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A Role of the Basal Ganglia in Movement: The Effect of Precues on Discrete Bi-directional Movements in Parkinson's Disease

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The effect of a precue on improving movement initiation (i.e., reaction time; RT) is well understood, whereas its influence on movement execution (i.e., movement time; MT) has rarely been examined. The current study investigated the influence of a directional precue (i.e., left vs. right) on the RT and MT of simple and discrete bi-directional movements in a large sample of Parkinson's disease patients and healthy control participants. Both patients and controls were tested twice, with testing sessions separated by 2 hours. Patients were tested first following an overnight levodopa withdrawal and again after they had taken their medication. Both patients and controls demonstrated a significant RT improvement when information was provided in advance. MT in both healthy participants and medicated patients was, however, *slower* with the provision of advance information, while unmedicated patients showed no significant MT effects. These results suggest that while the basal ganglia may not be involved in motor program selection, they may dynamically modulate movement execution.

Key Words: ■

Parkinson's disease (PD) is a progressive neurological disorder that affects the ability of older adults to execute movements (Marsden & Obeso, 1994). Aside from the importance of achieving greater understanding of a disorder that is considered to be the most common of the movement disorders (Water, 1998), comparing movement control in individuals with Parkinson's disease to that of a healthy control population can provide insight into the contribution of the basal ganglia to

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movement. Furthermore, manipulation of dopaminergic status may offer an opportunity to evaluate the extent to which individuals are able to "return to normal" through treatment.

Simple reaction time (RT) has repeatedly been demonstrated to show significant deficits in PD populations, and these deficits have been shown to be sensitive to dopaminergic medications (Brown, Jahanshahi, & Marsden, 1993; Cooper, Sagar, Tidswell, & Jordan, 1994; Daum & Quinn, 1991; Gauntlett-Gilbert & Brown, 1998; Hallett, 1990; Henderson & Goodrich, 1993; Jahanshahi, Brown, & Marsden, 1992a, 1992b; Jordan, Sagar, & Cooper, 1992; Mayeux, Stern, Sano, Cote, & Williams, 1987; Mazzucchi et al., 1993; Montgomery & Nuessen, 1990; Muller et al., 1999; Zimmermann, Sprengelmeyer, Fimm, & Wallesch, 1992). Simple RT allows one to examine deficits in the selection of a motor program (and the effect of medication in alleviating this slowness) but provides no information about the effect of task complexity on movement execution, or the cognitive processes implicated in PD bradykinesia or bradyphrenia. To answer these types of questions, a choice RT task may be employed. Although it is generally accepted that choice RT also shows an overall impairment in PD (Bloxham, Mindel, & Frith, 1984; Evarts, Teravainen, & Calne, 1981; Filipovic et al., 1997; Gauntlett-Gilbert & Brown, 1998; Girotti et al., 1986; Harrington & Haaland, 1998; Pullman, Watts, Juncos, & Sanes, 1990; Stelmach, Worringham, & Strand, 1986; Willingham, Koroshetz, Treadwell, & Bennett, 1995; Worringham & Stelmach, 1990), specific conditions under which PD patients demonstrate impairment are still the subject of some debate. One such condition is the provision of a motor precue. In healthy adults, reaction time improves with the provision of a precue that provides relevant information about a movement, even if the precue is provided before the actual movement event (Rosenbaum, 1980). Interestingly, these same directional precues had no significant effect on MT (Rosenbaum, 1980).

Authors as early as Donders (1969) have suggested that provision of advance information in a way that removes the selection phase of a task will invariably reduce RT in healthy participants. Evarts et al. (1981), however, may have provided the first evidence of a PD motor pre-programming deficit, using a precueing paradigm to establish the effect of advance information on RT. They demonstrated (albeit without the use of inferential statistical techniques) that although PD patients show no significant reaction time improvement with the availability of advance information, controls become significantly faster with the provision of a precue. A motor pre-programming deficit in PD is purported, therefore, to represent an inability to utilize informational cues to "pre-program" movement (Bloxham et al., 1984; Evarts et al., 1981; Filipovic et al., 1997; Girotti et al., 1986; Harrington & Haaland, 1998; Pullman et al., 1990; Stelmach et al., 1986; Willingham et al., 1995; Worringham & Stelmach, 1990). Gauntlett-Gilbert and Brown (1998) provide a particularly comprehensive quantitative review of the motor pre-programming hypothesis.

