Neuropsychology
2005, Vol. 19, No. 1, 54–65

0894-4105/05/$12.00 DOI: 10.1037/0894-4105.19.1.54

Maintenance of Response Readiness in Patients With Parkinson's Disease: Evidence From a Simple Reaction Time Task

Emily R. Stern, Jon C. Horvitz, Lucien J. Côté, and Jennifer A. Mangels
Columbia University

The authors explored the effect of Parkinson's disease (PD) on the generation and maintenance of response readiness in a simple reaction time task. They compared performance of idiopathic PD patients without dementia, age-matched controls, and younger controls over short (1-, 3-, and 6-s) and long (12- and 18-s) foreperiod intervals. After each trial, the authors probed memory for visual information that also had to be maintained during the trial interval. Patients and controls did not differ overall in their ability to maintain readiness over long delays. However, within the PD group only, errors in maintaining visual information were correlated with difficulty in maintaining readiness, suggesting that systems impaired in PD may facilitate the maintenance of processing in both motor and cognitive domains.

Parkinson's disease (PD) is a neurodegenerative disorder characterized primarily by motor deficits that include difficulty initiating internally generated movements (*akinesia*), slowness of ongoing movement (*bradykinesia*), resting tremor, and postural instability (Hornykiewicz, 1979). A growing body of evidence indicates that PD deficits also extend to cognitive functions, particularly executive control processes that are hypothesized to involve the dorsolateral prefrontal cortex, including maintenance and manipulation of information in working memory, set switching, verbal fluency, and planning (Bradley, Welch, & Dick, 1989; Brown & Marsden, 1990; Dalrymple-Alford, Kalders, Jones, & Watson, 1994; Dubois & Pillon, 1997; Kulisevsky et al., 2000; Mattay et al., 2002; Taylor, Saint-Cyr, & Lang, 1986).

By the time initial motor symptoms appear in PD, dopamine (DA) loss in the dorsal striatum has usually exceeded 80% (Rehman & Masson, 2001), disrupting the flow of information through multiple corticostriatal basal ganglia loops (Alexander & Crutcher, 1990; Cummings, 1993). It has been suggested that motor and cognitive functions are mediated by activity within distinct loops, for example, those originating in motor regions of the frontal cortex and in dorsolateral prefrontal regions, respectively. Parkinsonian motor and cognitive deficits may reflect disruptions of activity in multiple corticostriatal circuits (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Cummings, 1993; Saint-Cyr, 2003). As the disease progresses, motor and cognitive function may be further impaired by dysfunction in the mesocorticolimbic DA system, which projects from the ventral tegmental area to the ventral striatum and frontal cortex, as well as by dysfunction in noradrenergic, serotonergic, and cholinergic systems (Javoy-Agid & Agid, 1980; Jellinger, 1991).

Although the multiple corticostriatal basal ganglia circuits are likely to carry different types of information (Alexander & Crutcher, 1990), DA may serve a similar modulatory function within each of these loops (Horvitz, 2002). Recent theories have suggested that DA serves a gating function, such that task-relevant inputs to the striatum and frontal cortex are facilitated and task-irrelevant inputs, or "noise," are inhibited (Durstewitz, Seamans, & Sejnowski, 2000; Henze, Gonzalez-Burgos, Urban, Lewis, & Barrionuevo, 2000; Horvitz, 2002). DA may serve to stabilize task-relevant neural representations by reducing the vulnerability of such representations to interference by irrelevant stimuli (Durstewitz et al., 2000). Prefrontal DA plays a critical role in the maintenance of prefrontal neuronal activity during the delay period of a working memory task (Goldman-Rakic, 1995), and within the ventral striatum, DA is also critical for the maintenance of overt behavioral responses (Aberman, Ward, & Salamone, 1998). In light of this emerging conceptualization of DA as promoting maintenance of task-relevant neuronal activity within its various target structures, we hypothesized that a part of the motor impairment that characterizes PD might include a particular difficulty in maintaining an anticipatory state of readiness prior to making a movement.

A state of response readiness is observed when a warning stimulus (WS) explicitly signals the impending arrival of an imperative stimulus (IS) that requires a motor response, and it is typically studied in the context of the simple reaction time (SRT) task. In healthy adults, the advance information that the WS provides both enhances cognitive expectancy for the IS and generates a state of readiness within those components of the motor system that are associated with the planning of the actual response output. Generation of these anticipatory states by the WS allows the subject to respond more quickly to the IS, as compared with an unwarned condition (Frith & Done, 1986). Although generation and maintenance of a readiness state have been studied extensively in patients with PD (e.g., Jahanshahi, Brown, & Marsden, 1992;

Emily R. Stern, Jon C. Horvitz, and Jennifer A. Mangels, Department of Psychology, Columbia University; Lucien J. Côté, Neurological Institute, Columbia University College of Physicians and Surgeons, Columbia University.

Jon C. Horvitz is now at the Department of Psychology, Boston College.

This research was supported by a grant to Jennifer A. Mangels from the W. M. Keck Foundation and to Jon C. Horvitz from the National Institute of Drug Abuse (R29-DA11653). We thank Gillian Diercks and Emily Voigt for their assistance in testing patients and control subjects.

Correspondence concerning this article should be addressed to Emily R. Stern, Department of Psychology, Columbia University, 406 Schermerhorn Hall, 1190 Amsterdam Avenue, New York, NY 10027. E-mail: estern@psych.columbia.edu

Pullman, Watts, Juncos, Chase, & Sanes, 1988; Sheridan, Flowers, & Hurrell, 1987), a clear understanding of how these processes are affected by PD has not yet emerged.

A number of electrophysiological studies have shown that the *contingent negative variation*, a scalp-recorded slow wave potential that occurs between a WS and an IS in an SRT task and is thought to reflect anticipatory and readiness processes, is reduced in PD, thus providing support for the view that generation of readiness might be impaired in these patients (Brunia & van Boxtel, 2001; Oishi, Mochizuki, Du, & Takasu, 1995; Praamstra, Meyer, Cools, Horstink, & Stegeman, 1996; Wascher et al., 1997). This view gains additional, though indirect, support from the results of intracranial recordings demonstrating that the contingent negative variation is dependent in part on input to the supplementary motor areas and premotor areas from basal ganglia structures (Bares & Rektor, 2001; Kimura, 1990; Schultz & Romo, 1988). Yet, some behavioral studies comparing warned to unwarned SRT responses have found that PD patients are indeed capable of generating a state of response readiness as much as controls (Bloxham, Dick, & Moore, 1987; Heilman, Bowers, Watson, & Greer, 1976; Jahanshahi et al., 1992).

