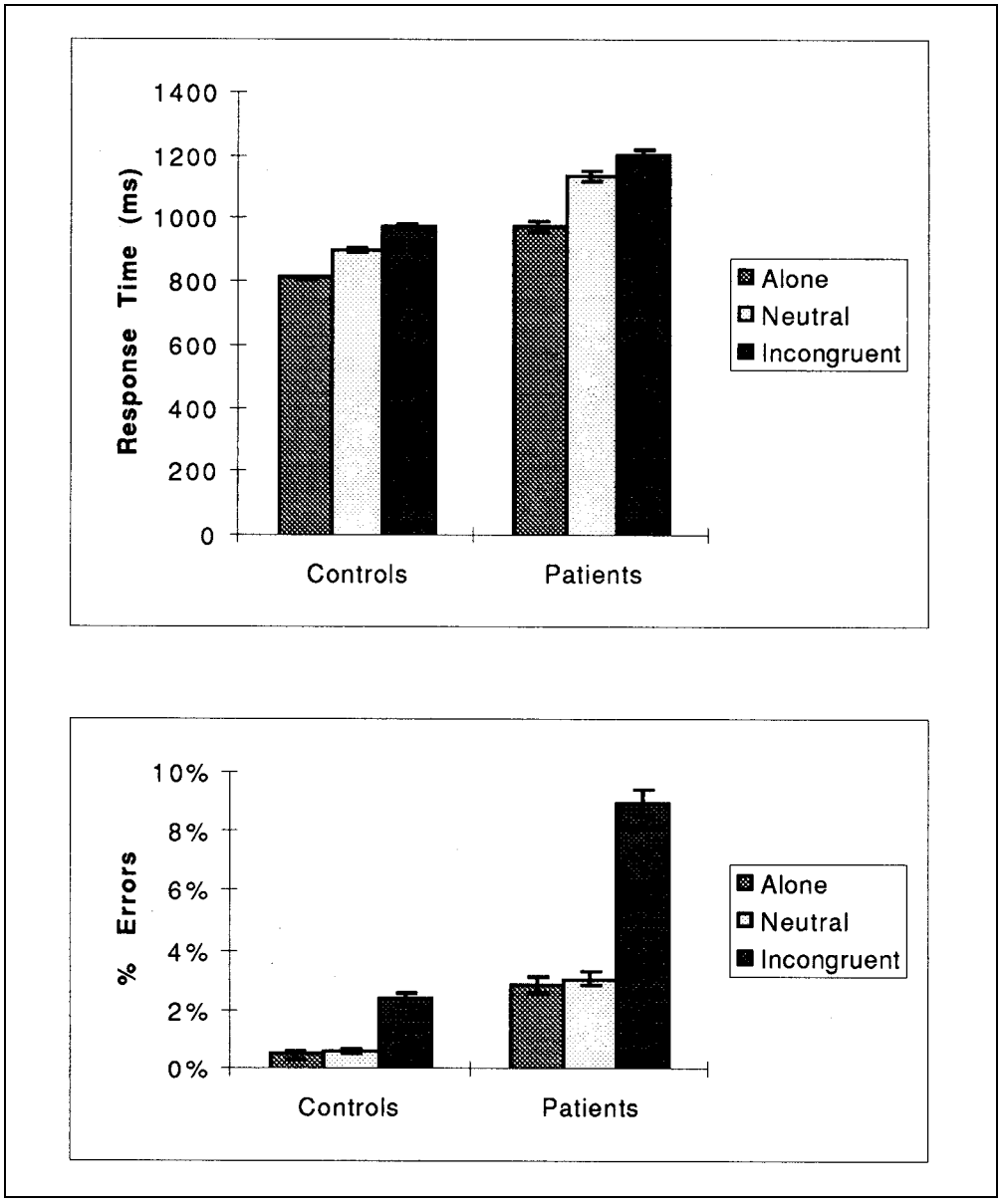

Figure 1. Response times and error rates by stimulus type (Alone, Neutral, and Incongruent) for Patients vs. Controls in Experiment 1. Error bars indicate standard error.

line for the unimpaired patients as opposed to an increase of only 163 msec for the control subjects. This interaction between unimpaired patients versus control subjects with the filtering effect is reliable: $F(2, 32) = 8.64, p < 0.001$. Given that the size of the interaction is larger than the difference in baseline reaction times of the unimpaired Parkinson patients and the controls, it is difficult to attribute the results to generalized slowing of all processes in the patients.

Despite complications of error rates and unequal baselines, it appears that Parkinson patients in general are less effective in filtering irrelevant information than are control subjects. The filtering difficulty is of a special form, however. It primarily reflects an increase in reaction time when a potentially conflicting irrelevant dimension is present regardless of whether the irrelevant dimension actually indicates a conflicting response. Such effect suggests that attentional filtering is composed of two distinct processes. One process detects the presence of dimensions. If more than one dimension is present, a complementary process must be implemented to select the relevant dimension. Either after the initial decision or even simultaneously, a second process determines the values of the present dimensions, and information is retrieved from memory regarding associated responses. It is in this second process that conflict may arise regarding which response is appropriate. The fact that Parkinsonian impairment from an irrelevant dimension is independent of whether the dimensional values are incongruent or not suggests that the basal ganglia is involved only in the first process. That is, the patients have difficulty specifying or maintaining specification of the correct dimension. Thus, their filtering problem seems closely allied with other manifestations of their

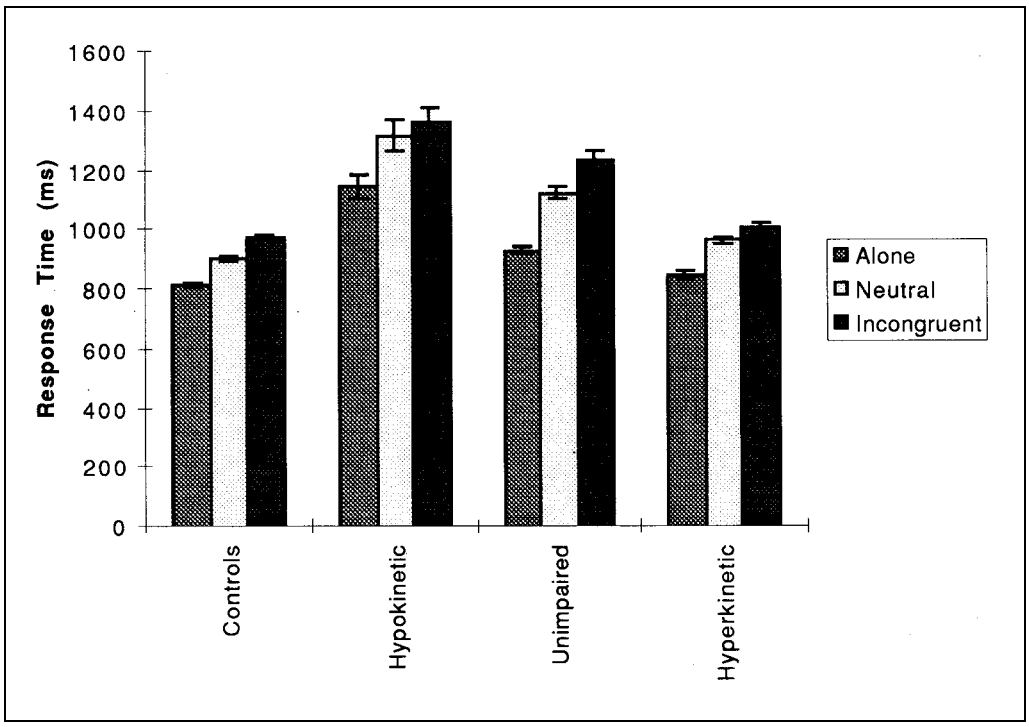

Figure 2. Response times by stimulus type (Alone, Neutral, and Incongruent) in Experiment 1, with patient data broken down by symptom-based subgroupings. Error bars indicate standard error.

problem with attentional set. Not only are they slow in switching set from one dimension to another, but set establishment is less effective.

EXPERIMENT 2: COLOR-SHAPE SET SWITCHING ON AND OFF MEDICATION

In Experiment 1, the effects of Parkinsonism on switching of set and filtering varied depending on the symptoms of patients while on medication. Patients who either remained hypokinetic or appeared relatively unimpaired in their motor symptoms retained large switching effects. Moreover, the efficiency of their filtering appeared impaired. In contrast, patients who were hyperkinetic under medication showed little or no switching or filtering deficit. These different motor symptoms may reflect the degree to which medication is compensating for the dopamine deficit. If so, the results would suggest that the set switching and filtering effects are attributable to dopamine effects.

To test this possibility, a set of 12 patients were tested in an on-off manipulation. Each patient was tested on the color-shape switching task on one or more occasions in which they were on their normal cycle of l-dopa-based medication and on one or more occasions in which they temporarily withheld their medication. Half of the selected patients had participated in the initial study, but all 12 were patients who we thought would fall into either the unimpaired or hyperkinetic classification when on medication. This would allow us to observe the effects on switching and filtering as the patients became more hypokinetic when off medication.

