

Activation of conflicting responses in Parkinson's disease: evidence for degrading and facilitating effects on response time

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Abstract

Response selection often occurs in a context of competition among conflicting responses. According to recent models, the basal ganglia may play an integral role in resolving this competition by focusing the selection and inhibition of responses. We hypothesized that basal ganglia dysfunction produced by Parkinson's disease (PD) disrupts selection among conflicting responses. Using a version of the Eriksen flanker task, we tested the specific prediction that individuals with PD would experience greater response interference when distractors in the visual field activate a response that conflicts with the target response. In addition, we investigated whether greater response interference induced by these distractors could actually reduce normal response time costs in PD when the task required production of the response opposite the target. Compared to 16 healthy controls (HC), 16 individuals with PD showed an exacerbated slowing when target and distracting stimuli corresponded to conflicting responses. No group differences occurred when targets and distractors corresponded to the same response. Furthermore, the slowing induced by the distractors was reduced in both groups, but more so in PD, when execution of a response opposite the target response (i.e. incompatible response) was required. Moreover, among individuals with PD, the magnitude of the interference produced by the distractors was related to clinical ratings of bradykinesia. These findings are consistent with the hypothesis that basal ganglia dysfunction due to Parkinson's disease disrupts processes that resolve response conflict.

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1. Introduction

In recent years, views of the functions mediated by the basal ganglia have undergone significant modification. Advances in our understanding of the neurocircuitry of the basal ganglia as well as extensive investigation of cognitive deficits that accompany basal ganglia disease have generated a shift from models that emphasize a selective role in motor functions to models featuring an integration of cognitive and motor aspects of behavior. One theme that has gained popularity over the last 25 years suggests that the basal ganglia play a critical role at the interface that links stimulus inputs to action (Brown & Marsden, 1998; Chevalier & Deniau,

1990; Chudler & Dong, 1995; Graybiel, 1995, 1997, 1998; Jackson & Houghton, 1995; Oberg & Divac, 1979; Robbins & Brown, 1990; Taylor & Saint-Cyr, 1995). This view is supported by an anatomical organization that emphasizes afferent input to basal ganglia from virtually the entire cortex and extensive basal ganglia outputs that are directed via the thalamus to areas involved in the preparation (e.g. supplementary and premotor areas) or initiation (primary motor areas) of specific motor responses (Albin, Young, & Penney, 1989; McGeorge & Faull, 1989; Mello & Villares, 1997; Parent & Hazrati, 1995). In a recent review of models of basal ganglia function, Gilles and Arbuthnott (2000) concluded that most models portray the basal ganglia interface as the junction where patterns of cortical inputs are detected that are then conveyed to the motor system to influence its output.

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Several recent models propose that the basal ganglia are ideally situated to implement response selection (Brown & Marsden, 1998; Kropotov & Etlinger, 1999; Redgrave, Prescott, and Gurney, 1999; Robbins & Brown, 1990; Rolls & Treves, 1998). According to the “response selection” hypothesis, the excitatory afferents received by the basal ganglia from cortex represent response commands elicited by cognitive computations carried out at the cortical level. These commands are linked to particular response alternatives that are mapped within the basal ganglia architecture and maintained in basal ganglia efferents to areas in frontal cortex that control motor planning and initiation (Kropotov & Etlinger, 1999). A unique feature of the basal ganglia is the presence of opposing processes that activate or inhibit the links between cortical response commands and basal ganglia output to the frontal cortex. Thus, the basal ganglia are hypothesized to implement a mechanism for selecting a particular response alternative for access to the motor system and inhibiting competing response alternatives (Mink & Thach, 1993; Mink, 1996; Redgrave et al., 1999). Indeed, cellular recording studies in animals show basal ganglia activity that is closely tied to the activation of a response or to the withholding of a response following the onset of an imperative stimulus, such as during performance on disjunctive tasks (e.g. go/no-go) (Aldridge, Anderson, and Murphy, 1978, 1980; Aosaki, Tsubokawa, Ishida, Watanabe, Graybiel, and Kimura, 1994; Gardiner & Kitai, 1992; Gardiner & Nelson, 1992; Kimura, Rajkowski, & Evarts, 1994; Kimura, 1986, 1992; Rolls, Thorpe, & Maddison, 1983; Schultz & Romo, 1988; Travis & Sparks, 1968).

These theoretical perspectives support two general hypotheses relevant to the current study: (1) a fundamental function of the basal ganglia is to coordinate response activation and inhibition to resolve conflict between response alternatives that compete for access to the motor system; and (2) diseases that alter information processing in the basal ganglia interfere with the efficient resolution of response conflict. The aim of the current study is to examine how Parkinson’s disease (PD), which alters normal basal ganglia function, affects the efficiency of response selection in situations that elicit conflicting responses. PD involves a progressive degeneration of neurons in substantia nigra pars compacta, neurons that release dopamine (DA) at the interface between cortical inputs and the basal ganglia. Thus, neuromodulatory influences exerted by DA at the striatum may be important to the efficient resolution of response conflict, and individuals with PD might experience greater difficulties selecting among conflicting response alternatives.