Motor pre-programming deficits are not universally considered to be responsible for choice reaction time deficits in Parkinsonian patients. Some researchers suggest that Parkinsonian patients and normal controls use different strategies for approaching reaction time experiments. (I.e., Parkinsonian patients recognize that they may have accuracy problems on the tasks, and hence are deliberately slow in all phases of movement; Brown et al., 1993; Henderson & Goodrich, 1993.) Other researchers propose that there are no specific programming deficits attributable to

basal ganglia dysfunction, but rather that these apparent deficits are the result of non-specific brain damage (Jahanshahi et al., 1992a). It has also been suggested that programming deficits are a result of impaired processing during stimulus perception, which leads to slower motor initiation (Kutukcu, Marks, Goodin, & Aminoff, 1999). This controversy suggests that further research is needed, using large patient samples, adequately matched controls, and a consideration of the effects of medication.

Recent models of the basal ganglia are potentially relevant to the motor pre-programming hypothesis. A number of existing theoretical models propose that the basal ganglia may modulate cortical output that guides the execution of movement (Almeida, Wishart, & Lee, 2002, in press; J. Contreras-Vidal & Stelmach, 1995; J.L. Contreras-Vidal, 1999; Humphries & Gurney, 2002). In this situation, it may be possible that the presentation of relevant precues may engage the basal ganglia during movement. A behavioral approach to the investigation of basal ganglia involvement in the processing of advance information is, therefore, important. The purpose of the present study is to test the effect of both advance information and medication on a sample of PD patients and well-matched controls.

It is expected that the provision of advance information will reduce the time required for participants to select a motor program, shortening RT in healthy controls. In contrast, the motor pre-programming hypothesis predicts that the RT of PD patients will not improve with the provision of advance information. Furthermore, as the amount of available dopamine increases (as with the administration of levodopa), the basal ganglia will become more active in the modulation of movement, and the additional striatal-thalamo inputs to the primary motor areas of the cortex will *increase* MT.

Method

Participants

Forty patients with Parkinson's disease (27 men and 13 women) with an average age of 65.02 ($SD = 8.84$; range, 38–78 years), and 40 controls (13 men and 27 women) with an average age of 62.13 ($SD = 9.59$; range, 36–86 years) participated in the study. No significant differences between group ages were found. Baseline cognitive ability was matched between the two groups by estimating their Wechsler Adult Intelligence Scale (WAIS) full scale IQ (FSIQ) with the National Adult Reading Test (NART; Nelson, 1982). FSIQ within the PD group ranged from 91.36 to 125.22 ($M = 110.63$, $SD = 7.92$) and was not significantly different from the mean FSIQ within the control group, which ranged from 88.05 to 124.40 ($M = 111.51$, $SD = 8.03$). Handedness was defined as the hand with which the participant wrote most comfortably, and all but 7 participants (3 patients and 4 controls) were right handed. During the course of testing, patients were assessed by an experienced clinician (using the Unified Parkinson's Disease Rating Scale) to determine the severity of their symptoms (Fahn, Elton, & Members of the UPDRS Development Committee, 1987). Severity of illness for patients in this sample ranged from mild to moderate, both "on" and "off" medication. In the non-medicated stage of testing, motor scores on the Unified Parkinson's Disease Rating Scale (UPDRS) ranged from 4.50 to 43.50 ($M = 24.49$, $SD = 9.79$), and in the medicated stage of testing (2 hours after medication), scores on the UPDRS ranged from 1.50 to 40.50 ($M = 17.16$, $SD = 8.99$). The difference between "off" and "on" scores was significant,

$t(39) = 7.10$, $p < .0001$; $\eta^2 = 0.564$, suggesting that the condition labels (*off medication* and *on medication*) presented herein are accurate reflections of the clinical symptoms of the patients.