We specifically recruited patients for this study who had a history of clinically manifest fluctuations in motor symptoms that varied with medication level. In this way, rather than simply assuming that dopamine levels were low when medication was delayed and high after medication, we could verify the efficacy of the medication by overt motor performance. As detailed in the "Methods" section, 9 of the 12 patients showed clear overt differences between the on and off states, either by clinical symptoms or by performance on motor tasks. The remaining 3 patients did not show clear differences in clinical symptoms in the on and off sessions but reported that subjectively they felt on and off, and performance on motor tasks corroborated these classifications, although with not as large differences as seen in the other patients.

Results

The mean reaction times and error rates for the second trial of pairs of trials are shown in Table 3. The overall pattern is as expected: Reaction times slow when off medication, but the change is greater in the switch than in the nonswitch condition: $F(1, 11) = 7.13$, $p < 0.01$, one-tailed test for reaction time. Likewise, when off medication the change in error rates from the nonswitch to the switch condition is increased: $F(1, 11) = 3.11$, $p = 0.05$, one-tailed test for errors. Figure 3 shows data for the different stimulus conditions of the second trial of a pair. When off medication, subjects exhibit less efficient filtering by the reaction time measure, but the result is only marginally reliable: $F(2, 22) = 2.88$, $p < 0.07$. The

Table 3. Reaction Time and Errors When Color-Shape Instruction Switches or Does Not in Experiment 2

	No switch	*Switch*	*Difference*
Patients on medication			
Reaction time (msec)	815	982	167
Error rate	.029	.085	.056
Patients off medication			
Reaction time	942	1151	209
Error rate	.011	.088	.077

error pattern, however, is contrary to expectation, with a tendency for more efficient filtering in the off-medication state. This contrary effect is marginally reliable: $F(2, 22) = 3.26, p < 0.06$.

Although changes in baseline reaction times present a problem that is difficult to correct for in the on-off manipulation, the pattern of results is largely consistent with the primary analyses that compare Parkinsonian subjects to control subjects. When off medication, switching time is increased. The results are less clear with respect to the efficiency of filtering, where contradictory results are obtained with reaction times and errors. Together with subgroup variations among Parkinson patients, the results suggest that at least switching deficits are dependent upon dopamine deficits in the basal ganglia.

EXPERIMENT 3: SHIFTING OF SET BETWEEN MOTOR SUBSEQUENCES

The color-shape experiments suggest a Parkinsonian deficit in shifting set between one stimulus dimension

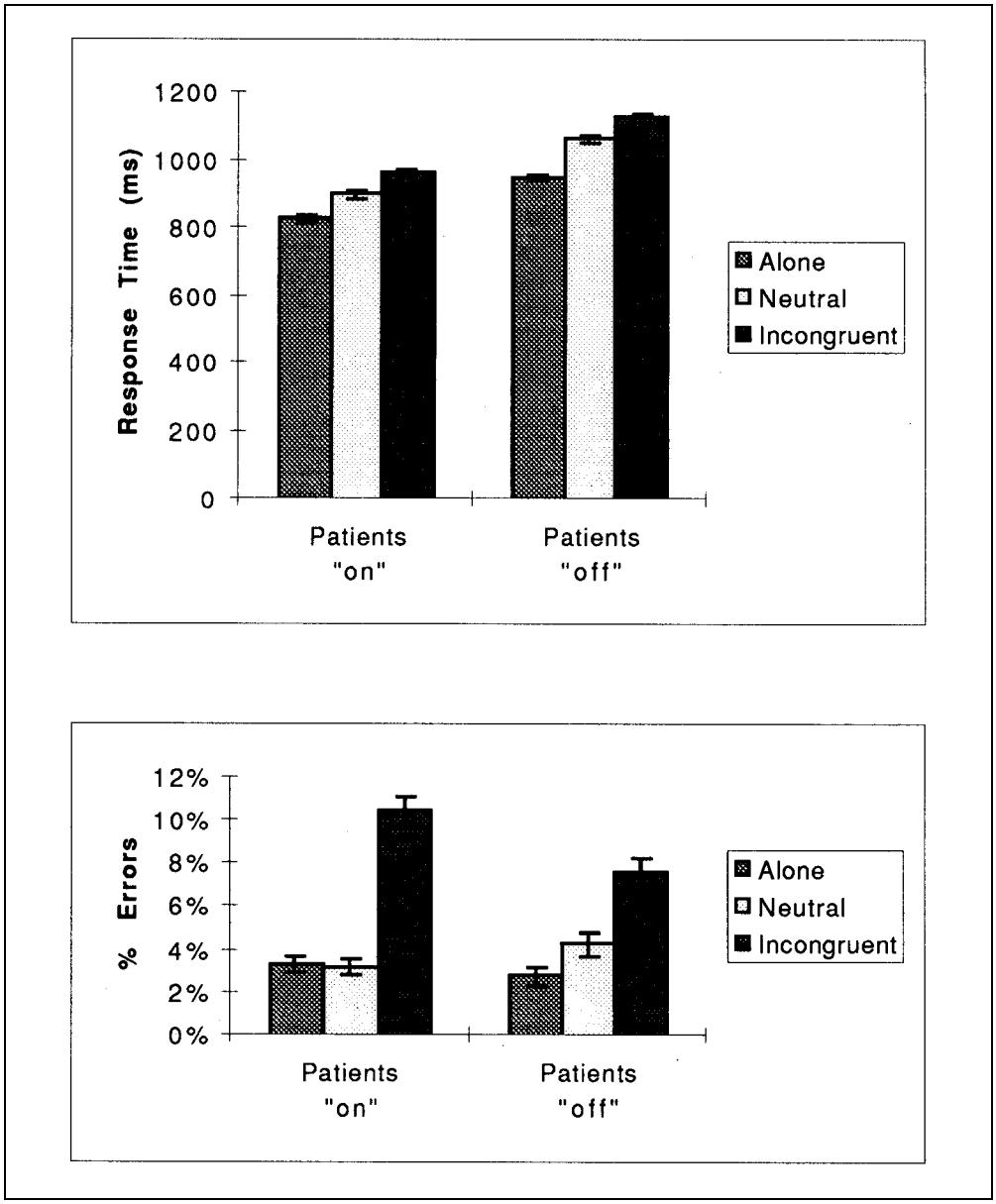

Figure 3. Response times and error rates by stimulus type (Alone, Neutral, and Incongruent) for patients on medication vs. off medication in Experiment 2. Error bars indicate standard error.

and another. A second pair of experiments involving the same patient and control subjects, with minor exceptions, tested for a switching deficit in a different domain, that of shifting set from one action series to another. We established a paradigm in which sequences of six keypress taps were clearly demarcated into two distinct chunks. We predicted that Parkinson patients would be slow to execute the second subsequence chunk when a switch was required compared to when the two subsequences were identical.

This experiment was motivated both by empirical phenomena and by theory of sequential representation. Quite some time ago, Cools (1980) demonstrated that manipulation of dopamine affected the rate at which rats switched from one swimming maneuver to another in attempting to escape from a water tank. The fact that different swimming maneuvers are complex sequences of action suggests a generalized hypothesis that the basal ganglia are involved in switching set between different action sequences. Later, Robertson and Flowers (1990) tested a similar notion. Parkinson patients repeatedly performed either one of two prelearned sequences, or they performed one and then switched to the other upon a switch signal. Although Robertson and Flowers did not measure transition times between sequences, they noted that patients made substantially more errors than control subjects when they had to switch between sequences. The increased errors occurred not only in the switched-to sequence but also in the sequence prior to the switch signal. Such results suggest that when two action sequences had to be held in readiness, there was incomplete filtering of one while performing the other.

A second motivating factor for these experiments stems from hierarchic conceptions of human sequential skill (see Keele, Cohen, & Ivry, 1990 for a review). Data from a variety of sources—transfer of learning, intervals between successive responses, preparation time, and error analysis—suggest that sequential representation of speech and language, of keyboard skills such as piano or typing, and of other skills is hierarchically arranged into chunks. That is, the succession of events is organized into subsequences. In some theories (e.g., MacKay, 1987; Rosenbaum, 1987) progression through a hierarchic representation occurs by a switching operation in which as one chunk is completed, the global representation of that chunk is inhibited and the next is activated.

We designed a paradigm that would allow for measuring the switching time associated with switching between sequential operations. Three keys to be tapped with the index finger were arranged in an equilateral triangle and labeled 1, 2, and 3. Participants learned to associate the letter A with the keypress sequence 123 and the letter B with sequence 132 (letter-sequence assignment was counterbalanced across subjects). In experimental trials a double-letter stimulus was given—AA, BB, AB, or BA. The subject's task was to press the keys as rapidly as possible in the order dictated by the two letters, first the three taps corresponding to the first letter and then the three taps corresponding to the second letter.

We predicted that at the transition point between the two subsequences, that is between taps 3 and 4, the intertap interval would increase as activation of the second subsequence occurred. Moreover, the increase would be greater when the letter code required a change from one action sequence to a different one. The additional increase in the switch case was predicted to be larger for Parkinson patients than for control subjects and greater for Parkinson patients off their normal medication than on.