The maintenance of readiness becomes relevant when the duration between the WS and IS exceeds the time it takes to generate this state to its optimal level and is best studied with an SRT task that uses multiple foreperiods. Most studies of PD patients that have included multiple foreperiods have used delays of a few seconds or less (Bloxham et al., 1987; Goodrich, Henderson, & Kennard, 1989; Heilman et al., 1976; Jahanshahi et al., 1992; Sheridan et al., 1987), which are generally too short to disentangle processes involved in readiness maintenance and readiness generation. Indeed, the scalp-recorded readiness potential, which is hypothesized to index processes involved in movement execution, begins 1,200–1,500 ms prior to movement onset and has the largest amplitude over the primary motor area contralateral to the limb being used (Brunia & van Boxtel, 2001; Rektor, Bares, & Kubova, 2001). In contrast to the short-lived processes directly involved in the execution of the response via the primary motor cortex, however, an anticipatory state of motor readiness, involving sustained activity within corticostriatal motor loops, could hypothetically be maintained over intervals lasting many seconds.

Yet, studies that have examined readiness over long intervals in PD patients have found mixed results. Bloxham et al. (1987) studied PD patients' performance on an SRT task with WS-IS delays of 0, 100, 200, 800, and 3,200 ms and found that the reaction times (RTs) of PD patients appeared to increase at the longest delay interval of 3,200 ms, whereas the RTs of age-matched controls appeared to decrease, although this difference did not reach significance. Similarly, Wascher et al. (1997) found no significant differences in the RTs of PD patients and controls across delay intervals of 1,200, 1,800, 2,400, 3,000, and 3,600 ms, although careful inspection of their results also suggests that the RTs of patients and controls began to diverge at the 3,000- and 3,600-ms intervals. Specifically, at the longer intervals, the WS appeared to be less beneficial to PD patients, whereas controls were able to maintain their faster RTs. Finally, in a study using longer WS-IS intervals (2–8 s), Labutta, Miles, Sanes, and Hallett (1994) found a significant increase in the RTs of PD patients over long delays; however, this delay-dependent slowing was not specific to PD patients, as it was also found in age-matched controls, suggesting that the slowing was a more general effect of aging.

In the current study, we evaluated the performance of patients with moderate to severe PD using an SRT task that included shorter delays similar to those used in previous studies (1, 3, and 6 s), as well as delays twice as long as those previously examined in PD (12 and 18 s). It should be noted that both motor and cognitive expectancy play a role in the generation and maintenance of readiness to respond to an IS (Brunia, 1993); therefore, we have chosen to describe our task as assessing overall *response readiness,* a more general term indicating that performance can be influenced by readiness in both systems. Our use of the term *response readiness* should not be confused with the term *readiness potential,* which generally refers to the electrophysiological changes occurring in the few seconds immediately preceding a voluntary motor response. Rather, the type of readiness that is assessed here can occur and be maintained any time during the period between a WS and an IS. Indeed, the longer delays included in our study were designed to tax both cognitive and motor maintenance to a greater extent than in previous investigations (Jahanshahi et al., 1992; Sheridan et al., 1987), providing greater opportunity for divergence in performance between PD patients and control subjects to emerge in these domains.

Although a learned WS-IS contingency can result in the WS automatically triggering a state of response readiness, this vigilance may dissipate over time unless maintained in a more active manner. Thus, the ability to maintain a state of readiness over the longer intervals we used may be related to other aspects of active maintenance, such as working memory for cognitive representations. Of note, DA has been shown to be necessary for the maintenance of information in working memory (Castner, Williams, & Goldman-Rakic, 2000; Romanides, Duffy, & Kalivas, 1999; Sawaguchi, 2001; Sawaguchi & Goldman-Rakic, 1991). To our knowledge, however, the relationship between DA, response readiness, and working memory for task-relevant information has not yet been investigated directly.

To measure subjects' ability to maintain task-relevant visual information in working memory, we probed memory for the different visual stimuli used as cues during the three different trial types in this experiment. In brief, all trials began with an orienting stimulus (OS), followed by one of three possible stimuli: (a) a WS that always signaled an upcoming IS (warned trials), (b) the IS only (unwarned trials), or (c) the end of the trial with no IS (catch trials). This latter condition was included to degrade the predictive value of the OS. We probed memory by asking whether the previous trial had contained an OS only; an OS and an IS; or an OS, a WS, and an IS. Of importance, given that the WS in warned trials was presented relatively briefly (1 s) during the trial, an accurate response to the memory probe in this condition would have required subjects to have maintained an explicit representation of the WS in working memory over delays ranging from approximately 1 to 18 s. Thus, this component of our experiment allowed us to determine if maintenance of a specific visual representation in working memory, necessary for successful performance on the memory probe, was related to maintenance of a sustained state of response readiness, necessary for fast responding over long WS-IS delay intervals.

Table 1
Performance of PD Patients, Older Controls, and Younger Controls on Neuropsychological Tests

Test	PD patients	Older controls	Younger controls
mMMSE/MMSE[a]	54.7 (0.7)/29.2 (0.3)	54.6 (0.5)/29.7 (0.2)	
BDI–II	7.22 (0.82)	2.4 (0.78)	
UPDRS total	42.5 (4.19)		
Tremor subscore[b] (max = 28)	2.3 (0.08)		
Rigidity subscore[c] (max = 20)	7.8 (0.09)		
Bradykinesia[d] (max = 28)	7.5 (1.2)		
Axial Impairment subscore[e] (max = 16)	3.9 (0.8)		
Digit Span Forward (mean digits recalled)	7.4 (0.5)	7.1 (0.4)	8.0 (0.2)
Digit Span Backward (mean digits recalled)	5.8 (0.4)	5.4 (0.4)	6.0 (0.3)
Phonemic fluency (mean words generated)	47.8 (3.8)	51.6 (2.0)	52.9 (2.2)
Visual Elevator (mean seconds per switch)	4.1 (0.3)	3.7 (0.3)	2.9 (0.1)
Telephone Search (mean seconds per item)	4.8 (0.4)	3.5 (0.2)	2.3 (0.07)

Note. Standard errors are in parentheses. PD = Parkinson's disease; mMMSE = modified Mini-Mental State Examination; MMSE = Mini-Mental State Examination; BDI–II = Beck Depression Inventory—II; UPDRS = Unified Parkinson's Disease Rating Scale.
[a] The mMMSE scores are out of 57 total points; the MMSE scores are out of 30 total points. [b] Combined scores of Tremor at Rest and Action or Postural Tremor subtests. [c] Scores of Rigidity subtest. [d] Combined scores of Hand Movements, Rapid Alternating Movements of Hands, Leg Agility, and Body Bradykinesia and Hypokinesia subtests. [e] Combined scores of Arising From Chair, Posture, Postural Stability, and Gait subtests.