The inclusion criteria for patients were: (a) clinically definite Parkinsonism with bradykinesia and at least one of rigidity, tremor, or postural instability; (b) absence of dementia (Mini-Mental Status score of >27/30)[1]; (c) predictable, documented response to immediate release L-dopa therapy; and (d) no other concomitant motor disability impairing movement. The exclusion criteria were: (a) significant cognitive impairment; (b) unpredictable response to L-dopa; (c) prior neurological disorder; and (d) current treatment with anticholinergic medication. Patients were allowed to be on other anti-Parkinsonian medications (including dopamine agonists) in addition to their L-dopa (except anticholinergics).

Apparatus

The tasks used in the study required subjects to respond to a visual stimulus, presented on a computer screen (a white apple symbol on a black background). All responses were completed using an external, color-coded, three-button response console (red, yellow, and green from left to right) connected to an Apple Macintosh LC475 personal computer with a 15-in. color monitor. Participants were instructed to hold down the "home key" (the yellow button in the middle of the console) with the index finger of their dominant hand. Both tasks required the participant to move the finger depressing the home key to one of the remaining two buttons. The computer recorded the time between presentation of the visual stimuli and lifting of the participant's finger from the home key (RT; reaction time), and the time taken to move his/her finger to a response key (MT; movement time). All participants were instructed to respond as quickly as possible but were told that they must not lift their finger from the home key (the yellow button) until they knew the direction in which they would be moving. The timing card in the response console was capable of 1 ms accuracy.

Both tasks started with an instruction to watch a fixation point (asterisk) in the center of the computer screen, while depressing the home key. For the uncued task, participants were not given any advance information concerning the location of the upcoming stimulus. For the cued task, an arrow appeared in place of the fixation point (i.e., in the center of the screen) for a period of 2 s, immediately following the disappearance of the fixation point, and correctly cued the location of the upcoming stimulus on all trials. The visual stimulus to which the subject responded was presented on the right or left side of the monitor, at a random interval (between 500 and 1500 ms) following the fixation point (uncued) or the arrow (cued). Each task consisted of 10 practice and 40 experimental trials, with the fastest and slowest reaction times discarded to form composite RT and MT scores. Both tasks were coded in PsyScope version 1.2.4, a well-validated platform for recording reaction times (Cohen, MacWhinney, Flatt, & Provost, 1993)[2].

Procedure

All patients involved in the study were asked to remain drug-free overnight, and to skip their morning anti-Parkinsonian medications. The average off-drug duration was 10.81 ± 2.52 hours. To avoid any confounding effects resulting from different levels of caffeine intake among participants, all participants were asked to have a

normal caffeine-free breakfast prior to testing. None of the participants reported any acute physiological conditions that may have precluded them from putting forth their best effort during the testing session.

All patients were tested at 0800 and retested at 1130 (after taking their medication), while controls were tested at 0930 and retested at 1300. This allows for a 2-hour time delay between testing patients in an "off" and "on" condition, as recommended by Gauntlett-Gilbert and Brown (1998). On average, therefore, patients may be considered to be optimally medicated at the time of the second evaluation, based on the results of infusion studies that suggest that peak "on" time is experienced at 146 ± 30 min for patients experiencing stable medication effects (Juncos, Mouradian, Fabrini, & Chase, 1995).

The review board for health sciences research involving human subjects at the University of Western Ontario approved the procedure and apparatus for this study, and informed consent was obtained from all participants.