A particular feature of the paradigm is worth noting. Consider the case in which A designates taps 123 and B designates 132. Consider further the first four taps in the AA and AB instances. In each case the first four taps are identical, being 1231. Only for the last two taps does keypress order vary as a function of the second letter. A similar circumstance holds for the BB and BA sequences. Because the change of subsequence representation is hypothesized to occur between taps 3 and 4 in the AB and BA cases, we presume those sequences will exhibit an increase in intertap interval at that point even though the identity of the following tap is the same as in the nonswitch case. Any Parkinsonian deficit, therefore, would be attributable to a change in internal representation rather than to an alteration of motor processes. Such an outcome would be congruent with the hypothesis that the basal ganglia are involved in switching of set generally and not just alterations of motor behavior.

Results

Switching Time

Interresponse times as a function of position in the sequence of six taps are shown in Figure 4. The first interval is actually the reaction time following the onset of the double-letter instruction to initiate responding. After the first tap, the next two intertap intervals greatly decrease below the initial reaction time. The intertap interval then increases between tap 3 and tap 4, the point at which a subsequence either repeats or is altered. The increase in time interval at that point is greater when the subsequence changes. Of particular interest is that the differential increase when the subsequence changes is substantially greater for the patients than for the control subjects. Because the critical issue concerns the magnitude of this switching effect, an analysis of variance was confined to positions 3 and 4 in the sequence. The analysis confirmed not only significant main effects of position and same versus different sequence and their interaction, but more critically the three-way interaction of position by sequence change by subject group was reliable: $F(1, 35) = 5.32, p < 0.05$.

As was the case for the color-shape study, interpretation of the switching effect is complicated by the fact

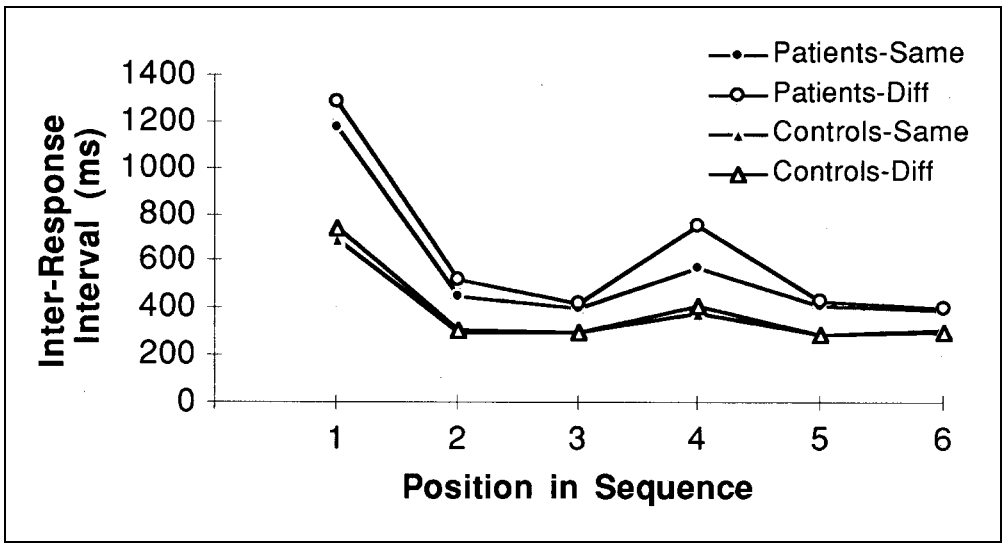

Figure 4. Interresponse times between successive taps in Experiment 3 as a function of position in the sequence, Parkinson patients vs. control subjects and whether the subsequence changed or remained the same between positions 3 and 4. Position 1 is the reaction time to begin the sequence.

that patients are slower at all positions and not just at the switch points, raising the possibility that their deficit reflects not switching per se but slowness of all processes. Again, consideration of differences among subgroups of patients provides some perspective. Figure 5 provides a breakdown of switching times for the same three subgroups of patients as earlier—those who remain hypokinetic even though on medication (N = 9), those whose movements are relatively unimpaired (N = 6), and those who are hyperkinetic (N = 6). In addition, the data for the control group are shown. The differences in response times between taps 3 and 4 are shown as a function of whether the subsequence changed or remained the same. Clearly, the largest switching effect is shown by the hypokinetic subjects, and they also are the slowest in reaction time. The dyskinetic patients differ little from the control subjects. The most analytic case is supplied by the unimpaired subjects. Although their interresponse interval prior to the switch is slower than that of the controls, averaging 364-msec response time

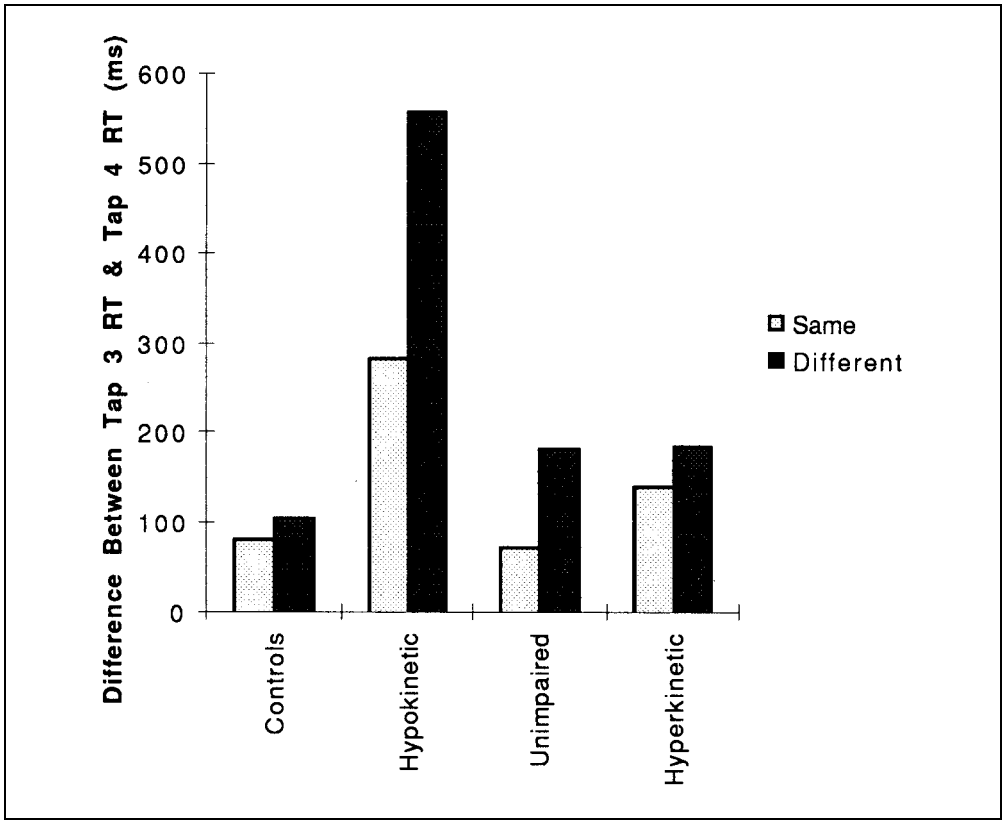

Figure 5. Difference between interresponse time between taps 2 and 3 (called Tap 3 RT) and interresponse time between taps 3 and 4 (called Tap 4 RT) as a function of patient type vs. controls and whether the subsequence remains the same or changes between positions 3 and 4 in Experiment 3.

at position 3 compared to 301 msec for controls, the difference between the two groups is not as marked as for the hypokinetic patients. Nonetheless, the unimpaired patients still show a larger switching effect than the controls. It is particularly analytic that for this subgroup of patients, when successive subsequences are the same, the increase in intertap interval from position 3 to position 4 is little different from that of the controls; the large increase in intertap interval for the unimpaired patients occurs only when the subsequence changes. An analysis of variance involving just the unimpaired and the control subjects showed a marginally significant three-way interaction of subject type by position in sequence by same versus different subsequence: $F(1, 22) = 2.87$, critical one-tailed $F = 2.95$ for $p < 0.05$. The same interaction was significant also when hypokinetic and control subjects were compared, $F(1, 23) = 11.59$, $p < 0.005$ but not when hyperkinetic and control subjects were compared.

The Efficiency of Filtering

As was the case for color-shape decisions, we can ask how efficiently the alternative course of action is filtered when set is established. Prior to the first tap, subjects might be expected to have a longer decision when two successive subsequences would be different because the planning of the sequence would take longer. However, once the first tap is made, it might be assumed that set has been established and maintained over the next two taps, which are designated taps 2 and 3 in Figure 4. Likewise, following the switch point and in the case where the subsequence changes, it might be assumed that set is reestablished for taps 5 and 6. For these tap positions that precede and follow the transition between the two subsequences, intervals can be compared in the cases where the two subsequences are the same or different. Greater slowness when the subsequences differ, even during the period when set has been established, would indicate partial failure of filtering.

As shown in Figure 4, data at tap positions 2 and 3 (before subsequence transition) and positions 5 and 6 (after transition) show that Parkinson patients are less efficient than the controls at filtering. An analysis of variance confined to these four tap positions indicates that the poorer filtering of the Parkinson patients is reliable. The interaction indicative of such a result is that of same versus different subsequences by patient versus control subject group: $F(1, 35) = 6.4$, $p < 0.025$. This interaction is not further modified by an interaction with position within the sequence either before or after the switch: $F < 1$. Thus, it appears that a different subsequence that will be relevant in a different part of the sequence is less completely filtered by patients compared to controls both prior to a switch and also following a switch. It is difficult to attribute poorer filtering simply to Parkinson patients being slower because there is no a priori reason that any slowing of processes would increase the interference from a subsequence that is temporarily incorrect but is correct at another place in the total sequence.