The flanker task, devised by Eriksen and Eriksen (1974), has been used extensively in cognitive psychology as a tool for investigating response conflict. In this task, subjects respond to a target stimulus (e.g. a left- or right-pointing arrow) flanked on each side by distracting stimuli that evoke either the same (e.g. arrows pointing in the same direction as the target) or the opposite (e.g. arrows pointing opposite the target) response. Even though subjects are instructed to ignore the distractors, the presence of incongruent flankers

in the stimulus array is associated with longer reaction times (RTs) and higher error rates. This decrement in performance is thought to result from activation of the conflicting response by the incongruent flankers, which interferes with the efficient selection of the target response (Coles, Gratton, Bashore, Eriksen, & Donchin, 1985; Eriksen & Schultz, 1979). According to a dual-processing route model proposed by Ridderinkhof, van der Molen, & Bashore (1995), interference effects induced by incongruent flankers occurs because the target and flanker stimuli follow separate processing routes (see also Eimer, Hommel, & Prinz, 1995). Flanking stimuli are processed along a faster, automatic route that leads to early activation of the corresponding response that is revealed by increased motor cortex activity contralateral to the response hand and in EMG activity of the corresponding response hand (Coles et al., 1985). In contrast, the target stimulus is processed along a slower, deliberate route. As a result, response selection is slowed due to the extra time needed to inhibit the early response activation associated with the incongruent flankers, while, in turn, “activating” the correct target response to a selection threshold. In addition to slowing response latency, the activation of the incongruent flanker response may also increase error rates. Thus, the flanker task provides a powerful context for investigating the effects of PD on the resolution of response conflict.

In the current study, we used a version of the flanker task in which the target arrow is located at the center (at visual fixation) of a five-element horizontal array and is flanked by two arrows on each side. The flanking arrows pointed in either the same (i.e. congruent) or the opposite (i.e. incongruent) direction of the target. Based on the response selection model of basal ganglia function, we predicted that PD would be associated with greater interference when flankers are associated with a conflicting response (i.e. are incongruent). To our knowledge, only three studies have investigated conventional flanker effects in PD (Praamstra, Stegeman, & Cools, & Horstink, 1998; Praamstra, Plat, Meyer, & Horstink, 1999; Lee et al., 1999). Praamstra and colleagues found an enhanced interference effect in samples of 7 and 10 PD patients, respectively, when compared to a healthy control (HC) group, whereas Lee et al., found a sample of 10 PD patients and healthy controls to have similar interference effects. Our study adds to these initial investigations by: (a) replicating flanker task performance in a larger sample of PD patients ($n = 16$); and (b) characterizing the relationship of flanker effects with basic clinical features in PD. Interpretation of the flanker findings within the context of clinical features, such as the severity of motor and cognitive symptoms, is essential for determining links between experimental cognitive studies and the difficulties that affect daily activities in individuals with PD.

We investigated response conflict in PD further by introducing a second experimental factor into the flanker task, stimulus–response (S–R) compatibility. Subjects were required to make either compatible (e.g. left pointing arrow, left button press) or incompatible (e.g. left pointing arrow,

right button press) responses to the target arrow. Response time is generally slowed for incompatible compared to compatible responses, an effect attributed to the extra time required to translate or map a stimulus to a less familiar response (Bashore, 1990; Sanders, 1990). Introducing the S–R compatibility manipulation in the context of the flanker task allowed us to investigate two important and unique findings. First, for conditions in which flankers are absent or are congruent with the target, we can directly investigate how PD affects the translation of stimuli into responses, a process presumed to be important during response selection. However, for conditions involving incongruent flankers, a more interesting prediction arises. Assuming that incongruent flankers would generate greater response conflict in PD, we hypothesized that this interference might reverse response time effects when incompatible responses were made. That is, the typical cost associated with making an incompatible response would be reduced significantly in PD compared to healthy controls because the stronger response induced by the incongruent flankers corresponds to the required incompatible response. In fact, Bashore and Osman (1987) first demonstrated in healthy young adults that production of an incompatible response to a target arrow that is flanked by incongruent arrows reduced the slowing induced by the incompatible response, a pattern that has since been replicated (Ridderinkhof et al., 1995). Thus, we predicted that the greater interference induced by incongruent flankers in PD would dramatically slow compatible responses, but reduce the magnitude of the slowing of incompatible responses among PD compared to healthy controls.

2. Methods

2.1. Participants

Sixteen adults with Parkinson's disease and 16 healthy controls participated in this study. The groups were similar in age ($F(1, 31) = 0.05, p = 0.82$); years of education ($F(1, 31) = 2.511, p = 0.12$), and performance on the Mattis dementia rating scale (DRS; Coblenz et al., 1973; Mattis, 1988), ($F(1, 31) = 0.03, p = 0.86$). The DRS scores for both groups were well above the cutoff score conventionally used to indicate dementia. Table 1 contains a summary of the characteristics of our sample. Severity of symptoms for the

PD group was determined by the 5-stage Hoehn and Yahr (1967) rating scale. The average score was 1.80 (S.D. = 0.35; range = 1–2.5), indicating a mild overall symptom profile. In addition, individuals with PD were rated according to a modified Unified Parkinson's disease rating scale (Fahn and Elton, 1987) symptom checklist in order to identify the severity of specific symptoms common to PD (e.g. bradykinesia, falling, chorea, tremor, etc.). All PD subjects were taking medications to improve DA function (e.g. agonists, precursors). All participants had normal or corrected vision. Each participant provided informed consent to participate in the study, which was approved by the human investigation review board at Indiana University.