Method

Subjects

Ten patients with PD (age, $M = 70.3$ years, $SD = 8.29$ years; education, $M = 17.2$ years, $SD = 2.39$ years), 14 age- and education-matched older controls (age, $M = 69.29$ years, $SD = 9.38$ years; education, $M = 17.1$ years, $SD = 2.56$ years), and 20 younger controls (age, $M = 20.45$ years, $SD = 1.28$ years; education, $M = 14.9$ years, $SD = 1.35$ years) participated in the experiment. The younger controls were included to disentangle age-specific deficits from PD-specific deficits, given that significant neurological changes can also occur with normal aging, among them DA loss in the prefrontal cortex and to a lesser extent the basal ganglia (Braver et al., 2001; Cordes et al., 1994; Grady, 2000; Reeves, Bench, & Howard, 2002; Rehman & Masson, 2001).

All PD patients were diagnosed by a neurologist (author Lucien J. Côté) as having idiopathic PD without signs of extrapyramidal dysfunction. Mean duration of illness was 7.95 years (range, 3–13 years). Patients were tested 1–2 hr after taking their daily dose of L-dopa medication (Sinemet). Eight of these patients also were taking Selegiline, with 4 of the 8 additionally taking a DA agonist (e.g., Permax, Mirapex, Requip, or Tazmar). Two patients were taking only a DA agonist in addition to their L-dopa medication.[1] None of the patients were taking anticholinergic medications.

PD patients demonstrated moderate to severe symptomatology (Hoehn and Yahr score [Hoehn & Yahr, 1967]: range, 3–4, $M = 3.2$, $SD = 0.35$). To further specify the nature of the motor impairment in these patients, in Table 1 we report the total scores and selected subscores from the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987). We grouped selected tests from the UPDRS into tremor, rigidity, bradykinesia, and axial impairment subscores using the scheme of Levy et al. (2000).

Both PD patients and older controls were screened for dementia with a modified version of the Mini-Mental State Examination (mMMSE; Folstein, Folstein, & McHugh, 1975; Stern, Sano, Paulson, & Mayeux, 1982), with a cutoff for dementia at 50 out of 57 total points. All subjects were also given the Beck Depression Inventory—II (BDI–II; Beck, Steer, & Brown, 1996), with a 10-point cutoff for depression. Mean scores on these tests are presented in Table 1. Only those patients who were nondepressed and who did not have dementia were included in the study. A one-way analysis of variance (ANOVA) indicated no significant differences between groups on the mMMSE/MMSE.

All subjects gave informed consent before participating in the experimental session, in accordance with Columbia University Medical Center and Morningside Institutional Review Board regulations.

Design and Procedure

The majority of PD patients were tested in their home environment, as it was often difficult for them to travel to the laboratory. All older and younger controls came into the laboratory for testing. The majority of patients and older controls performed four separate blocks of the SRT task (total number of trials = 152). The first block of trials for 1 PD patient was excluded because of the patient's inability to adequately understand the task. Three older control subjects did not perform the fourth block of trials, 2 because of reported fatigue and 1 because of computer error. It was necessary for younger controls to perform only three blocks of trials (total number of trials = 114), given that the variability of their performance was lower overall than that of the older subjects.

The stimuli for the SRT task consisted of three colored circles vertically positioned to resemble a stoplight: a red OS at the top of the display, a yellow WS in the middle of the display, and a green IS at the bottom of the display. These stimuli were displayed on a portable computer situated approximately 60 cm from the subject.

[1] To determine the influence of direct DA receptor agonists on patient performance, we compared patients who were taking DA agonists in addition to L-dopa ($n = 6$) to those who were not ($n = 4$). Independent-samples Mann–Whitney test analyses indicated no significant differences between the two groups on RTs, memory performance, or neuropsychological measures. Therefore, all results reported were based on the group as a whole.

Subjects initiated a trial by pressing and holding a button in the middle of a response box. The trial then began with the presentation of the red light. This stimulus was not highly predictive of the precise nature of the next event and served primarily to orient subjects to the start of a trial. On 25% of the trials ($n = 38$ for older adults and PD patients), the OS was presented for 16, 19, or 22 s, after which the trial simply terminated and no response was required (OS → end of trial; catch trials). On another 25% of the trials, the OS was presented for 16, 19, or 22 s, followed by the IS, to which the subject responded by lifting his or her finger off the middle button and pressing a button 4 cm to the right (OS → IS; unwarned trials). On 50% of the trials, however, the red light was followed by presentation of a yellow light in the middle of the display for 1 s. The yellow light served as a WS in that it indicated to the subject that the IS would be presented with 100% probability (OS → WS → IS; warned trials). RTs were measured using a PsyScope button box (New Micros, Dallas, TX) with a temporal resolution of 1,000 bytes per second (1 ms). The delay between presentation of the WS and IS varied on a trial-by-trial basis between 1, 3, 6, 12, and 18 s. Figure 1 illustrates the trial structure for the catch, unwarned, and warned trials.

For warned trials, the presentation length of the OS was determined to be the total trial length subtracted from the WS-IS delay length on that particular trial (16, 19, or 22 s minus 1, 3, 6, 12, or 18 s), the one exception to this occurring on trials in which the delay was 18 s. On these trials, the total trial length was 20, 21, or 22 s. All trials were approximately the same length to avoid problems that PD patients might have with starting and stopping movements at different intervals, yet total trial length was varied around an average of 19 s to reduce the influence of overt timing on the part of the subjects. Finally, six warned trials with a 9-s WS-IS delay interval were added during the last two blocks of the experiment. RTs from these trials were analyzed to determine whether subjects had learned to time the five WS-IS delay intervals. Given that PD has been shown to impair both timing (Gibbon, Malapani, Dale, & Gallistel, 1997) and skill learning (Krebs, Hogan, Hening, Adamovich, & Poizner, 2001), it was important for us to establish that these factors were not responsible for any observed differences between patients and controls. Although the jitter in the total trial length was designed to make temporal information less consistent and therefore less useful to subjects' performance, introduction of the 9-s interval in the final blocks provided an objective measure of learning and timing. Subjects who were explicitly timing the interval lengths and had learned the intervals (1, 3, 6, 12, and 18 s) during the first two blocks might be expected to perform more slowly on a 9-s delay interval that was new to the last half of the experiment.

All subjects were given nine practice trials and instructions on the meanings of the different types of trials. Subjects who lifted the middle button before the IS was presented received a warning beep and were instructed to continue with the trial by re-pressing and holding the button, although these trials were analyzed separately as false alarms and were excluded from the primary RT analysis.

At the end of the unwarned and warned trials, the sum of the RT (time to lift middle button after seeing the IS) and the movement time (MT; time to move finger from middle button to right button) in milliseconds was presented to subjects on the screen (for catch trials, a zero was presented). Then, for all trial types, subjects received a memory question asking which colored lights they had just seen. Subjects were required to press 1 if they had seen a red light only (e.g., lights associated with a catch trial); 2 if they had seen a red and a green light (e.g., lights associated with an unwarned trial); and 3 if they had seen a red, a yellow, and a green light (e.g., lights associated with a warned trial).