EXPERIMENT 4: SEQUENCE SWITCHING ON AND OFF MEDICATION

Six of the Parkinson patients who participated in Experiment 2, in which medication level was manipulated, also participated in this experiment. One of the subjects showed an idiosyncratic form of responding in which the six taps of the sequence appeared to be organized with no chunking. For him, there was no alteration in intertap intervals at the subsequence break point whether the subsequence was the same or not. His data were excluded. The data from the remaining five patients, both in the on condition in which patients were medicated and in the off condition in which medication was temporarily withheld, are shown in Figure 6.

The data pattern conforms to expectations. When on medication, although the patients slow between positions 3 and 4, there is little difference between the situations where the subsequence changes or does not. In contrast, when off medication, a sizable switching effect appears in that the increase of intertap interval is greater for changed subsequence than for the unaltered subsequence. Unfortunately, an analysis of variance shows this critical interaction between medication level, position in sequence, and type of subsequence change not to be significant: $F(1, 4) = 2.2$, $p > 0.05$.

Statistical power is extremely limited with such a small sample of subjects, especially given the elimination of one of the six. Such lack of power may explain why the predicted effect falls short of significance. However, it also is the case that of the remaining five patients, only four of the patients showed the predicted pattern in which the switching effect was larger off medication than on. It is instructive to consider the deviant patient. That patient showed little difference in switching on and off medication, although there was a marginally larger effect when on. That patient also did not differ in the experimenter's ratings of motor proficiency on and off medication. This is not to say that the medication is not normally useful for this patient but only that at the times of testing, there was no observable difference in motor behavior in the two conditions. Although it is not possible to achieve reliable results given this departure, the observation nonetheless is important in suggesting a close coupling between the responsivity of the motor system to dopamine medication and responsivity of switching mechanisms.

Given the similarity of the on-off switching results to those observed in the color-shape paradigm, where a larger sample of patients was available, we can say that the effects of the on-off manipulation on sequence switching are highly compatible with the hypothesis that

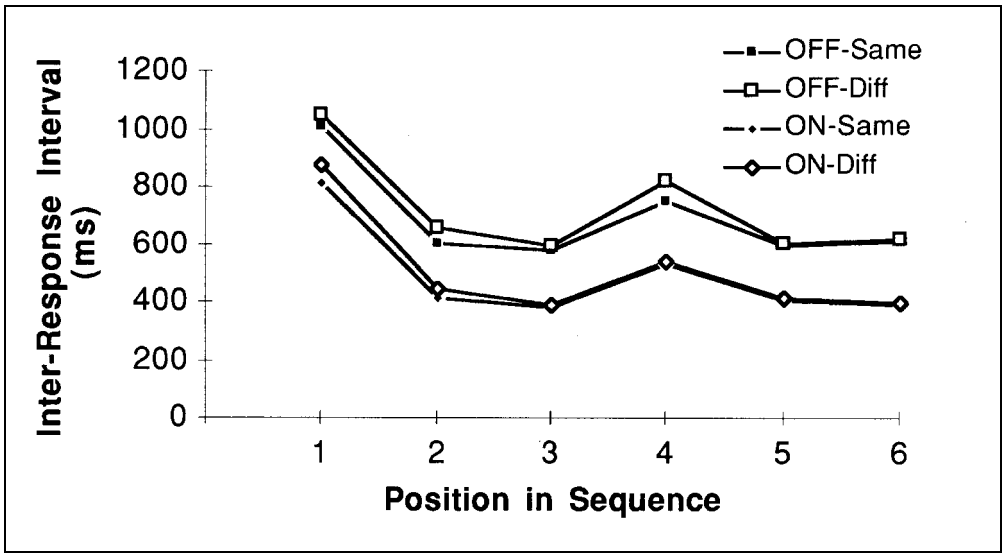

Figure 6. Interresponse times between successive taps in Experiment 4 as a function of position in the sequence, whether the five patients were on medication or off, and whether the subsequence changed or remained the same between positions 3 and 4. Position 1 is the reaction time to begin the sequence.

the basal ganglia are involved in switching of set across various domains. A statistically convincing demonstration would require a larger number of patients.

GENERAL DISCUSSION

Switching Deficit

This study was designed to test a hypothesis that the basal ganglia are involved in the switching of set across a variety of domains. The analysis was focused on a particular variant of basal ganglia dysfunction that occurs in Parkinson's disease. Both components of the study, that dealing with switching of attentional set between color and shape and that dealing with switching between subsequence representations, support the hypothesis. In both instances Parkinson patients are slower in switch than in nonswitch cases compared to age-matched control subjects.

One difficulty of interpretation, however, concerns the fact that Parkinson patients are slower in nonswitch conditions as well as switch conditions than are control subjects. Such a result raises the possibility that the slowness in switching simply reflects generalized slowness. If such were the case, it would be difficult to attribute a specific switching operation to the basal ganglia. However, consideration of differences among subgroups of patients suggests that a switching component is specifically impaired in Parkinson's disease. One subgroup when on normal levodopa medication exhibits substantial slowness, even in nonswitch conditions. That group shows a large switching deficit that could be attributed to nonspecific slowing. However, a second subgroup, although exhibiting relatively normal-looking motor function when on medication, continues to exhibit a switching deficit even though baseline reaction times are less impaired relative to controls. Only for patients exhibiting hyperkinetic symptoms suggestive of overmedication does switching time approach normal.

The conclusion of a switching deficit in Parkinsonism is in accordance with previous research showing switching deficits in a problem-solving setting such as on the WCST (e.g., Owen et al., 1993). In problem-solving settings, switching deficits are inferred not by the duration of a switching process but by the likelihood of altering a hypothesis regarding problem solution or by the number of trials to discover the correct basis of problem solution. In these cases, there is no direct measure of switching at the point in time where it would be expected to occur. The present finding of a switching deficit in terms of the time to execute a shift between two clearly specified sets suggests a generalized switching problem in Parkinsonism. The Parkinsonian deficit may be observed either in increased time to switch or in at least occasional failure to switch when it would be appropriate.

Our conclusion of a deficit in the time to switch set appears at odds with results from research using a simple attentional task. Rafal et al. (1984), Sharpe (1990), and Wright et al. (1990) all found no deficit in Parkinson patients in the time to respond to an invalidly cued signal in a Posner-cueing paradigm. Moreover, failure to find a switching deficit is not confined to spatial cueing paradigms. Rafal et al. did not find a switching deficit in a movement precueing experiment, and Filoteo et al. (1994) found that Parkinson patients were faster to switch relative to controls for successive trials in which the target switched between local and global levels of representation. This apparent discrepancy, we argue, reflects a distinction between two different attentional mechanisms. One mechanism involves a bias or expectancy for a signal to be of a particular type or in a particular place or to require a specific response. Regardless of bias, whatever signal occurs or wherever it

occurs, the signal elicits a single relevant response. The other mechanism is a form of selective attention in which a change in instructional set reconfigures the conditions of relevancy, dictating which stimulus feature or which internal representation becomes relevant to the next response. The basal ganglia, we suggest, are involved in switches of the latter sort, that is, set switching, but not in switches of the former. Put another way, the basal ganglia appear to be part of a circuit that involves so-called executive functions (Allport et al., 1994; Meiran, 1996; Norman & Shallice, 1986; Rogers & Monsell, 1995).

The switching deficit appears to be related to dopamine deficiency in the Parkinson patients rather than to some other indirect effect such as prolonged Parkinsonism that may affect other neurotransmitter systems. A subset of patients who were either relatively unimpaired or hyperkinetic when on medication tended to become more hypokinetic off medication; when off medication, switching deficits increased. Although this effect was statistically reliable only in the color-shape study, which involved a larger number of subjects, the direction of effects were the same in the sequencing study. These results bolster findings that at least some aspects of "frontal" deficits in Parkinson patients are related to l-dopa medication levels (Lange et al., 1992; Owen et al., 1993), adding that time to execute a switch is related to dopamine depletion. As in some of the previous studies, the present results are particularly compelling because a within-subject comparison was made rather than relying on comparisons between medicated and never-medicated patients, allowing other potential factors such as disease duration to be ruled out as causes of performance differences.

More generally, our results suggest a relationship between the effect of dopamine on motor deficits and its effects on cognitive deficits. It has been suggested that motor symptoms can perhaps act as an index of the degree of striatal dopamine depletion in general (e.g., Dubois, Boller, Pillon, & Agid, 1991). Finding a cognitive switching effect in our on-off studies, in which dopamine levels were inferred by overt motor performance, supports this assertion. Additionally, group differences among medicated patients show a covariation between motor and cognitive deficits. Patients who are relatively unimpaired in their motor behavior when medicated show a switching deficit, but the magnitude of the switching effect is smaller than that of patients who are hypokinetic when medicated. In contrast, patients who are hyperkinetic when medicated show a normal switching effect. This finding is in accordance with results of Flowers and Robertson (1985), who, using a test of cognitive set similar to the WCST, found differential accuracy performance among Parkinson patients grouped by severity of symptoms.