2.2. Experimental task and procedures

The flanker task involved presentation of stimuli on a 17 in. computer monitor (CPU 650 MHz Pentium, Windows 98, Microsoft, Seattle, WA) and the recording of responses to the stimuli through a standard keyboard. The spacebar and the zero key from the numeric keypad served, respectively, as left- and right-hand response keys. The monitor was placed at a distance of 70 cm and positioned so that the stimulus array appeared at eye level. Stimuli consisted of white arrows (3 cm × 3 cm) on a black background, pointing in either the left or right direction. The maximum number of arrows for a particular trial was five, with the arrows aligned in a horizontal array that spanned 20 cm (see Fig. 1).

Participants rested their left index finger on the spacebar and their right index finger on the zero key of the numeric keypad. For each trial, a fixation stimulus (asterisk) appeared in the center of the screen for 250 ms. It was extinguished and replaced by a right- or left-pointing target arrow that remained on the screen until the subject made a button press. The direction in which the center arrow pointed was mixed randomly in a block of trials with the constraint that the two directions occurred with equal frequencies. Participants were instructed to select the direction of their response on the basis of the direction in which the center target arrow pointed and to ignore distractor arrows on the flanks. For one-third of the total trials, the target arrow was presented in isolation (absent flanker condition; Fig. 1A). For the remaining two-thirds of trials, a pair of distractor arrows appeared to the right and to the left of the target arrow. In the congruent flanker condition, the distractor arrows pointed in the same direction as the target (Fig. 1B), whereas in the incongruent flanker condition, the distractor arrows pointed in the opposite direction of the target arrow (Fig. 1C). Whether the target appeared in isolation or was flanked by congruent or incongruent arrows was determined randomly, with the constraint that each condition occurred with equal probability (i.e. one-third of the total trials).

On half of the trials, participants were instructed to ignore the flankers and make a button press with the hand on the same side as the target arrow pointed (e.g. right pointing arrow, right button press). That is, they were required to make

Table 1
Sample characteristics for healthy control (HC) and Parkinson's disease (PD) groups (standard deviations in parentheses)

	HC	PD
Sample size	16	16
Age	65.4 (8.7)	64.8 (6.5)
Education	14.1 (3.0)	15.7 (2.8)
Dementia rating scale	140.0 (2.9)	140.2 (3.0)
Years since diagnosis	–	8.3 (5.9)
Hoehn and Yahr rating	–	1.8 (.35)

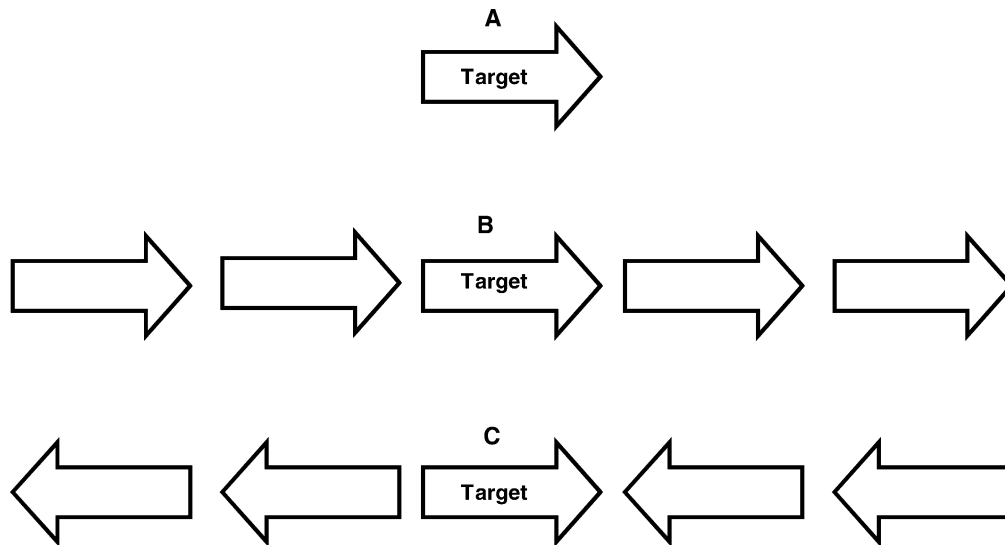


Fig. 1. Each trial consisted of a centrally located target arrow. In the absent flanker condition (A), the target arrow was presented in isolation. In the remaining conditions, distracting arrows flanked both sides of the arrow and pointed in the same direction (congruent flanker condition, B) or the opposite direction (incongruent flanker condition, C).

compatible responses to the target. This is the conventional flanker task that is used to determine the degree of interference from incongruent flankers. For the remaining trials, the display was identical, but the task was altered. Instead of using the hand on the side that matched the direction of the target arrow, participants were instructed to select the response opposite that indicated by the target arrow (e.g. left pointing arrow, right button press). That is, they were required to make incompatible responses to the target. Thus, we manipulated two experimental factors, flanker congruence and stimulus–response compatibility, with the former factor having three levels (absent, congruent, incongruent) and the latter having two levels (compatible, incompatible).