Between each block of trials, subjects performed various neuropsychological tests that are sensitive to frontal lobe function, including phonemic fluency tests, the Digit Span subtest of the Wechsler Adult Intelligence Scale—Third Edition (Wechsler, 1997), and the Visual Elevator (set-switching) and Telephone Search (selective attention) subtests from The Test of Everyday Attention (Robertson, Ward, Ridgeray, & Nimmo-Smith, 1994). The Visual Elevator subtest is a timed test requiring subjects to switch between counting in ascending and descending order on the basis of symbols and directions printed on a card. The Telephone Search subtest is a timed test requiring subjects to pick out targets presented in a field of

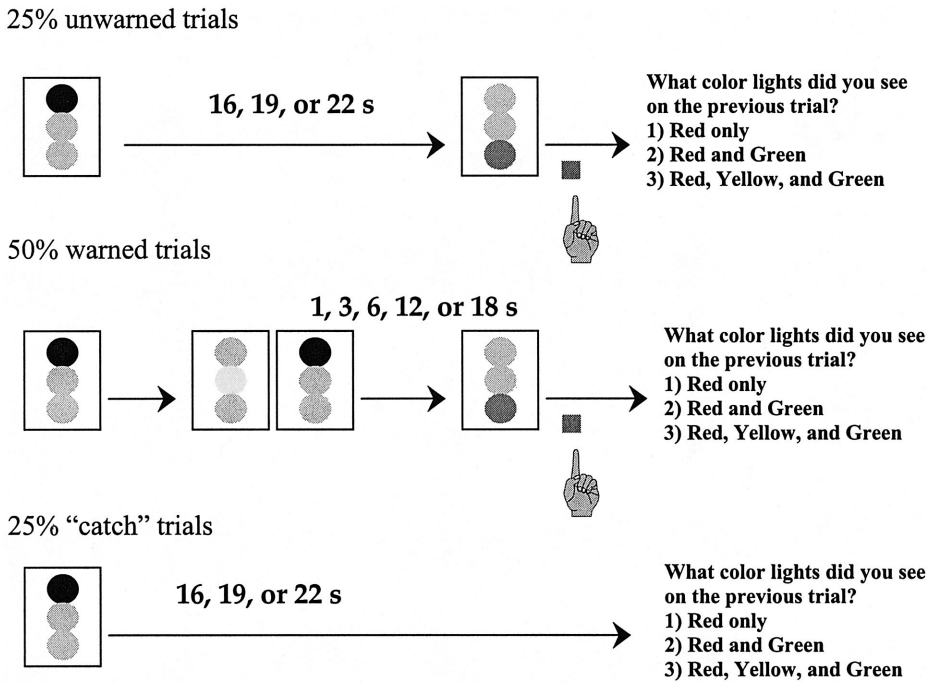

Figure 1. Experimental paradigm. Black circle = red light; dark gray circle = green light; very light gray circle = yellow light.

distracters where the array of stimuli is arranged to resemble pages from a telephone book. The order in which these tests were given was counterbalanced. At the end of the testing session, all subjects were fully debriefed and given contact information for the experimenters.

Data from all behavioral measures were analyzed using a mixed-design ANOVA with appropriate Huynh–Feldt corrections when violations of sphericity occurred. Main effects and interactions significant at the $p < .05$ level were further analyzed with Tukey's honestly significant difference (HSD) tests.

Results

Neuropsychological Tests

Scores on the mMMSE/MMSE, the BDI–II, the UPDRS, Digit Span (Forward and Backward), phonemic fluency, Visual Elevator, and Telephone Search tasks can be found in Table 1. PD and control groups did not differ on Digit Span Forward, Digit Span Backward, and phonemic fluency tests. This lack of difference between PD patients and controls is somewhat unexpected given that impairments on these tasks have been found in previous studies (McFadden, Mohr, Sampson, Mendis, & Grimes, 1996; Woods & Troster, 2003). Yet, Goldman, Batsy, Buckles, Sahrmann, and Morris (1998) have reported that out of 10 neuropsychological tests of memory, learning, and attention, PD patients and age-matched controls performed comparably on Digit Span and phonemic fluency tests only. Other studies have also found that among patients with advanced PD but without dementia or depression, performance on Digit Span and phonemic fluency tasks was often similar to that of age-matched controls (Green et al., 2002; Uekermann et al., 2003).

A one-way ANOVA comparing PD patients, older controls, and younger controls revealed significant group differences on the Visual Elevator task, $F(2, 41) = 9.22$, $p < .001$, and Telephone Search task, $F(2, 39) = 35.59$, $p < .001$, both of which are timed tests. On the Visual Elevator task, PD and older control subjects took a significantly longer amount of time to switch between counting in ascending and descending order, as compared with younger controls (PD patients vs. younger controls, $p < .001$; older vs. younger controls, $p < .005$), but no differences were found between PD patients and older controls, suggesting that this result was primarily an age effect. Yet, on the Telephone Search task, PD patients were significantly slower than both older and younger controls (PD patients vs. older controls, $p < .01$; PD patients vs. younger controls, $p < .001$), and older controls were slower than younger controls ($p < .001$), indicating that performance on this task was affected by both aging and PD. Although a significant difference between PD patients and older controls was found for scores on the BDI–II, $t(17) = 4.15$, $p < .001$, both groups obtained scores that were not indicative of depression according to Beck et al. (1996).

Experimental Task

Differences in total trial length. Given that total trial length varied between 16, 19, and 22 s, we first conducted a 2 (trial type, warned vs. unwarned) × 3 (total trial length, 16, 19, or 22 s) × 3 (group, PD vs. older control vs. younger control) ANOVA on mean RTs to determine whether it was possible to collapse over this variable. There was no main effect of trial length or interaction between trial length and group; however, we did find a significant interaction between trial length and trial type, $F(2, 82) = 3.1$, $p = .05$. Whereas there was no effect of total trial length for warned trials, there was a trend for RTs to decrease as the OS–IS delay increased in unwarned trials, $F(2, 82) = 2.8$, $p = .07$, which may have been due to an aging interval effect (for further discussion of this effect, see Niemi & Naatenen, 1981). It is possible that overall trial length was more salient in the unwarned trials because there was no intervening stimulus during this period. Nonetheless, given that any effects of trial length were small and did not significantly differ between groups, we chose to pool data across the different trial lengths for all further analyses to maximize power.

Unwarned versus warned trials. Trials in which RTs exceeded 2,000 ms were excluded from analysis of RTs or MTs (1.64%, 0.054%, and 0% of all trials for PD patients, older controls, and younger controls, respectively). There were no instances of unusually long MTs accompanying normal RTs.

A 2 (trial type, unwarned vs. warned trials) × 2 (measure, RT vs. MT) × 3 (group, PD vs. older control vs. younger control) ANOVA was performed. All main effects and interactions were significant, including a three-way interaction between trial type, measure, and group, $F(2, 41) = 3.49$, $p < .05$. Main effects indicated that RT was slower overall than MT, $F(1, 41) = 472.52$, $p < .001$, and that PD patients were slower overall than older controls, who were themselves slower than younger controls, $F(2, 41) = 21.69$, $p < .001$.