The close relationship of motor function to the cognitive switching functions may have practical importance. Although a switching function appears impaired in Parkinsonism, the results nonetheless suggest that those impairments can be ameliorated by the same medication that improves motor function. Moreover, the results suggest that therapeutic intervention in the basal ganglia perhaps should not target only those regions that subserve motor control.

Attentional Filtering

Our current framework makes a distinction between attentional setting and attentional filtering. Once a set that specifies the relevant response is established, one may ask how effectively the set filters out irrelevant stimulation. The results in both the color-shape paradigm and in the sequence-switching paradigm suggest that Parkinson patients filter less effectively than control subjects, a result in accordance with an exemplary analysis of filtering by Maddox, Filoteo, Delis, and Salmon (1996). Previous experiments that have examined cognitive set have shown that Parkinson patients have difficulty filtering competing responses (e.g., Robertson & Flowers, 1990) and also are more distracted than controls by the addition of a novel dimension that has no responses associated with it (Downes et al., 1989). In our color-shape paradigm, for a given trial the distracting dimension is one that at other times is relevant for response. We can compare how distracting the alternative dimension is depending on whether its value is associated with an incompatible response or whether it is neutral and elicits no response. We find that the presence of the distracting dimension is more detrimental to response time for the Parkinson patients than for the controls, and, as might be predicted from the results of Downes et al., the patients' difficulty in filtering is apparent regardless of whether the irrelevant feature calls for a conflicting response or whether the irrelevant feature is neutral.

These findings suggest that filtering itself is not a unitary phenomenon. Research by Stablum et al. (1994) suggests that patients with posterior cortical lesions have a deficit of one type of filtering in which the value of an irrelevant dimension—that is, whether it is congruent or incongruent with the relevant dimension—has an increased effect on decision processes. They show that patients with putative frontal cortical damage due to closed-head injuries do not show such a filtering problem but instead have particular problems with what we call set. Our finding that Parkinson patients show a filtering deficit even with neutral stimuli suggests that the problem is more akin to a frontal problem, a topic to which we will return, and suggests again partial failure of executive control in specifying the relevant dimension.

Generalizing a Switching Function of the Basal Ganglia to Motor Involvement

The close coupling of color-shape and subsequence switching effects to motor symptomatology suggests that related mechanisms may underlie the cognitive and motor deficits. Although we have no new evidence to present, here we suggest a framework from a switching viewpoint for at least some of the motor deficits presented in Parkinson's disease.

Among the problems of Parkinson patients are those of rigidity, involving excessive cocontraction of opposing muscles and bradykinesia, in which movements are slow in execution. A number of investigations suggest that a functional deficit in force regulation underlies such symptoms. Bradykinetic patients especially have difficulty recruiting force. In one seminal study, Hallett and Khoshbin (1980) examined the electromyographic patterns that accompany ballistic extensions of the forearm. They reported that the typical agonist-antagonist burst pattern of normal subjects was intact in bradykinetic patients and the components of the pattern were of proper timing. Nonetheless, a single burst cycle was insufficient to propel the movement the required distance. The patients typically exhibited several cycles, suggesting that the force generated on an individual cycle was insufficient for the required movement.

Another problem often seen in Parkinsonism is so-called micrographia, in which executed movements are smaller than normal. In a series of repetitive movements, successive motions tend to become progressively smaller. Margolin and Wing (1983) studied this phenomenon by examining a series of back and forth strokes. For some subjects, successive strokes tended to become smaller in extent but of the same duration; for other subjects successive strokes tended to lengthen in duration but with maintained extent. In most cases, however, both tendencies were present, and both became exacerbated off medication. Margolin and Wing suggested a force deficit as an underlying cause and the two manifestations—lengthened duration or shortened extent—as strategic adaptations. If successive movements are made with less force, the patient can choose either to maintain duration, in which case the stroke length will diminish, or to maintain extent, in which case duration will increase.

Subsequently, more direct measures of force regulation have shown Parkinsonian effects. Parkinson patients are slower than normal subjects in achieving a target force (Stelmach & Worringham, 1988), indicating slowness of force recruitment. Of particular interest is a study by Wing (1988) that examined changes in force in the pinching movements of two asymmetric Parkinson patients. Both patients exhibited greater Parkinsonian symptoms on one side of the body than the other. The task was to either increase or decrease the pinch force in response to a step change in a target. Wing found the impaired side to be slow in either increasing or decreasing force from the current level, a result also found in monkeys with pallidal lesions of the basal ganglia (Mink & Thach, 1991). More recently, Corcos, Chen, Quinn, McAuley, and Rothwell (1996) have shown that the Parkinson deficit in adjusting force is increased when patients are off their medication.

Studies of these sorts suggest, therefore, that a proximate cause of at least some motor deficits seen in Parkinson's disease involves difficulties in regulating force. How in turn might force regulation be seen as an instance of set switching?

One prominent theory of movement established over the last couple decades is the equilibrium point theory (e.g., Bizzi, Polit, & Morasso, 1976; Feldman, 1986; see Keele, 1986 for a review). The essence of this theory is that movement is a consequence of altered postural set. Consider the arm held in front of one's body. To maintain position, a set of agonist-antagonist muscles must be activated and maintained such that the opposing forces in all directions are equal, preventing movement. To move the arm to another position, the current muscular pattern must be supplanted by a second pattern. According to equilibrium point theory, it is sufficient that the muscular pattern that corresponds to the desired position be activated. As long as the arm is not currently at the new position, the elastic properties of the muscles will passively generate forces that will cause the arm to move to the newly set position. Once the position is achieved, all the elastic properties will be in equilibrium and the movement will stabilize.

A modification of equilibrium point theory suggests that the change in equilibrium point occurs not discretely from initial point to target but rather changes in analogue fashion through a desired trajectory (Bizzi, Accornero, Chapple, & Hogan, 1984). The importance of the concept of moving equilibrium point can be appreciated by realizing that most movements are intended to approach an end point not via a straight line but through a specific trajectory, as in reaching around one object to grasp another or in drawing a circle. Thus, movement would involve the continual resetting of the equilibrium point through the desired path of action.

Once stated in this form, the force of movement may be seen as a consequence of regulating the rate of change in equilibrium point settings. Such a mechanism is a form of set shifting. The general theory posits that the basal ganglia are involved in the shifting of set from one internal specification to another. The experiments outlined here have provided evidence that the basal ganglia are involved in shifting set to respond to one perceptual dimension or another, color or shape. The experiments provide additional evidence for basal ganglia involvement in set shifting between one subsequence and another. We argue that the same rubric can

be extended to force regulation, a computation that appears impaired in Parkinson's disease and which may be the proximal cause of some of the motor disorders in Parkinsonism.

Relationship to Frontal Lobe Function and the Parsing of Executive Processes

We have argued that the basal ganglia are involved in an executive process of switching of set. There is evidence that frontal cortical regions are involved in the same kind of process; patients with actual or putative damage in the frontal lobes suffer on tasks in which switches must occur from one cognitive set to another (e.g., Stablum et al., 1994; Stablum et al., 1996). Given the anatomical evidence for circuit interconnections between the frontal lobe and the basal ganglia (Alexander & Crutcher, 1990; Alexander et al., 1986), it is not unreasonable that both regions are involved in the same global process of switching.

It is possible that the switching deficits of the present studies reflect not basal ganglia functioning but rather frontal deficits. One way this could occur is through dopamine deficits in the frontal lobe resulting from Parkinsonism. It is also possible that basal ganglia defects may indirectly result in frontal lobe malfunction. The on-off experiments we have presented would argue against a chronic frontal lobe deficit, because switching facility varies with short-term alterations in medication, but the experiments do not convincingly argue against the possibility that the switching effects reflect dopamine-mediated frontal effects. Thus, an important task before us is to attempt to differentiate between frontal and basal ganglia contributions to switching.

Our working hypotheses are of two somewhat related sorts. One differentiates between the concepts of representation and implementation. The other differentiates between planning and implementation of a plan. In the former, we would suppose that frontal regions serve as repositories of instructions, which when selected constitute working memories (e.g., Goldman-Rakic, 1995; Rafal et al., 1996). Such instructions might be either low level, such as the correspondence between a particular color and a particular key, or high level, such as the instruction to respond to colors rather than to shapes or to produce one subsequence rather than another. When an instruction is activated, it may be said to constitute a working memory. By this view, one might expect that damage to the basal ganglia affects not the quality of working memories but how efficiently switching can occur between one intact memory and another, an implementational process. In contrast, damage to frontal cortical regions might affect the quality of the working memories themselves. A similar idea has been proposed by Houk and Wise (1993), who suggest that the basal ganglia may provide a mechanism for registering and canceling cortically generated working memories.

The second and similar hypothesis involves a differentiation between intending to switch (or planning) and the actual implementation of a switch. This hypothesis was stimulated by recent work of Stablum and colleagues (Stablum et al., 1994, 1996), who have examined patients suffering from closed-head injuries following head impact. These patients have putative, low-level damage primarily to frontal brain regions. In one of their paradigms, subjects alternated between performing one task and another. In one case the time of alternation was perfectly predictable; in the other case it was less so. It appears that the patients had no more difficulty than control subjects in switching to the occurrence of a new task when it was unpredicted, but they did have difficulty making use of predictability, when present, to plan a switch prior to the actual occurrence of the new task.