Every subject completed six experimental blocks, each of which contained 120 trials, yielding a total of 720 experimental trials. A compatible response was required for the first three blocks of experimental trials, while incompatible responses were required in the remaining three blocks of trials. Each subject completed a block of 30 practice trials under compatible response instructions and a block of 30 practice trials under incompatible response instructions before beginning the experimental blocks. Short rests of 1–5 min were offered between each block of trials, whereas one longer rest period (>10 min) was enforced after the first three blocks of trials.

Reaction times and accuracy rates were the dependent variables of interest. To reduce outliers, we first discarded extreme RT values ($RT < 100$ ms or $RT > 3000$ ms) and then discarded RT values in each condition that exceeded two standard deviations of the individual's mean for that condition. Incorrect responses were excluded from response time analyses. The PD and HC groups did not differ in the number of trials discarded, and, on average, eight trials were discarded in each condition due to trimming procedures or errors. Based

on criteria (e.g. sample size, sphericity assumption) outlined by Stevens (1996), all repeated-measures ANOVAs report the univariate results. Sphericity was measured using Mauchly's test, and Bonferroni adjustments were applied to the omnibus main effects and planned comparisons.

3. Results

First, we describe the omnibus ANOVA to evaluate interactions among flanker, compatibility, and group factors. This analysis reveals a greater influence of incongruent flankers on response latency in PD compared to healthy controls. Specifically, planned comparisons show that individuals with PD were slower to make a compatible response when flankers were associated with a conflicting response (i.e. were incongruent). However, PD patients showed a larger reduction in interference than controls when an incompatible response was made to a target flanked by arrows that pointed in the direction of the incompatible response (i.e. were incongruent). Next, we describe a significant relationship between the magnitude of the interference from incongruent flankers and clinical ratings of bradykinesia among PD patients.

3.1. RT and accuracy

Consistent with conventional flanker effects, RT for PD and HC groups was influenced by flanker arrays (flanker, $F(2, 60) = 83.22, p < 0.001$). Fig. 2 shows that RT was slowed when a target was presented in an array of flankers as opposed to in isolation, and incongruent flankers slowed RT to a greater extent than did congruent flankers. For the first of two planned comparisons, we compared the conventional flanker effect between PD and HC groups by calculating the

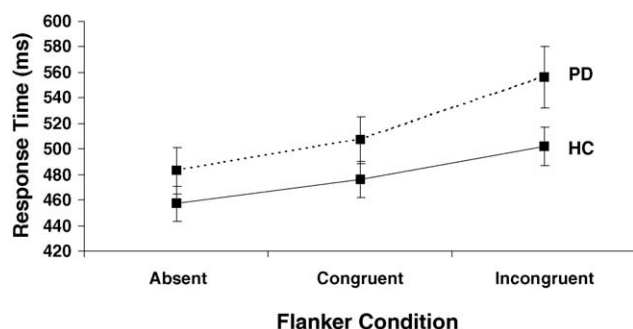


Fig. 2. Mean response times under each flanker condition for Parkinson's disease (PD) and healthy control (HC) groups using the conventional flanker task instructions (i.e. compatible). The PD group shows exaggerated response time slowing in the incongruent flanker condition relative to healthy controls.

reaction time difference between the incongruent and congruent flanker conditions under the compatible response instructions. The reaction time slowing due to incongruent flankers was larger in PD patients (48 ms) than in controls (26 ms).

Both groups were also slowed when making incompatible as compared to compatible responses (i.e. the conventional cost of incompatibility; compatibility, $F(1, 30) = 20.52, p < 0.001$). Although production of an incompatible response slowed RT for both groups in each of the flanker conditions, the magnitude of the slowing varied among the two groups as a function of the flanker array (flanker \times compatibility \times group, $F(2, 60) = 3.13, p = 0.05$). As summarized in Table 2 and depicted in Fig. 3, when the target was presented in isolation or flanked by congruent arrows, the cost in RT associated with an incompatible response was similar in magnitude for both groups. However, when the flanking arrows were incongruent, the cost to RT was smaller for the PD than for the HC group. For the second planned comparison, we compared the cost of incompatibility under incongruent and congruent flanker conditions between the groups. We calculated the incompatibility effect as the difference in reaction time between the compatible and incompatible response instructions under both congruent and incongruent flanker conditions. These incompatibility costs are illustrated in Fig. 3. Overall, the cost of incompatibility was significantly reduced under the incongruent as compared to the congruent flanker condition ($F(1, 30) = 8.59, p < 0.01$). Most important, this effect interacted with group such that the