Closer inspection of the data revealed that the three-way interaction was driven by an interaction between trial type and measure and that this interaction also varied as a function of group. As can be seen in Figure 2, the warning signal caused a significant decrease in RT but no change in MT, $F(1, 41) = 57.45$, $p < .001$, an effect that was slightly weaker in the younger controls because a floor effect appeared to have limited the benefit of the WS in this group. Despite the ability of all groups (including PD patients) to demonstrate some benefit in RTs from the WS, post hoc analyses revealed that on both warned and unwarned trials, PD patients exhibited a significantly slower RT than did older controls ($p < .005$) and younger controls ($p < .001$). Additionally, older controls exhibited a significantly slower RT than did younger controls ($p < .05$). For MT, PD patients were also slower overall than older or younger controls ($p < .001$), but older and younger controls did not differ from each other.

Given that subjects were able to decrease RTs in unwarned trials as total trial length increased, we performed a 2 (trial type, unwarned trial at 22-s interval vs. warned trial) × 3 (group, PD vs. older control vs. younger control) ANOVA to determine whether subjects still exhibited a benefit from the WS when their RT was (overall) fastest at the unwarned 22-s trial length. Results revealed significant effects of trial type, $F(1, 41) = 108.16$, $p < .001$, and of group, $F(2, 41) = 17.51$, $p < .001$, as well as an interaction between factors, $F(2, 41) = 6.29$, $p < .005$, such that younger controls decreased their RTs in the warned trials comparatively less than the PD patients or older controls. Thus, it appears as though all subjects benefited significantly from the WS on warned trials even when there may have been a certain amount of readiness generated in the longest unwarned trial intervals because of an aging interval effect.

Warned trials. RT as a function of WS-IS interval and group is illustrated in Figure 3. To examine whether the benefits of the

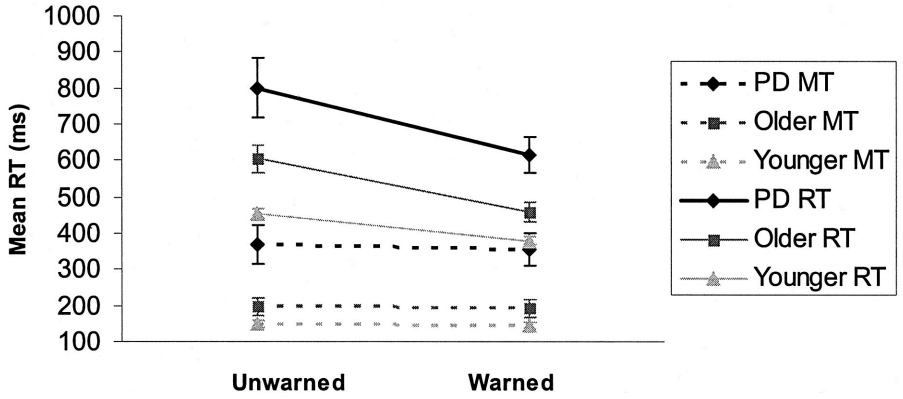

Figure 2. Overall mean reaction times (RTs) and movement times (MTs) for unwarned and warned trials. Error bars represent standard error of the mean. PD = Parkinson's disease.

WS on RTs found in these groups were equivalent across all WS-IS delays, we performed a 3 (group, PD vs. older control vs. younger control) × 5 (warned delay intervals of 1, 3, 6, 12, and 18 s) repeated measures ANOVA. Results indicated a significant effect of warned interval, $F(4, 164) = 7.35$, $p < .001$, $\varepsilon = .69$, and of group, $F(2, 41) = 17.50$, $p < .001$, but no interaction between variables. Post hoc analyses revealed that RTs for the 1-s WS-IS delay were significantly slower than those for the 6-, 12-, and 18-s delay intervals, suggesting that the 1-s interval may have been too brief (within the context of the experiment) to allow a sufficient amount of expectancy to be generated. The RTs for the other intervals, however, were not significantly different from each other, revealing that there was no evidence of slowing across the groups as a whole as the interval increased in length. Moreover, the lack of an interaction between group and interval indicates that PD patients and controls were similar in their lack of significant slowing as delay increased.

Given that PD patients were slower than either control group, we also conducted this analysis using a change score reflecting the difference between overall unwarned RT and the warned RT at a given interval. This analysis controlled for both overall slowing in the PD group and potentially reduced any variability in the group means that was due to individual differences in overall RT. This change score was computed by subtracting the average mean RT for all unwarned intervals from the mean RT at a warned interval and dividing this value by the average mean RT for all unwarned intervals. This was done for each of the five warned intervals. As expected, change scores were always less than or equal to zero, indicating that change was always in the direction of an equal or decreased RT as a function of the WS. As with the data from the raw mean RTs, a 3 (group) × 5 (warned delay intervals) repeated measures ANOVA on the change scores did not show a significant interaction between group and delay length variables.

Although it would seem reasonable to conclude from these analyses that PD patients do not exhibit a significant deficit in maintaining readiness over long WS-IS delays, inspection of the individual data revealed a large amount of variability in the specific WS-IS interval that produced the fastest RT (optimal readiness effect), particularly in the PD group. Thus, the possibility remains that patients may have shown a decline in the ability to maintain their optimal level of readiness at the longest interval (18 s) that was obscured in the group data because this optimal time varied across subjects.

To address this possibility more directly, we computed the difference between change scores corresponding to each subject's fastest RT and their RT at the longest interval (18 s), the rationale being that this value would be smaller in subjects who were more effective in maintaining an optimal state of readiness irrespective

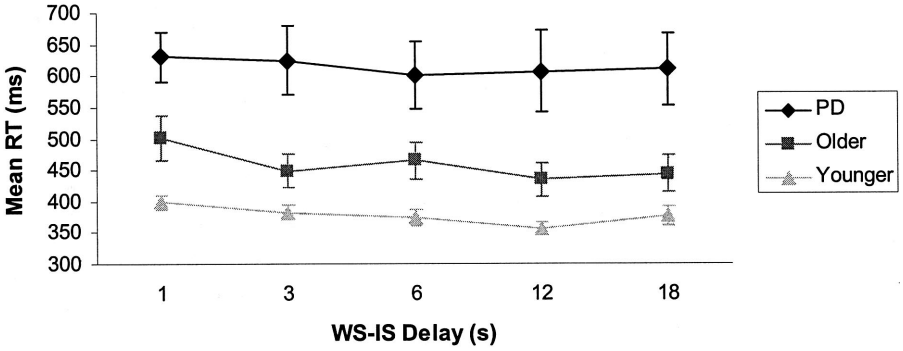

Figure 3. Mean reaction times (RTs) across warning stimulus–imperative stimulus (WS-IS) delays. Error bars represent standard error of the mean. PD = Parkinson's disease.

of when that level was initially obtained. A one-way ANOVA comparing difference scores of each group indicated no significant group differences, findings that are consistent with the above data, again suggesting no impairment in the maintenance of readiness specific to PD patients. Identical results were found when we computed the difference between change scores for each subject's RT at the 18-s interval and at the middle interval of 6 s.