The ideas of Houk and Wise (1993) and of Stablum and colleagues (1994, 1996) suggest that the concept of executive function may be parsed into components dealing with representation and planning on the one hand and with implementational processes on the other and that these might be associated with different but interconnected brain systems. We might predict that patients with frontal damage in critical areas, although showing no deficit in the switching process per se, might fail to anticipate the need for a switch when such need can be anticipated. Such an effect would appear to be a switching deficit, but only in the case where a switch can be predicted prior to an actual stimulus. Parkinson patients with basal ganglia impairment, in contrast, might be slow in switching but show no anticipatory deficit. Current work in our laboratory is pursuing such suggestions.

It is likely that even the basic process of switch implementation itself is in need of parceling. Such speculation is motivated by anatomical pathways within the basal ganglia (Alexander & Crutcher, 1990). Information flows through the basal ganglia via two routes, a so-called direct route and an indirect route. The net outcome of the direct route is to release inhibition imposed on the thalamus, allowing cortical activation. The net outcome of the indirect route is to increase inhibition on the thalamus, hence reducing cortical activation. One might speculate that the switching of set involves both inhibiting prior sets and activating new sets. Indeed, Downes et al. (1993) have proposed that Parkinson switching deficits may occur because inhibitory mechanisms are slow to build up and disinhibitory mechanisms are slow to release previous sets. Reaction time tasks such as those presented in this paper should be helpful in further analyzing the component mechanisms of executive control, such as inhibitory processes, and localizing such components to specific parts of the striatal-thalamocortical circuitry.

METHODS

Subject Descriptions for Experiments 1 and 3

Patients

Twenty-two volunteers diagnosed with idiopathic Parkinson's disease participated in one or both of the primary studies comparing patients with controls. Patients were recruited through the Martinez, California Veterans Administration outpatient clinic or through Parkinson's disease support groups in the San Francisco region. All patients gave written informed consent and were paid for their participation. Before the experiment, patients were administered the Mini-Mental State Examination, or MMSE (Folstein, Folstein, & McHugh, 1975). Two patients were excluded from the color-shape study and one patient was excluded from the sequencing study due to low scores (25 and 24 out of 30) on that exam, leaving a total of 17 patients (11 males, 6 females) in the color-shape study and 21 patients (14 males, 7 females) in the sequencing study. Mean score on the MMSE was 29.4 for the color-shape group and 28.9 for the sequencing group. For one patient who participated in both studies, personal statistics were not gathered. For the remaining 16 patients in the color-shape study, mean age was 60.2 years; mean years of education was 16.3; mean duration of disease was 9.1 years. For the remaining 20 patients in the sequencing study, mean age was 62.2 years; mean years of education was 16.5; mean duration of disease was 9 years.

Patients' motor symptoms were assessed prior to experimentation by conducting the "Motor Examination" section (questions 18 through 31) of the Unified Parkinsonism Rating Scale: Mentation, Behavior, and Mood (Stern, 1988). Neck rigidity (question 22) and postural stability (question 30) assessments were omitted, resulting in a possible score range of 0 (normal performance) to 100 (maximally disabled). For most patients motor impairment was also assessed with the Hoehn and Yahr scale (Hoehn & Yahr, 1967).

During the course of a session, lasting about 2.5 hr, symptomatology of a patient often changed as medication level wore off or became more prominent. We were concerned with relating cognitive performance to current motor state rather than to assessments conducted prior to experimentation. Therefore each patient was more informally assessed for current symptoms at the time of a particular experiment by noting the presence or absence of rigidity, tremor, difficulties in movement, and dyskinesias. Based on these evaluations, each patient was classified into one of three subgroups according to the degree and type of motor symptoms that were present during their participation in the experiment.

The subgroups for the 17 patients who participated in the color-shape experiment are described here; the groupings of the participants in the sequencing experiment largely overlap with these and were very similar. Hyperkinetic patients were those who had visible dyskinesias. For the six patients who fell into this group, mean motor exam score was 14.8 (ranging from 1 to 30). Hoehn and Yahr scores for four of the six patients ranged from 2 to 3.5; the remaining two patients were not assigned a score. Hypokinetic patients were those who had apparent Parkinsonian symptoms, especially bradykinesia, and those who had no dyskinesias. For the six patients who fell into this group, mean motor exam score was 27.5 (ranging from 9 to 40). Hoehn and Yahr scores for four of the six patients ranged from 1.5 to 4; the remaining two patients were not assigned a score. Patients in the unimpaired group were those with very mild or no motor symptoms. Five patients fell into this group. Mean motor score was 7.4 (ranging from 0 to 9); their Hoehn and Yahr scores ranged from 0 to 1.5. For the sequencing study, six of the Parkinson subjects were classified as hyperkinetic, nine as hypokinetic, and six as unimpaired.

Because behaviors indicative of these categories are somewhat transient, the classification of individuals within each category does not correspond perfectly to the more formal motor examination scores. For example, there is one patient in the hypokinetic group with a motor exam score of 9, thus overlapping with scores of the unimpaired group. Additionally, for some of the patients who participated in both studies, their group classification differed in the two experiments because of changes in symptomatology as the session progressed. Such categorization at the time of a particular experiment rather than based on earlier formal assessments proved its worth because it lent a great deal of order to the experimental results, an order in accord with expectations. Moreover, the average examination scores for each group were ordered as would be expected.

At the time of participation in the experiment, all patients were on their normal medication schedules. Medications of the participants in the color-shape experiment, ordered by motor symptoms groupings, are reported in Table 4. Two patients had undergone pallidotomy surgery as a treatment for Parkinson disease symptoms. Of the four additional patients who participated only in the sequencing study, one was not interviewed. The remaining three were taking carbidopa-levodopa medication and selegiline, and one was taking bromocriptine and amantadine in addition. One had undergone pallidotomy surgery.

Aged-Matched Controls

Eighteen volunteers (eight males, ten females), who by self-report were free of neurological disorders, served as aged-matched controls in the sequencing experiment. A subset of this group (four males and nine females) served as aged-matched controls for the color-shape experiment. All gave written informed consent and were paid for their participation. Eight were spouses or caretakers

Table 4. Medications and On-Line Symptom Classifications of Parkinson Patients in Experiment 1[a]

Motor symptoms subgrouping	*Patient*	*Levodopa*	*MAO-B inhibitor*	*Dopamine agonist*	*Anticholinergic*	*Pallidotomy*
	p1	x	x	x		
	p2	x	x	x	x	
Hyperkinetic	p3	x	x	x	x	
	p4	x	x	x		
	p5	x	x	x		
	p6	x	x		x	
	p7	x	x	x		x
	p8	x	x		x	
Hypokinetic	p9	x	x	x		
	p10	x	x	(x)		
	p11	x	x			x
	p12	x	x			
	p13	x	x	x	x	
	p14	x		x		
Unimpaired	p15	x				
	p16		x	(x)		
	p17	x	x			

[a] Levodopa refers to carbidopa-levodopa (Sinemet and/or Sinemet CR); MAO-B inhibitor refers to some form of selegiline; dopamine agonist refers to bromocriptine or pergolide, and (x) refers to participation in a drug study of pramipexole in which the patients could be receiving a placebo; anticholinergic include trihexyphenidyl and amantadine.

of patients, and the remaining 10 were recruited from the Eugene, Oregon, community. The mean age was 63.3 years. Two participants were not asked about education level; for the remaining 16 the mean years of education was 14.9. Five control participants were not administered the MMSE; for the remaining 13 the mean score was 29.8. For the subgroup that participated in the color-shape experiment, mean age was 61.8 years, mean years of education was 15.2, mean MMSE score was 29.8. Controls did not differ significantly from patients on age, years of education, or MMSE score.

Experimental Design for Experiment 1

Stimuli

Two colors, red and blue, were assigned, respectively, to response keys 1 and 2. A third color, green, was not assigned to any key and acted as a neutral distractor. The colors appeared as circular color patches with a diameter of approximately 0.76° of visual angle (viewing distance was approximately 60 cm). Two shapes, triangle and square, were assigned to the same two response keys, 1 and 2, respectively. A third shape, hexagon, was not assigned to any key and acted as a neutral distractor. The shapes appeared as black figures outlined with a line weight of three pixels. In height each shape subtended a visual angle of approximately 3.0°. In width, the square was approximately 3.0°, the hexagon was 3.4°, and the triangle was 4.0°.

There were three types of stimulus figures, termed Alone, Neutral, and Incongruent. For Alone figures, a color or shape appeared without any distractor from the other dimension. For Neutral figures, a color or shape appeared with the neutral distractor (green or hexagon) from the other dimension. For Incongruent figures, a color or shape appeared with the distractor that had the alternative response key associated with it. There were therefore four Alone figures (red, blue, triangle, square), four Neutral figures (red and hexagon, blue and hexagon, triangle and green, square and green), and two Incongruent figures (red and square, blue and triangle). For the Neutral and Incongruent figures, the circular color patch appeared centered within the outlined shape. Stimuli were presented on a white background.

Each stimulus figure was accompanied by a dimension instruction (the word *Color* or *Shape*), which informed the subject which dimension to respond to. The word appeared approximately 2.5° of visual angle above the center of the stimulus figure, and the word was approximately 0.6° of visual angle in height. In width, the word

Color subtended approximately 2.2° of visual angle, and *Shape* subtended approximately 2.6° of visual angle. The dimension instruction remained on the screen as long as the figure appeared.