Results

Two analyses of variance (ANOVA) were conducted, using the RT and MT scores for the two tests as dependent variables. Clinical Group (PD patients vs. controls) was used as a between-subjects variable, and both Time Period ("pre-dopamine" and "post-dopamine" in patients, "time 1" and "time 2" in controls) and Cueing Level (i.e., cued and uncued) were used as within-subjects variables. The motor pre-programming hypothesis was further tested using four paired t tests on the RT scores—one for each participant group at each time period of the study. Means and standard deviations for the response time data are presented in Table 1.

Reaction Time Results

The main effect of clinical group was significant, $F_{1,78} = 22.37$, $p < .0001$, with PD patients demonstrating a significantly slower RT than controls. The main effect of

Table 1   Means (and Standard Deviations) for RT and MT, Across Cueing and Medication Conditions, for PD Patients and Controls

| Subject		PD Patients		Controls	
Cued RT	OFF	402.34	(102.46)	Time 1	336.45 (49.26)
	ON	379.25	(61.06)	Time 2	336.37 (51.89)
Uncued RT	OFF	413.95	(95.40)	Time 1	346.03 (49.75)
	ON	415.52	(84.32)	Time 2	356.62 (41.79)
Cued MT	OFF	359.58	(124.00)	Time 1	228.07 (78.41)
	ON	320.39	(112.19)	Time 2	225.06 (86.05)
Uncued MT	OFF	359.18	(151.51)	Time 1	192.41 (64.20)
	ON	299.81	(119.52)	Time 2	195.38 (85.56)
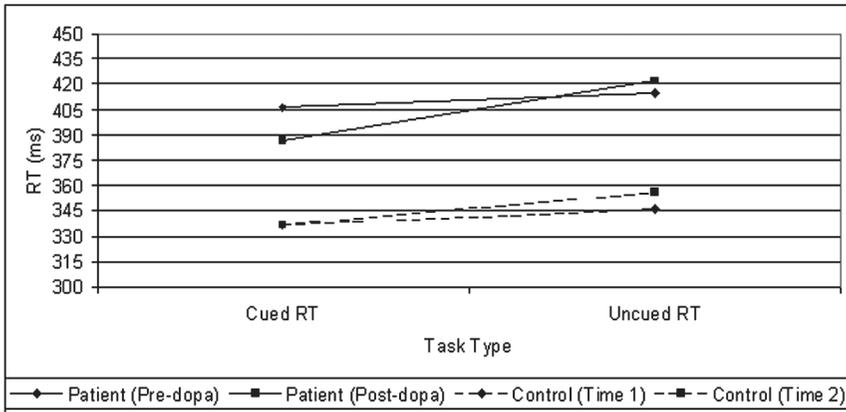
Figure 1 — Reaction times: patient versus control. This figure shows changes in reaction time across patients and controls, using both Cueing Level and Drug Treatment Phase as factors.

cueing was also significant, $F_{1,78} = 13.486$, $p < .0001$, revealing that cued RT was significantly faster than uncued RT. None of the interactions with clinical group were, however, significant, suggesting that PD patients were not differentially impaired by the provision of advance information, and further suggesting that dopaminergic intervention was not effective for improving RT. A graphical comparison of patient and control results across the cueing levels is presented in Figure 1.

Due to the fact that within-cell effect sizes were small for the RT task, results were also investigated outside the three-factor ANOVA, using four paired *t* tests (comparing cued and uncued RT)—one for each participant group at each time period of the study. Multiple comparison bias was controlled using a Bonferroni adjustment to the experiment-wise alpha. (I.e., the experiment-wise alpha was adjusted to be $0.05/4 = 0.0125$.) Neither the patient group nor the control group demonstrated a significant difference between cued and uncued RT at time 1 ("off-medication"). At time 2, however ("on-medication"), cued RT was significantly faster than uncued RT for both patients, $t(39) = 4.095$, $p < .0001$, and controls, $t(39) = 3.286$, $p < .0020$.