Finally, to ensure that subjects were not explicitly timing the WS-IS delay intervals, we performed a 3 (group, PD vs. older control vs. younger control) × 2 (actual vs. expected RT for 9-s interval) repeated measures ANOVA on RT data obtained from the 9-s delay interval present in the last two blocks of the experiment. To determine the expected RT for the 9-s delay interval if subjects did not deviate from their overall pattern of responding, we created a trendline fitting the mean RT data for each subject between the 6- and 18-s delay intervals. Using the slope value of these trendlines, we were able to compute the expected RT for the 9-s delay interval and compare it to each subject's actual RT. We found no significant differences between expected and actual RTs for any of the groups, suggesting that subjects were not explicitly timing delay intervals.

Memory errors. As a whole, the PD patient group made 6.71% errors on warned trials, 1.84% errors on unwarned trials, and 0.26% errors on catch trials. In contrast, older controls made 1.5% errors on warned trials, 4.32% errors on unwarned trials, and no errors on catch trials. Younger controls made 2.76% errors on warned trials, 1.18% errors on unwarned trials, and 0.13% errors on catch trials. Note that trials in which subjects made memory errors were included in the RT analyses above, as the errors were made after subjects had responded.

A repeated measures 3 (group) × 5 (percentage of errors in the five warned delay intervals) ANOVA was conducted on only those memory errors for which subjects reported seeing an unwarned trial, although in fact they had received a warned trial (forgetting the WS). This type of error was not only the most abundant among PD patients but also indicates impairment in their ability to maintain information about the experimental stimuli in working memory. Errors were calculated as the percentage of memory errors made out of the total number of trials in which an error was possible. Significant effects of the warned delay interval, $F(4, 164) = 12.11$, $p < .001$, $\epsilon = .819$, and of group, $F(1, 41) = 3.45$, $p < .05$, were found, as can be seen in Figure 4. PD patients made significantly more memory errors than did older controls ($p < .05$) but not younger controls ($p = .13$), although older and younger controls did not differ significantly in percentage of memory errors ($p = .67$). All groups increased errors as the delay interval increased; however, a significant Memory Error × Group interaction emerged when PD patients and older controls were compared, $F(4, 88) = 3.07$, $p < .05$, $\epsilon = .567$, indicating that this increase was greater in PD patients than in their age-matched controls. Independent-samples t tests between groups for each warned interval (1, 3, 6, 12, and 18 s) further revealed that PD patients and older controls showed a significantly different percentage of memory errors only at the warned delay interval of 18 s, $t(22) = 2.41$, $p < .05$. Thus, although all groups exhibited some increase in memory errors as the WS-IS delay intervals increased, PD patients made significantly more errors than did older controls only at the longest delay interval.

Relationship between memory errors and readiness maintenance. To examine the relationship between memory errors and readiness maintenance, we analyzed whether the difference between the RT change score at the longest delay interval of 18 s and the optimal responding interval was correlated with the total number of memory errors for which subjects forgot the WS. We conducted a similar analysis using the difference in RT change scores between the 18-s and 6-s delay intervals. Separate correlations were calculated for each group.

Results indicated that within the PD patient group, the total amount of memory errors was highly correlated with the difference score between optimal responding and the 18-s delay interval (Spearman's $\rho = .86$, $p = .001$), as well as the difference score between the 6-s and 18-s intervals (Spearman's $\rho = .84$, $p < .005$). Thus, patients who showed the largest difference score (and thus the greatest amount of RT slowing) also showed the largest number of memory errors. As shown in Figure 5, these correlations remained highly significant even after the removal of an outlier subject who made an exceptionally large number of memory errors (Spearman's $\rho = .81$, $p < .01$, for optimal and 18-s intervals; Spearman's $\rho = .79$, $p = .01$, for 18- and 6-s intervals). No such correlation was found among the older or younger control groups. Additionally, no significant correlations were found between memory errors and mean, raw warned RTs or MTs or the change score for MT in the PD group. Thus, it is unlikely that the difference score and memory error relationship found in the PD group was due to overall slowing in movement execution. Rather, it appears that in PD patients, deficits in the ability to maintain response

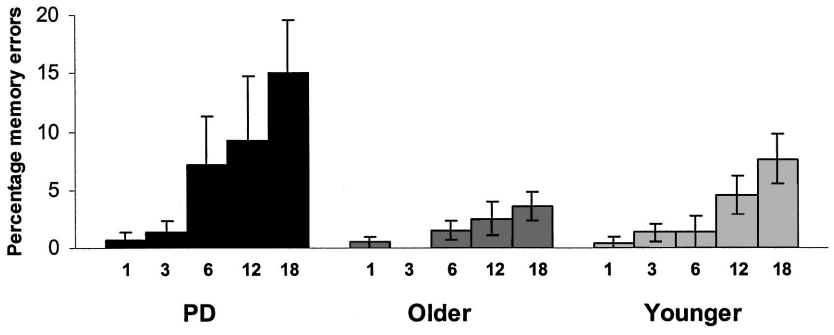

Figure 4. Percentage of memory errors in each warned delay interval. Error bars represent standard error of the mean. PD = Parkinson's disease.

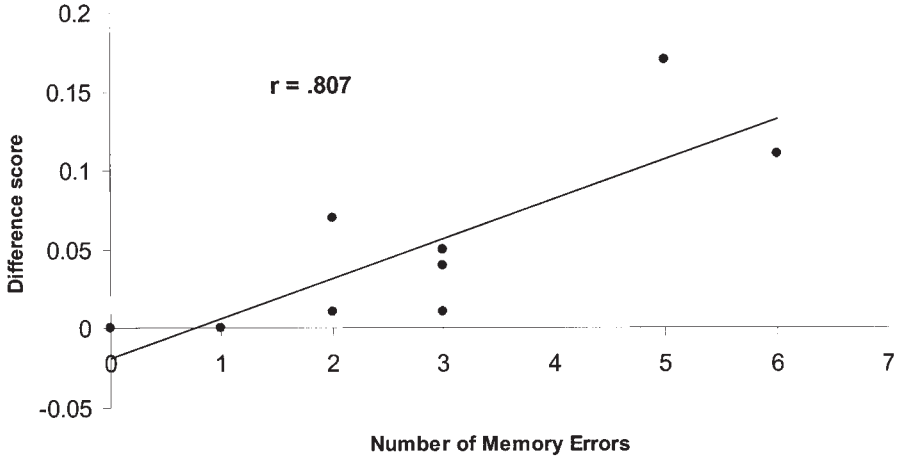

Figure 5. Correlation between memory errors and readiness maintenance in the Parkinson's disease group. The difference score represents the value for the change score at the optimal interval subtracted from the value of the change score at the 18-s interval. Data from an outlier subject with memory errors over two standard deviations from the mean are not shown.

readiness over long delay intervals may be partially understood in terms of their commensurate increase in memory errors.