Response Keys

Key 1 corresponded to the 0 key on the number pad, and Key 2 corresponded to the decimal key on the number pad. To make it easier for the Parkinson patients, a thin piece of wood approximately 18 × 36 mm was attached to the 0 key, and a similar piece of wood was attached across the decimal and the Enter keys so that the patients would have large keys to press. The wood key surfaces were labeled 1 and 2.

Sequence of Events in a Trial

Each trial consisted of a pair of stimuli that appeared and were responded to sequentially. Each trial began with the message: "Next Trial . . . " that appeared slightly to the left and slightly below the center of the screen for 1 sec and was designed to make the paired nature of the trial more salient. Immediately after the "Next trial . . . " message disappeared, a color-shape figure and a dimension instruction appeared simultaneously. The first instruction and color-shape figure of the trial appeared centered vertically and approximately 2.3° of visual angle to the left of the center of the screen. It remained on the screen until the subject responded, at which point both the instruction and figure disappeared. Immediately after the response, unless an error was made, the second stimulus of the trial appeared centered vertically and approximately 2.3° of visual angle to the right of the center of the screen. It also consisted of a dimension instruction and a color-shape figure appearing simultaneously, and it remained on the screen until the subject responded. After the subject responded, there was a 500-msec interval before the next trial began with the "Next trial . . . " message. If for either stimulus the subject pressed any key other than the correct response, the incorrect response was immediately followed by a 1-sec error message before the program continued.

Design

The combination of possible dimension instructions and color-shape figures produced 12 stimuli: 2 Dimension instructions (Color or Shape) × 2 values per dimension (red/blue or triangle/square) × 3 stimulus types (Alone, Neutral, or Incongruent). The 12 stimuli were presented as the first and the second stimulus of trials in a completely crossed fashion, producing a total of 144 trials. Blocks of 144 trials were presented in a different random order for each subject. Two blocks were presented for a total of 288 trials.

Procedure

All subjects participated in the experiment immediately after participating in 384 trials of an experiment that is not reported here and that served as a training period for the current experiment. That experiment used the same stimulus figures, dimension cues, and stimulus-response mappings as this experiment. At the start of this experiment, subjects were shown an initial screen showing the color-to-key mappings, and the correspondence was explained to them verbally. Subjects were encouraged to respond quickly but to avoid making mistakes. Subjects completed 24 trials of practice with just the color mappings. Subjects then were shown a screen showing the shape-to-key mappings, which were emphasized verbally, and subjects were given 24 practice trials with just the shape mappings. It was then explained to subjects that the subsequent trials would be a mixture of color and shape trials and that they would have to pay attention to the dimension instruction in order to respond correctly. Subjects were again instructed to respond quickly but accurately. Following this procedure, the main experiment reported here began. Subjects pressed the keys with either hand, using either one or two fingers. Subjects were allowed to rest as long as they wished between blocks.

Data Analysis

Responses that were incorrect were excluded from reaction time analyses; responses that followed incorrect responses to Stimulus 1 were excluded from both reaction time and error analyses. Reaction times of 200 msec or below were considered to be anticipatory responses and were also excluded from reaction time and error analyses.

Experimental Design for Experiment 3

Stimuli and Apparatus

Subjects were seated a comfortable distance from the computer monitor. A keypad with three response keys was placed in front of the participant, allowing access with the dominant hand. The three keys on the pad were labeled 1, 2, and 3 and were arranged in an equilateral triangle, approximately 3 to 4 cm from one another.

The letters A and B were associated with the sequences 1–2–3 and 1–3–2; letter-sequence association was counterbalanced across subjects. On each trial, two letters appeared side by side on the monitor screen; thus each trial called for six keypresses. The four possible letter pairs were AA, BB, AB, BA. Participants were instructed to initiate response as quickly as possible once the letter pairs appeared, and the letters remained on the screen until the fourth keypress was executed. The letter pairs for the next trial appeared immediately following the sixth keypress. Trials were presented in a pseudoran-

dom order such that no more than four consecutive identical letter pairs were allowed. When response errors were made, an error message appeared on the screen for 1.5 sec, followed by the next letter pair. There were a total of 48 trials, with a short break in the middle of the set.

Procedure

Subjects completed two stages of training trials before beginning the experimental trials. In the first stage a single letter was presented and remained on the screen until the response was completed. A 1-sec interval separated trials. Ten trials of practice with one letter were followed by 10 trials of practice with the other, and these were followed by 20 trials of intermixed letters. In the second stage of training, letters were again presented one at a time, but the letter disappeared after the first keypress of the sequence, and there was no delay between trials. This stage consisted of 130 trials with a break in the middle. Following this stage, subjects began the experimental trials.

Methods for Experiment 2

Patients

Thirteen individuals diagnosed with idiopathic Parkinson's disease volunteered to participate. Patients were recruited as in other studies. All participants gave written informed consent and were paid for their participation. One patient was unable to complete the experiment, resulting in 12 patients (10 males, 2 females) who completed the study, 6 of whom had previously participated in the primary color-shape study in which all subjects were medicated. The age of the patients ranged from 48 to 71 with a mean age of 60.2 years; disease duration ranged from 3 to 20 years, with a mean duration of 9.4 years.

Medication State

Each patient participated in at least one set of 288 trials in the on state and at least one set of 288 trials in the off state. The on state was achieved by patients attempting to be optimally medicated on their usual medications. All 12 patients were taking carbidopa-levodopa medication; 8 patients were taking the MAO-B inhibitor selegiline; 9 patients were taking the dopamine agonist bromocriptine, pergolide, or pramipexole; 1 patient was taking amantadine. Additionally, one patient had undergone pallidotomy surgery as a treatment for PD symptoms.

The off state was achieved by delaying the normal dose of medication. For four patients this was done by skipping the first morning dose so that the duration since last medication ranged from 11 to 17 hr. Seven patients delayed a dose later in the day, and for those patients the duration since last medication ranged from 3 to 6 hr. The remaining patient took medication via a duodenal pump that delivered Sinemet continuously. By simply increasing or decreasing the delivery rate of the pump, this patient could achieve on and off states very quickly.

For each on and off set, the efficacy of the medication was evaluated by observing clinical symptoms, by conducting short motor tests (handwriting samples and counting the number of times thumb and forefinger could be tapped together per 5 sec), and by noting the patient's subjective impression of medication state. For five of the patients, the on and off states could be differentiated by clear clinical symptoms, where dyskinesia was apparent in the on state, and tremor and/or akinesia was apparent in the off state. For one patient, no dyskinesia was present in the on state; however, akinesia was apparent in the off state but not in the on state. Three patients had only subtle differences in clinical symptoms but had clear differences in size and fluidity of handwriting; each of these three patients also produced more finger taps per 5 sec in the on state than in the off state. The remaining three patients each reported that they felt on and off but did not show unequivocal overt signs. One of these patients had no differences in overt clinical symptoms but did produce somewhat faster, although not larger, handwriting and produced a few more taps per 5 sec in the on state than in the off state. The second of these patients appeared to be somewhat akinetic in the on state although reporting that he was at peak-level medication; in the off state he had a softer voice and sometimes a slight tremor. The third patient appeared somewhat akinetic in the on state but in the off state was slightly more so, had occasional tremor, and produced fewer finger taps per 5 sec.

Procedure

Patients participated in one or more sessions. Each session was completed in a single day and consisted of at least one set of trials completed in the on state and at least one set of trials completed in the off state. Six patients participated in both the color-shape and the sequence experiment, and for those patients both tasks were performed in each session.

Seven patients participated in two experimental sessions. For three of these patients, one session was eliminated from analysis because the patient's medication state changed during a set of trials; for a fourth patient one session was eliminated because he was unable to complete the set of trials in the off state. All other patients participated in one session. This left data from one session for nine patients and data from two sessions, which were averaged together, for three patients. One patient completed the on set first, and for one patient who completed two sessions, the order of on and off sets was counterbalanced. For all other sessions the off

set was completed first. However, most patients had practiced the task fairly extensively before participating in the first on or off set. Two patients had completed three sets of 288 practice trials over two previous days; two patients had completed two sets of 288 trials on a previous day; two patients had completed one set of 288 trials on a previous day; three patients had completed one set of 288 trials immediately before beginning the first off set; and three patients had not completed a practice set.

Experimental Design

Experimental design was identical to that of the study comparing on patients to control subjects, with the one exception that the 288 trials were divided into four blocks rather than two blocks, in order to give the patients more opportunities to rest.

Methods for Experiment 4

Patients

Six of the 12 participants in the color-shape on-off experiment participated in the sequence experiment as well. Mean age for this subgroup was 60.5 years; mean disease duration was 11.7 years.

Medication State

In the on state, all patients were taking levodopa-carbidopa. In addition three were taking an MAO-B inhibitor, a dopamine agonist, or both; one was taking both those medications plus amantadine. For one patient, the off state was achieved by skipping the first morning dose so that duration since last medication was approximately 13 hr. For three patients, the off state occurred 3 to 5 hr after last medication; for one patient on and off states were achieved very quickly by adjusting the drug delivery rate of a duodenal pump. The efficacy of medication during each set of trials was assessed by the same procedures as for the color-shape experiment. For four patients, on and off states could be distinguished by clear clinical symptoms; for the remaining two patients overt symptoms did not unequivocally distinguish the two states, although the patients reported a subjective difference.