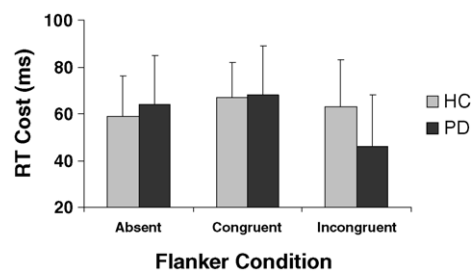


Fig. 3. RT cost in each flanker condition following instructions to select the opposite target response (i.e. the incompatible response). Across absent and congruent flanker conditions, the Parkinson's disease (PD) (dark bars) and healthy control (HC) (light bars) groups show similar RT costs. For the incongruent flanker condition, the PD group shows a significantly reduced RT cost relative to the HC group.

reduced cost of incompatibility was larger among PD patients than among controls under the incongruent flanker condition ($F(1, 30) = 5.48, p < 0.03$). To summarize, incongruent flankers slowed the production of compatible responses to a larger degree in PD than in HC, but facilitated reaction time to a greater extent in PD than in HC when making incompatible responses.

For both groups, accuracy rates decreased when the target arrow was flanked by incongruent arrows (flanker, $F(2, 60) = 5.30, p < 0.05$) and when incompatible responses were made (compatibility, $F(1, 30) = 8.33, p < 0.01$; see Table 2). Accuracy rates also varied with the nature of the stimulus array and the compatibility of the responses (flanker \times compatibility, $F(2, 60) = 4.83, p < 0.05$). As shown in Table 2, the decrease in accuracy when a compatible response was made to a target flanked by incongruent as compared to congruent arrows or no flankers was eliminated when incompatible responses were made in both PD patients and controls (group \times flanker \times compatibility, $p > 0.10$).

3.2. Relationship to clinical features of PD

The conventional flanker effect, quantified as the difference in RT between the incongruent and congruent flanker conditions under compatible response instructions, was significantly correlated with higher ratings of bradykinesia in the PD group ($r = 0.68, p < 0.01$), but not with ratings of tremor, overall clinical ratings of PD severity, or performance on the DRS (all $p > 0.05$). Moreover, PD patients with higher rat-

Table 2

Mean response times (ms) and accuracy rates (percentiles) for healthy control (HC) and Parkinson's disease (PD) groups (standard deviations in parentheses)

	Absent flankers		Congruent flankers		Incongruent flankers	
	RT	Accuracy	RT	Accuracy	RT	Accuracy
Compatible responses						
HC	457 (56)	99.0 (0.8)	476 (58)	99.3 (0.8)	502 (60)	98.1 (2.3)
PD	483 (72)	98.7 (1.7)	507 (73)	98.1 (2.5)	556 (96)	96.0 (4.7)
Incompatible responses						
HC	516 (93)	97.3 (3.2)	543 (93)	98.4 (1.9)	565 (107)	98.1 (2.2)
PD	549 (104)	96.4 (2.9)	575 (125)	96.2 (4.3)	602 (136)	95.9 (3.0)

ings of bradykinesia, but not tremor, experienced the largest reductions in the cost of incompatibility in association with incongruent flanker arrays ($r=0.52$, $p<0.05$). Overall, PD patients with the largest incongruent flanker effects showed the greatest reduction of the incompatibility effect under the incongruent flanker condition ($r=-0.69$, $p<0.01$).

4. Discussion

According to contemporary models, the basal ganglia influence the motor system through the focused selection of a desired response and inhibition of competing responses (Basso & Wurtz, 2002; Mink, 1996). The purpose of the present study was to examine how basal ganglia dysfunction due to Parkinson's disease disrupts this influence in an experimental situation that induces response conflict. Our results yielded three main findings relevant to the response selection hypothesis. First, consistent with our prediction and the results from two previous studies (Praamstra et al., 1998, 1999), making a familiar response to a target stimulus (i.e. a compatible response) was slower among PD patients than among healthy peers when irrelevant flankers in the stimulus field corresponded to a conflicting response (i.e. were incongruent). Second, in the absence of response conflict from distractors (as in the flanker absent and congruent conditions), the pattern of response time effects for both PD patients and healthy controls was similar for compatible or incompatible responses to the target stimulus. Finally, and most interestingly, we found that response conflict induced by incongruent flankers produced opposite effects on response latencies for compatible and incompatible responses, and these effects were more dramatic in PD patients than in healthy controls. Specifically, RT was slowed more dramatically in PD than in controls when compatible responses were made to a target flanked by incongruent distractors. However, the reduction in the cost of incompatibility observed when incongruent distractors flanked the target (i.e. when the response elicited by incongruent flankers matched the incompatible response) was larger in PD than in controls. Thus, incongruent flankers can degrade or facilitate reaction time in PD depending on the experimental conditions.