Relationship between memory errors and other variables in PD patients. There were no significant correlations within the PD group between number of memory errors and any of the demographic or neuropsychological measures, except for rigidity. Specifically, we found a significant correlation between the rigidity subscores on the UPDRS and memory errors at the longest delay interval (18 s; Spearman's $\rho = .65$, $p = .042$). The correlation between rigidity subscores and total memory errors did not reach significance.

Block effects: Improvement and fatigue. To examine the effects of practice and fatigue on performance, we performed a 4 (block) $\times$ 2 (trial type, unwarned vs. warned) $\times$ 2 (group, PD vs. older control) ANOVA on mean RTs. Because of the need to exclude one block of trials for 3 older controls and 1 PD patient, this analysis was done with only 9 PD patients and 11 older controls. A main effect of trial type was found, $F(1, 18) = 62.54$, $p < .001$, whereas no main effect of block or interactions was found. However, when we limited our analysis to the first three blocks in order to include almost all subjects (9 PD patients and 14 older controls), a significant three-way interaction between block, trial type, and group emerged, $F(2, 42) = 3.18$, $p = .05$. Post hoc comparisons revealed that older controls showed a marginally significant decrease in RTs over the three blocks in the warned condition only, $F(2, 26) = 2.72$, $p = .09$, whereas the RTs of PD patients did not change significantly over the three blocks for either warned or unwarned conditions. Thus, it appears as though the RTs of PD patients and older controls did not change significantly over the course of the experiment in the unwarned trials, whereas the RTs of older controls decreased marginally as the experiment progressed through the three blocks, most likely because of practice. Although the effects of practice and fatigue are confounded in our task, these results suggest that fatigue over the course of the experiment did not significantly affect RT performance.

False alarms. Trials in which subjects lifted their finger off the middle response button either before the IS appeared (warned and unwarned trials) or before the end-of-trial signal appeared (catch trials) were counted as false alarms. For warned trials, we were particularly interested in false alarms in which subjects failed to inhibit a movement to the WS, perhaps suggesting a heightened level of stimulus and motor readiness. As expected, there was a main effect of trial type, $F(2, 82) = 41.89$, $p < .001$, indicating that the total percentage of false alarms was significantly higher for warned trials than for the other two trial types (5.7% for warned trials, 0.63% for unwarned trials, and 0.85% for catch trials, respectively). In addition, a significant effect of group was found, $F(2, 41) = 3.2$, $p = .05$, such that PD patients made fewer false alarms overall than did older or younger controls (1.05% for PD patients, 3.1% for older controls, and 3% for younger controls). Tukey's post hoc comparisons indicated a trend for PD patients to make fewer false alarms to warned trials than did older controls ($p = .06$) but not younger controls. These findings provide some limited support for the view that PD patients exhibited less overall task vigilance or readiness at the start of each trial.

Discussion

Results from our study were consistent with those found in previous studies comparing warned versus unwarned SRT task performance (Bloxham et al., 1987; Heilman et al., 1976; Jahanshahi et al., 1992). We found that PD patients responded more quickly overall on warned trials compared with unwarned trials, indicating that they can benefit from receiving advance information about an upcoming movement. Thus, our findings provide additional evidence that a state of response readiness can be generated even when nigrostriatal DA function has been compromised.

A second question was whether PD patients could effectively maintain this state over sustained delay periods. Prefrontal DA promotes the maintenance of delay-period activity of working

memory-related frontal neurons (Durstewitz et al., 2000; Goldman-Rakic, 1990, 1995; Romanides et al., 1999); further, ventral–striatal DA critically mediates the maintenance of overt motor acts (Aberman et al., 1998). We therefore predicted that maintenance of an anticipatory state of readiness would be compromised in PD patients. However, there was no evidence to suggest that the PD group as a whole experienced greater difficulty in maintaining readiness over long delays, although PD patients did demonstrate significantly slower MTs when compared with control subjects, indicating the presence of a central motor dysfunction. Although a failure to find group differences in the mean data could have been influenced by differences in the delay interval at which each subject exhibited their fastest mean RT (optimal performance), a significant interaction also failed to emerge when we defined readiness maintenance as a difference score between RT at their longest delay and RT at their optimal level of readiness.

It is interesting, however, that among PD patients this measure of readiness maintenance was positively correlated with the number of memory errors. Thus, those patients with larger difference scores, indicative of greater difficulty maintaining optimal readiness, also showed the greatest number of errors in explicitly remembering which stimuli were presented during the warned trial. Working memory was not correlated with raw RT or MT scores or change MT scores in PD patients, indicating that those patients who made more memory errors did not also have slower response initiation and execution times. The fact that we did not find this change RT–memory error correlation among older or younger control subjects suggests that this relationship was specific to PD patients. It is possible, however, that if our study had included a more difficult working memory task with a larger range of memory errors, a correlation between memory errors and readiness maintenance would have emerged for controls as well. Although the relationship between maintenance of readiness and working memory may be causal, the direction of causality cannot be ascertained from these data alone. Specifically, it is not possible to determine whether patients exhibited RT slowing because they forgot they had seen a WS and thus made an error on the memory trials, or whether they used feedback from their own RTs to aid judgment of trial type (i.e., associating relatively longer RTs with unwarned trials).

A noncausal explanation of this correlation is supported by theoretical suggestions of a dissociation between cognitive and motor symptoms in PD on the basis of their respective reliance on prefrontal and motor corticostriatal basal ganglia loops (Brown & Marsden, 1990; Cummings, 1993; Saint-Cyr, 2003). Memory impairment may not be directly causing RT slowing; rather, this relationship may result from dysfunction in a specific basal ganglia circuit that impacts both processes or from dysfunction in separate circuits similarly affected by PD. Considering the abundant evidence suggesting that both maintenance and manipulation of information in working memory functions are dependent on prefrontal regions (Baddeley, 1992; Goldman-Rakic, 1990, 1995; Romanides et al., 1999; Smith & Jonides, 1997), basal ganglia loop activity originating in the prefrontal cortex may mediate accurate performance on the working memory maintenance component of the trial, whereas maintenance of readiness before a response may depend on activity within basal ganglia circuits originating in (more posterior) frontal regions associated more directly with motor functions.