Procedure

During each on and off period, patients participated in the sequence experiment either before or after participation in the color-shape experiment. All six patients participated in two experimental sessions. Data gathered during sets for which the patient clearly switched from one medication state to the other were excluded. For three patients, the order of on and off sets was counterbalanced; the remaining three patients started with the off set. All patients were well practiced at the task before beginning the first on or off set.

Experimental Design

Experimental design was identical to that of the primary sequencing study with the exceptions that the second stage of training trials was shortened to 26 trials, and the number of experimental trials was increased to 144.

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REFERENCES

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. *Trends in Neurosciences, 13,* 266–271.

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, D. 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.

Bizzi, E., Accornero, N., Chapple, W., & Hogan, N. (1984). Posture control and trajectory formation during arm movement. *Journal of Neuroscience, 4,* 2738–2744.

Bizzi, E., Polit, A., & Morasso, P. (1976). Mechanisms underlying achievement of final head position. *Journal of Neurophysiology, 39,* 435–444.

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.

Brown, R. G., & Marsden, C. D. (1988). Internal versus external cues and the control of attention in Parkinson's disease. *Brain, 111,* 323–345.

Brown, R. G., & Marsden, C. D. (1990). Cognitive function in Parkinson's disease: From description to theory. *Trends in Neurosciences, 13,* 21–29.

Clark, C. R., Geffen, G. M., & Geffen, L. B. (1989). Catecholamines and the covert orientation of attention in humans. *Neuropsychologia, 27,* 131–139.

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, A. R., Van den Bercken, J. H. L., Horstink, M. W. I., Van

Spaendonck, K. P. M., & Berger, H. J. C. (1984). Cognitive and motor shifting aptitude disorder in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 47,* 443–453.

Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L., & Peterson, S. E. (1990). Attentional modulation of neural processing of shape, color, and velocity in humans. *Science, 248,* 1556–1559.

Corcos, D. M., Chen, C. M., Quinn, N. P., McAuley, J., & Rothwell, J. C. (1996). Strength in Parkinson's disease: Relationship to rate of force generation and clinical status. *Annals of Neurology, 39,* 79–88.

Downes, J. J., Roberts, A. C., Sahakian, B. J., Evenden, J. L., Morris, R. G., & Robbins, T. W. (1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: Evidence for a specific attentional dysfunction. *Neuropsychologia, 27,* 1329–1343.

Downes, J. J., Sharp, H. M., Costall, B. M., Sagar, H. J., & Howe, J. (1993). Alternating fluency in Parkinson's disease. *Brain, 116,* 887–902.

Dubois, B., Boller, F., Pillon, B., & Agid, Y. (1991). Cognitive deficits in Parkinson's disease. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology, vol. 5* (pp. 195–240). New York: Elsevier.

Feldman, A. (1986). Once more on the equilibrium-point hypothesis (gamma model) for motor control. *Journal of Motor Behavior, 18,* 17–54.

Filoteo, J. V., Delis, D. C., Demadura, T. L., Salmon, D. P., Roman, M. J., & Shults, C. W. (1994). Abnormally rapid disengagement of covert attention to global and local stimulus levels may underlie the visuoperceptual impairment in Parkinson's patients. *Neuropsychology, 8,* 210–217.

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.

Folstein, M. F., Folstein, S. E., & McHugh, P. (1975). Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12,* 189–98.

Fuster, J. M. (1985). The prefrontal cortex and temporal integration. In A. Peters & E. G. Jones (Eds.), *Cerebral cortex, vol. 4* (pp. 151–177). New York: Plenum.

Goldman-Rakic, P. S. (1995). Toward a circuit model of working memory and the guidance of voluntary motor action. In J. C. Houk, J. L. Davis, & D. G. Beiser (Eds.), *Models of information processing in the basal ganglia* (pp. 277–294). Cambridge, Mass: MIT Press.

Goldman-Rakic, P. S., & Selemon, L. D. (1990) New frontiers in basal ganglia research. *Trends in Neurosciences, 13,* 241–243.

Hallett, M., & Khoshbin, S. (1980). A physiological mechanism of bradykinesia. *Brain, 103,* 301–314.

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

Horak, F. B., & Anderson, M. E. (1984) Influence of globus pallidus on arm movements in monkeys: I. Effects of kainic acid-induced lesions. *Journal of Neurophysiology, 52,* 290–304.

Houk, J. C., & Wise, S. P. (1993). Outline for a theory of motor behavior: Involving cooperative actions of the cerebellum, basal ganglia, and cerebral cortex. In P. Rudomin, M. A. Arbib, & F. Cervantes-Perez (Eds.), *From neural networks to artificial intelligence* (pp. 452–470). Heidelberg: Springer-Verlag.

Keele, S. W. (1986). Motor control. In J. K. Boff, L. Kaufman, & J. P. Thomas (Eds.), *Handbook of human perception and performance : vol. II* (ch. 30, pp. 1–60). New York: Wiley.

Keele, S. W., Cohen, A., & Ivry, R. I. (1990). Motor programs: Concepts and issues. In M. Jeannerod (Ed.), *Attention and performance XIII* (pp. 77–110). London: Erlbaum.

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, 107,* 394–404.

MacKay, D. G. (1987). *The organization of perception and action: A theory for language and other cognitive skills.* New York: Springer-Verlag.

Maddox, W. T., Filoteo, J. V., Delis, D. C., & Salmon, D. P. (1996). Visual selective attention deficits in patients with Parkinson's disease: A quantitative model-based approach. *Neuropsychology, 10,* 197–218.

Margolin, D. I., & Wing, A. M. (1983). Agraphia and micrographia: Clinical manifestations of motor programming and performance disorders. *Acta Psychologica, 54,* 263–283.

Marsden, C. D., & Obeso, J. A. (1994). The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain, 117,* 877–897.

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

Mink, J. W., & Thach, W. T. (1991). Basal ganglia motor control: III. Pallidal ablation: Normal reaction time, muscle cocontraction, and slow movement. *Journal of Neurophysiology, 65,* 330–351.

Norman, D. A., & Shallice, T. (1986). Attention to action: Willed and automatic control of behavior. In R. J. Davidson & D. Shapiro (Eds.), *Consciousness and self-regulation: Advances in research* (ch. 4, pp. 1–18). New York: Plenum.

Owen, A. M., Roberts, A. C., Hodges, J. R., Summers, B. A., Polkey, C. E., & Robbins, T. W. (1993). Contrasting mechanisms of impaired attentional 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 Neuroscience, 13,* 254–258.

Posner, M. I., & Dehaene, S. (1994). Attentional networks. *Trends in Neuroscience, 17,* 75–79.

Posner, M. I., & DiGirolamo, G. J. (in press). Executive attention: Conflict, target detection, and cognitive control. In R. Parasuraman (Ed.), *The attentive brain.* Cambridge: MIT Press.

Posner, M. I., & Snyder, C. R. R. (1975). Facilitation and inhibition in the processing of signals. In P. M. A. Rabbitt & S. Dornic (Eds.), *Attention and performance V* (pp. 669–682). London: Academic Press.

Rafal, R., Gershberg, F., Egly, R., Ivry, R., Kingstone, A., & Ro, T. (1996). Response channel activation and the lateral prefrontal cortex. *Neuropsychologia, 34,* 1197–1202.

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.

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). Costs of a predictable shift between simple cognitive tasks. *Journal of Experimental Psychology: General, 124,* 207–231.

Rosenbaum, D. A. (1987). Successive approximations to a model of human motor programming. In G. Bower (Ed.),

The psychology of learning and motivation, vol. 21 (pp. 153–182). New York: Academic Press.
Saint-Cyr, J. A., Taylor, A. E., & Nicholson, K. (1995). Behavior and the basal ganglia. In W. J. Weiner & A. E. Lang (Eds.), *Advances in neurology, vol. 65: Behavioral neurology of movement disorders* (pp. 1–28). New York: Raven Press.
Sharpe, M. H. (1990). Patients with early Parkinson's disease are not impaired on spatial orienting of attention. *Cortex, 26,* 515–524.
Stablum, F., Leonardi, G., Mazzoldi, M., Umilta, C., & Morra, S. (1994). Attention and control deficits following closed head injury. *Cortex, 30,* 603–618.
Stablum, F., Mogentale, C., & Umilta, C. (1996). Executive functioning following mild closed head injury. *Cortex, 32,* 261–278.
Stelmach, G. E., & Worringham, C. J. (1988). The preparation and production of isometric force in Parkinson's disease. *Neuropsychologia, 26,* 93–103.
Stern, M. B. (1988). The clinical characteristics of Parkinson's disease and Parkinsonian syndromes: Diagnosis and assessment. In M. B. Stern & H. I. Hurting (Eds.), *The comprehensive management of Parkinson's disease* (pp. 3–50). New York: PMA Publishing.
Wing, A. M. (1988). A comparison of the rate of pinch grip force increases and decreases in Parkinsonian bradykinesia. *Neuropsychologia, 26,* 479–482.
Wright, M. J., Burns, R. J., Geffen, G. M., & Geffen, L. B. (1990). Covert orientation of visual attention in Parkinson's disease: An impairment in the maintenance of attention. *Neuropsychologia, 28,* 151–159.