Movement Time Results

The main effect of clinical group was significant, $F_{1,78} = 36.96$, $p < .0001$, with PD patients demonstrating a significantly slower MT than healthy control participants. The main effect of cueing was also significant, $F_{1,78} = 21.342$, $p < .0001$, and cued MT was significantly slower than uncued MT. The two-way interaction of clinical group and cueing level was significant, $F_{1,78} = 5.63$, $p < .020$, with PD patients demonstrating less impairment from the provision of advance information than controls. Furthermore, the two-way interaction of Clinical Group and Time Period was significant, $F_{1,78} = 7.18$, $p < .01$, with patients demonstrating greater improvement in their movement time between testing sessions than controls (i.e., a significant medication effect). Finally, the three-way interaction of Clinical Group, Time
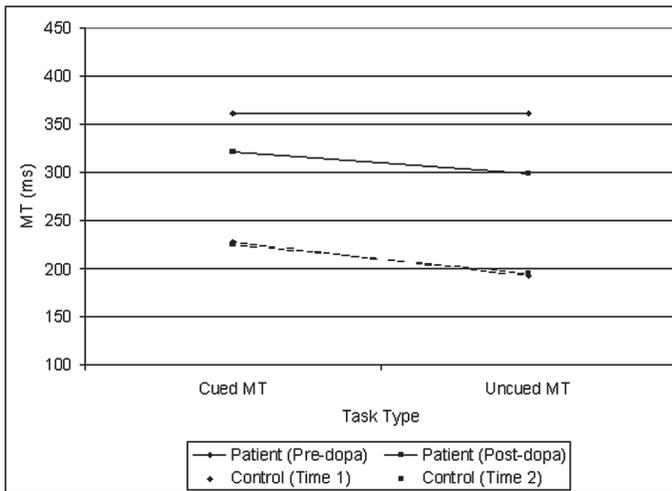
Figure 2 — Movement times: patient versus control. This figure shows changes in movement time across patients and controls, using both Cueing Level and Drug Treatment Phase as factors.

Period, and Cueing Level was significant, $F_{1,78} = 3.92, p < .05$, with post hoc analysis demonstrating that both cued and uncued movement times improved when "on" dopaminergic medications. Interestingly, similar to controls, the cued movement time was now slower among PD patients in the "on" state than uncued movement time. A graphical comparison of patient and control results across the cueing levels is presented in Figure 2.

Discussion

The results of the reaction time testing in this study suggest that the provision of directional advance information (a directional precue) reduced the time required to respond to a stimulus. Contrary to previous initiation-of-movement studies, RT improved for *both* patients and controls. These results do not agree with previously published motor pre-programming findings (Bloxham et al., 1984; Evarts et al., 1981; Filipovic et al., 1997; Gauntlett-Gilbert & Brown, 1998; Harrington & Haaland, 1991, 1998; Stelmach et al., 1986; Willingham et al., 1995), which demonstrate a PD *reaction time* deficit unrelated to availability of a movement precue. The present study involved substantially more participants than any previous study (for a review, see Gauntlett-Gilbert & Brown, 1998), and so the power of the comparison is correspondingly higher (allowing for the detection of smaller differences between the cued and uncued tasks).

The present results are the first explicit empirical demonstration of *slower* movement time in healthy controls following the provision of directional advance information (precue). Rosenbaum (1980), in one of the original examinations of precue effects on MT, showed that directional precues only influence reaction time but not movement time, although this may be due to the small *n* size in this early

study ($n = 10$). The power of the present finding is reinforced by the fact that individuals with PD more closely approximate the movement time difference between cued and uncued tasks (demonstrated by control participants) when dopamine levels are brought closer to normal levels through dopamine replacement medications (i.e., as the basal ganglia approach normalcy). A recent study reported a seemingly opposite effect, in that a moving visual cue (a ball that rolled to a target grasping location) was able to speed up movement time, while a static visual cue (a ball sitting stationary at the target grasping location) showed no MT improvement (Majsak, Kaminski, Gentile, & Flanagan, 1998). However, if this study is considered from a *precueing* perspective, availability of advance information was also manipulated in this study. It should be noted that the static visual cue acts as a precue (providing advance information about target location) and thereby slows movement time. In the "moving visual cue" condition, on the other hand, advance information about the target location is unavailable and cannot, therefore, be incorporated into execution of the movement (i.e., movement time is not slowed). From a precueing perspective, the present results would actually be predicted from the research of Majsak et al. (1998).