These findings offer intriguing insights about how PD affects response selection and the resolution of response conflict. Importantly, the results reveal that PD influences response selection in a specific manner, excluding the possibility that PD leads to generalized, non-specific response slowing in our task. Although PD patients were marginally, but not statistically, slower than healthy controls, the size of reaction time and error rate effects between the groups were equivalent when a target was presented in isolation or surrounded by congruent flankers for both compatible and incompatible responses. Rather, the differential effects of PD on performance were specific to incongruent flanker conditions. Furthermore, the finding that the cost to RT associated with making an incompatible response is reduced

significantly among PD patients compared to healthy controls when the target is surrounded by incongruent flankers is inconsistent with generalized slowing.

According to dual-processing models, the flankers and target are processed along separate routes, a fast, automatic route and a slow, deliberate route, respectively (Ridderinkhof et al., 1995). In support of this view, considerable evidence from event-related brain potential (ERP) studies shows that, despite the irrelevance of flankers to response selection, incongruent flankers activate motor cortex contralateral to the response hand corresponding to the direction indicated by the flankers and this activation precedes activation of the motor cortex controlling the response hand signaled by the central target (Coles et al., 1985; Eimer, 1998; Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988; Smid, Mulder, & Mulder, 1990; Spencer & Coles, 1999). This differential activation of motor cortices, reflected in the appearance of the lateralized readiness potential (LRP), indicates that flanker processing occurs in parallel with target processing, and, in fact, activates the response system more quickly. Moreover, subthreshold EMG activity in the muscles of the arm and hand that correspond to the response elicited by the flankers also precedes EMG activity for the target hand (Coles et al., 1985).

Thus, one explanation of our finding is that the response associated with the incongruent flankers is more strongly activated in PD than in controls. In fact, Praamstra et al. (1998, 1999) showed that the LRP corresponding to the response signaled by the incongruent flankers was larger in amplitude and earlier in onset in individuals with PD than in healthy controls. They also found that the onset of the LRP in congruent flanker trials was earlier in PD than in healthy controls, although, like our study, behavioral data did not reveal a response time advantage in PD compared to healthy controls relative to flanker neutral or absent conditions. Thus, a fundamental change in PD may relate to the manner in which competing, irrelevant information overactivates the response system. This could explain why PD patients showed an RT facilitation for incompatible responses as the stronger activation of the response associated with the incongruent flankers corresponded to the correct response. Hyperactivation of brain areas involved in stimulus-driven response selection (i.e. premotor cortex) has been demonstrated in PD patients using functional imaging and may relate to the current findings (Hanakawa, Fukuyama, Katsumi, Honda, & Shibasaki, 1999; Sabatini et al., 2000; Samuel et al., 1997). Whether these changes correspond to compensatory processes secondary to PD pathology or direct effects of dopamine dysfunction remains an area of debate and investigation (Berardelli, Rothwell, Thompson, & Hallett, 2001; Praamstra et al., 1998).

The idea that certain stimuli can overactivate the response system is somewhat counterintuitive to conventional views of PD. For example, Alexander, DeLong, and Strick's (1986) influential model of basal ganglia circuitry emphasizes an overactive inhibitory influence on the response system in PD. Several ERP and EMG studies show that PD is often

accompanied by slower activation and deactivation of motor cortex and muscle force (Chen, Kumar, Garg, & Lang, 2001; Franz & Miller, 2002; Praamstra et al., 1999). Adding to the complexity, several recent investigations suggest that response selection in PD can also be disinhibited (Filoteo, Rilling, & Strayer, 2002; Hayes, Davidson, Keele, & Rafal, 1998; Jackson & Houghton, 1995; Praamstra & Plat, 2001). For example, using ignored repetition tasks to induce negative priming, Filoteo et al. (2002) and Wylie and Stout (2002) showed both a reduction and an exaggeration of response inhibition in PD patients, respectively, that appeared to reflect subtle differences in task demands (Stout, Wylie, & Filoteo, 2002). Individuals with PD are also slower to inhibit ongoing responses during performance of the stop-signal task (Guggel, Rieger, & Feghoff, 2004), have greater difficulty inhibiting invalidly prepared responses during performance on disjunctive (go/no-go) and cueing tasks (Franz & Miller, 2002; Owen, Roberts, Hodges, & Summers, 1993; Wascher, Verleger, Vieregge, Jaskowski, Koch, & Kompf, 1997), and have greater difficulty inhibiting responses to previously relevant stimuli (Gauntlett-Gilbert, Roberts, & Brown, 1999; Hayes et al., 1998). Given these findings, it is also possible that the stronger influence of incongruent flankers in the present data reflects poor inhibition that would normally counter the automatic activation of the incorrect response.

A subtle paradox regarding inhibition can even be observed in the current study. PD patients were not slowed differentially compared to healthy controls when making incompatible responses to a target stimulus that was presented in isolation or surrounded by congruent flankers. This finding is in agreement with several previous studies that have reported normal spatial S–R incompatibility effects in PD using the Simon task (Brown, Jahanshahi, & Marsden, 1993; Cope, Georgiou, Bradshaw, Ianssek, & Phillips, 1996; Praamstra & Plat, 2001). Making an incompatible response requires inhibition of the more automatic, compatible response. In fact, ERP studies show an initial deflection of the LRP corresponding to the activation of the compatible response that precedes the activation of the correct, but incompatible response (Bashore, 1990). The absence of an incompatibility disadvantage in PD could be accounted for by a slowed activation of the compatible response, which in turn allows for easier selection of the incompatible response. Alternatively, the critical difference may be that activation and inhibition operate differently along the proposed deliberate pathway than along the automatic pathway. Although the current study is unable to distinguish these influences, we suspect that the routes (i.e. fast, automatic versus slow, deliberate) that engage activation and inhibition may prove to be critical for understanding the effects of PD and dopamine depletions on response selection. As an elegant illustration, Seiss and Praamstra (2004) recently used a priming task to study the automatic activation and inhibition of the response system in PD. A prime stimulus (arrow pointing to the right or left) was presented subliminally using a brief duration and masking procedures before the onset of a target arrow to which

participants responded with a left or right button press. In the absence of a delay between prime offset and target onset, the prime activates the corresponding response and reaction time is facilitated when the prime response is compatible with the target response but slowed when prime and target responses are incompatible (i.e. elicit conflicting responses). These effects are reversed when a delay (e.g. 100 ms) is introduced between prime and target arrows, suggesting that the prime-induced response activation is automatically inhibited by the response system after a brief delay. Thus, the inhibition of the prime response slows reaction time for compatible target responses but speeds incompatible responses. Individuals with PD failed to show this reversal, called the negative compatibility effect, and the authors argued that PD causes a reduction in inhibitory processes that are automatically activated during response selection.

Neurophysiological studies offer a view that may be compatible with deficits in both activation and inhibition. Recent neurophysiological investigations of dopamine's action at the neostriatum in rodent brain suggests a neuromodulatory role that enhances the signal-to-noise ratio for selecting particular cortical inputs while attenuating others (Kiyatkin & Rebec, 1996; Rebec, 1998). In a recent study, Boraud, Bezard, Bioulac, and Gross (2000) investigated the influence of passive movements on basal ganglia output neurons in DA-depleted MPTP-treated monkeys. Based on the hypothesis that dopamine depletions alter the basal ganglia's ability to activate a desired motor program and inhibit competing programs, these investigators recorded the ratio of active-to-inhibited basal ganglia output neurons during passive movements in both healthy and MPTP-treated monkeys. Compared to healthy monkeys, the percentage of output neurons inhibited during passive movements decreased and the number of neurons responding less specifically increased in MPTP-treated monkeys, suggesting an overall reduction of response selectivity. Based on the finding that transcranial magnetic stimulation of the motor cortex induces dopamine release in the motor regions of the neostriatum, Strafella, Paus, Fraraccio, and Dagher (2003) concluded that "... the effect of dopamine release in the vicinity of highly active corticostriatal terminations could be to increase the signal-to-noise ratio by strengthening that synapse while suppressing neighboring ones". These findings indicate that dopamine depletions may disrupt the coordination of response activation and inhibition.

Future investigations in PD that include response conflict tasks designed to more clearly elucidate the temporal dynamics of response activation, inhibition, and the coordination of these processes in conjunction with measures of online brain activity, such as ERPs and neuroimaging, should be a particularly fruitful line of inquiry. To date, brain imaging studies of flanker performance have revealed the involvement of several critical brain areas, including the dorsolateral prefrontal cortex, the anterior cingulate cortex, and the temporoparietal junction (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Casey, Thomas, Welsh, Badgaiyan, Eccard,

Jennings, & Crone, 2000; Hazeltine, Poldrack, & Gabrieli, 2000; Rafal, Gershberg, Egly, Ivry, Kingstone, & Ro, 1996; Ro, Cohen, Ivry, & Rafal, 1998). Each of these cortical regions projects extensively to the basal ganglia (Middleton & Strick, 2000a,b). To our knowledge, only one study has investigated and demonstrated changes to basal ganglia activity during flanker task performance (Casey et al., 2000), but no studies have looked at functional imaging of PD patients performing the flanker task. Interestingly, direct manipulation of basal ganglia structures, such as the subthalamic nucleus during deep brain stimulation treatment for PD, is known to disrupt performance on related measures of response conflict (e.g. stroop task; Schroeder et al., 2002).