The inclusion of a parkinsonian population allows us to evaluate current models purporting a role of the basal ganglia in the initiation and control of movement. It is well known that the basal ganglia receive a variety of cortical inputs during the planning and execution of movement. Among these inputs, involvement of the premotor (PM), supplementary motor area (SMA), and prefrontal cortex is thought to be noteworthy. Experimental evidence supports the involvement of the SMA in the internal planning of movement, while PM neurons guide responses to external stimuli (Nolte, 1999) such as a precue. In their projections to the basal ganglia, these higher cortical centers are proposed to provide neural feedback (via the thalamus) to motor areas for maintenance of a motor program (Almeida et al., in press; J. Contreras-Vidal & Stelmach, 1995; J.L. Contreras-Vidal, 1999). In the context of our experiment, since movement characteristics were kept constant (i.e., distance, type of response required) through a number of repetitions, we propose that a consistent and repetitive pattern of neural activation would be likely for these types of simple movements. This notion is supported in recent literature describing neuronal activation patterns in tasks that involve changes from controlled to more automatic processing (Jansma, Ramsey, Slagter, & Kahn, 2001). It is therefore hypothesized that established motor programs are selected and executed rapidly, through cortico-cortical connections. The basal ganglia output to the cortex in this situation serves as a comparator and is not used if the active motor program does not require it.

From this perspective, the availability of a directional precue (as the primary independent variable) in our experiment may be considered useful in evaluating additional processing done by the basal ganglia during movement. Our results demonstrate that a directional precue can improve reaction time in both healthy and basal ganglia-disordered populations, which would suggest that the basal ganglia are not directly involved in using advance information to select a motor program. However, it is probable that a directional precue may be processed by the basal ganglia during movement execution, thereby slowing movement. When the basal ganglia are unable to actively participate in the modulation of movement during execution (as in the "off" medication condition), the precue does not slow movement execution.

Although every effort was made to evaluate the effects of dopaminergic medications on the motor activities assessed within the present study, the present design is limited by its reliance on a test-retest paradigm in which "on" periods always follow "off" periods, as this confounds medication and practice effects. Future studies may wish to examine the effects directional precues within *de novo* patient populations (i.e., patients that have not been treated with dopaminergic medication). This type of medication control paradigm would allow for an assessment of the extent to which chronic levodopa treatment affects the basal ganglia.

It should also be emphasized that the present study involved the use of simple motor tasks, and so some caution should be exercised in the interpretation of these results. Furthermore, there is some indication within the literature that the basal ganglia may be differentially involved in the mediation of precues involving direction and amplitude (Jones, Phillips, Bradshaw, Iansek, & Bradshaw, 1993; Pullman, Watts, Juncos, Chase, & Sanes, 1988; Pullman et al., 1990). Interestingly, Pullman et al. (1988, 1990) argues that the effect of advance information may be unique to the provision of directional information, while Jones (1993) suggests that neither component demonstrates a specific impairment. Given this lack of consensus, future studies should attempt to control medication state in studies that examine movement time on more complex tasks, with different methods of cueing. It would also be interesting to expand on the "uncued" condition by evaluating the effect of providing a movement precue that contains no information (i.e., a precue that must be processed, but which contains no useful information). As the present study proposes an information processing explanation for the effects of precues on movement time, it would be relevant to exert greater control over the presentation of information.

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Note

[1]The Mini-Mental Status Examination has been demonstrated to be sensitive to the dementia typically seen in PD.