Before turning to a discussion of the clinical implications, a final comment about flanker effects is worth making. Although considerable evidence from ERP studies supports a response-end locus of flanker effects, the role of early, perceptual processing in accounting for flanker effects has been of recent interest (Sanders & Lamers, 2002; Van't Ent, 2002). Perceptual factors (e.g. spacing between flankers and targets, size of stimuli) are known to attenuate, but not eliminate, flanker effects (Miller, 1991). Although participants in our study had normal or corrected-to-normal vision per self-report, a direct measure of visual acuity would have been preferred as PD patients are known to have certain visuospatial discrimination deficits as well as electroretinogram abnormalities stemming from reduced dopamine function in the retina (Nightingale, Mitchell, & Howe, 1986; Peppe, Stanzione, Pierelli, DeAngelis, Perantozzi, & Bernardi, 1995; Peppe et al., 1998). Thus, it is possible that flankers exerted a greater influence because target processing was disrupted by reduced acuity. While the influence of perceptual factors cannot be excluded completely in the present study, their role can be challenged indirectly. First, processes engaged to locate the target amid the array of flankers are unlikely to have influenced flanker effects as a fixation stimulus was used to cue the exact location of the target. Second, assuming a greater perceptual influence by flankers in PD, congruent flankers should have improved RT for compatible responses but slowed RT further for incompatible responses. Neither pattern was observed in PD. Finally, if the incongruent flanker condition creates greater perceptual conflict, thus slowing overall processing time, there is no clear reason why PD patients should be facilitated by this conflict under incompatible responses instructions, especially since incompatibility effects were similar in PD and healthy groups under flanker absent and congruent conditions. Despite this reasoning, future work could assess the role of perceptual conflict in PD more directly by manipulating various attributes of the targets and flankers (e.g. perceptual similarity, feature discriminability). Another strategy is to extend the current flanker findings into a different modality (e.g. verbal, somatosensory) that is less likely to involve dopamine modulation in early sensory stages. The use of the LRP to measure PD-related changes in processes engaged between stimulus onset and response selection (stimulus-locked LRP or s-LRP) and between re-

sponse selection and an overt response (response-locked LRP or r-LRP) would also be useful in elucidating the stage or stages of processing responsible for the observed effects. An elegant example of this approach can be found in Low, Miller, and Vierck (2002) who demonstrated that PD slows both s- and r-LRP components during the production of a motor sequence.

From a clinical perspective, the current results provide interesting insights into the nature of cognitive-motor processing in PD. First, our results demonstrate a relationship between difficulties resolving response conflict and the degree of clinically-rated bradykinesia in PD patients. In contrast, there was no relationship between the enhanced flanker effects and ratings of tremor. Interestingly, differences in cognitive performance between bradykinesia-predominant and tremor-predominant PD groups have now been described in several studies. For instance, compared to tremor-dominant PD patients, bradykinesia-predominant patients show enhanced negative priming (i.e. are slower to respond to a previously ignored stimulus; Wylie & Stout, 2002) and are slower to shift between successive responses (Hayes et al., 1998). As with the current results, these specific deficits are independent of generalized motor slowing.

A second important clinical implication relates to the finding that the response activated by irrelevant, incongruent flankers actually diminished RT costs to a greater extent in PD than in healthy controls if this response corresponded to the correct response (i.e. incompatible response condition). Within the PD group, those individuals showing the largest interference from incongruent flankers when making compatible responses also showed the largest RT reductions from the presence of incongruent flankers when making incompatible responses ($r = -0.69$). These findings suggest that activation of the response system by stimuli in the environment may, conversely, slow or facilitate action in PD, an idea consistent with a growing literature that shows improvements in motor performance in PD when the environment contains cues that promote the selection of a particular action. For example, such cues have been found to improve stride length during walking (Morris, Ianssek, Matayas, & Summers, 1994), increase handwriting size (Oliveira, Gurd, Nixon, Marshall, & Passingham, 1997), improve performance on speeded RT tasks (Gueye, Viallet, Legallet, & Trouche, 1998; Jahanshahi, Brown, & Marsden, 1992, 1993), and improve speed and accuracy during motor sequencing and learning tasks (Cunnington, Ianssek, Bradshaw, & Phillips, 1995; Cunnington, Ianssek, Johnson, & Bradshaw, 1997; Cunnington, Ianssek, & Bradshaw, 1999; Georgiou, Ianssek, Bradshaw, Phillips, Mattingley, & Bradshaw, 1993). Given the current findings, it is interesting to speculate that a possible mechanism for the motor performance benefit in PD induced by environmental cues relates to how these cues improve the focused selection of a particular response and the inhibition of competing responses. Future investigations aimed at relating cue-induced benefits in motor performance to RT effects measured by response conflict paradigms could

test this idea. As well, future studies could test the hypothesis that PD patients with bradykinesia-predominant symptom profiles, who show greater interference from incongruent flankers, are more likely to experience motor benefit from environmental cues compared to patients with tremor-predominant profiles.

5. Conclusion

According to response selection models of basal ganglia, a primary function is the focused selection and inhibition of competing responses (Mink, 1996). The present results support the idea that basal ganglia dysfunction induced by Parkinson's disease produces greater response time interference from irrelevant distractors in the visual field that are associated with conflicting responses. As demonstrated, this interference can degrade or facilitate response time effects in PD relative to healthy controls depending on the compatibility between the target and the desired response. Furthermore, individuals with bradykinesia-predominant PD profiles appear to have greater difficulties resolving conflict among concurrently activated response alternatives. Future studies aimed at characterizing the temporal dynamics of selection, inhibition, and the interaction of these processes under conditions of response conflict have the potential to integrate and inform theories of PD and basal ganglia that span the clinical, cognitive, and basic neurosciences.

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