It is possible that mesocortical DA loss may contribute to some of the motor and/or memory deficits observed in the present study. Although PD results primarily from nigrostriatal DA loss, mesocortical DA depletion often occurs in advanced PD at levels beyond those observed in age-matched controls (Scatton, Javoy-Agid, Rouquier, Dubois, & Agid, 1983). Yet, there is evidence to suggest that L-dopa administration in patients with moderate to severe PD largely restores DA levels in the cerebral cortex comparable to those of age-matched controls (Scatton et al., 1983), while failing to restore normal DA functioning in the striatum (Antonini, Schwarz, Oertel, Pogarell, & Leenders, 1997; Torstenson, Hartvig, Langstrom, Westerberg, & Tedroff, 1997). The fact that all of our PD patients were tested while taking L-dopa necessitates caution when considering the role of striatal DA in these processes; however, support for the view that this pathway remained impaired in patients despite their being tested while taking L-dopa comes from evidence of their significantly slower RTs and MTs in all conditions. Further, patients taking DA agonists in addition to L-dopa did not show any significant differences from those taking L-dopa alone, again suggesting that the medication was not able to fully compensate for disease progression.

One might additionally consider the possibility that working memory deficits observed in PD patients result from dysfunction in other neurotransmitter systems, specifically the cholinergic system, which has been implicated in cognitive impairment and dementia in PD and Alzheimer's disease patients (Minger et al., 2002; Picciotto & Zoli, 2002). However, impairment is often observed in patients on anticholinergic medications or in patients with incident dementia. Jellinger (1991) reported that whereas acetylcholine depletion is often high in PD patients with dementia, PD patients without dementia show values only marginally different from those of age-matched controls. Although the influence of cholinergic impairment on working memory performance of our patients cannot be conclusively ruled out, our study excluded patients taking anticholinergic medication or exhibiting dementia. Thus, we think it is likely that the observed deficits reflect dysfunction in striatal DA transmission and consequent dysregulation of activity through corticostriatal basal ganglia loops. Results from a study by Levy et al. (2000) looking at UPDRS scores of PD patients with and without dementia while they were on and off L-dopa suggest that, whereas tremor and rigidity are dependent on DA transmission, signs of axial impairment (gait and postural instability) and bradykinesia are not dependent on DA. The significant correlation between memory errors at the 18-s delay interval and rigidity scores further supports the idea that performance on the working memory portion of our experiment was DA dependent.

It is curious that we did not find a correlation between performance on Forward or Backward Digit Span tasks and either the memory maintenance or readiness maintenance components of our experiment. One possibility is that a correlation between readiness and cognitive maintenance emerged in the context of our experimental task because of dual-task requirements. Although it seems likely that maintaining trial type information and maintaining readiness would be processes that complement each other, perhaps even facilitating performance, it is also possible that these two tasks compete for processing resources. There has been much evidence to suggest that PD patients are more impaired relative to controls when engaging in more than one cognitive or motor task

(Brown & Marsden, 1991; Marchese, Bove, & Abbruzzese, 2003). Dubois, Boller, Pillon, and Agid (1991) suggested that PD patients are not impaired on regular Digit Span tasks but show impairments with the addition of interfering stimuli. Recently, Saint-Cyr (2003) proposed that the corticostriatal basal ganglia loops, originally thought to be segregated, parallel circuits (Alexander & Crutcher, 1990), are actually anatomically integrated to a degree. This would imply that concurrent activity in different basal ganglia loops may cause interference that could result in an impairment in performance on tasks that use both of these circuits. Thus, although Digit Span performance would probably not engage both prefrontal and motor loops, the dual maintenance requirements of our experiment may have resulted in interference between these circuits and a mutual decrement in performance.

Not all PD patients exhibit the same symptoms and clinical progression of the disease. Indeed, many authors have attempted to differentiate subsets of PD by various factors such as disease course (rapid or slow), age of onset, predominant type of motor symptoms, L-dopa responsiveness, and the presence of cognitive dysfunction (Benecke, 2002; Foltynie, Brayne, & Barker, 2002; Gasparoli et al., 2002; Green et al., 2002). Green et al. found that only 67% of the PD patients they tested were impaired on the Wisconsin Card Sorting Task (Heaton, Chelune, Talley, Kay, & Curtis, 1993), a standard neuropsychological test of frontal lobe function, and even fewer patients were found to be impaired on other tests of cognitive function. This fact is underscored by our findings, which suggest that only a subset of our PD patient group exhibited a significant deficit in readiness maintenance.

In conclusion, PD patients in our study exhibited significant and characteristic slowing of MTs and RTs, yet they appeared unimpaired in their ability to use a WS to generate a state of readiness, as evidenced by decreased RTs in warned compared with unwarned conditions. Further, the PD group overall did not show difficulty maintaining this state of readiness; however, there was a correlation between memory errors and RT slowing over the longer WS-IS delays. This indicates that those patients who had greater difficulty maintaining visual information in working memory also had greater difficulty maintaining an anticipatory state of readiness before a response. The variability in performance found in our group may be used to shed light on inconsistencies already present in the literature.

It is less clear whether the impairments we found in the PD group are attributable to varying levels of DA depletion in patients. Studies showing the involvement of DA in maintaining delay-period activity (Durstewitz et al., 2000; Goldman-Rakic, 1990, 1995; Romanides et al., 1999) make it an appropriate candidate as the neurotransmitter system underlying maintenance of task-relevant visual information as well as motor and cognitive readiness. In addition, even though all of our patients were on L-dopa, it has been suggested that such treatment does not fully restore DA levels in the striatum (Antonini et al., 1997). That all of our patients were significantly impaired in motor functions despite L-dopa treatment is further support for the idea that DA dysfunction in the striatum remains considerable even after L-dopa treatment. However, it is still possible that a portion of cognitive deficits seen in the PD group may result from additional dysfunction in serotonergic, noradrenergic, and/or cholinergic systems, which is more likely to occur in more advanced PD. Our use of stringent exclusion criteria, including restricting our sample of patients to those who did not have dementia or depression and were not taking anticholinergic medication, increases the likelihood that the majority of impairments found were due to dysfunction in the DA system. Additional studies examining these issues with a larger sample of patients that compare performance on and off L-dopa may help to further clarify these issues.

References

Aberman, J. E., Ward, S. J., & Salamone, J. D. (1998). Effects of dopamine antagonists and accumbens dopamine depletions on time-constrained progressive-ratio performance. *Pharmacology, Biochemistry, and Behavior, 61,* 341–348.

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

Antonini, A., Schwarz, J., Oertel, W. H., Pogarell, O., & Leenders, K. L. (1997). Long-term changes of striatal dopamine D2 receptors in patients with Parkinson's disease: A study with positron emission tomography and [11C]raclopride. *Movement Disorders, 21,* 33–38.

Baddeley, A. (1992, January 31). Working memory. *Science, 255,* 556–559.

Bares, M., & Rektor, I. (2001). Basal ganglia involvement in sensory and cognitive processing: A depth electrode CNV study in human subjects. *Clinical Neurophysiology, 112,* 2022–2030.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for Beck Depression Inventory—II.* San Antonio, TX: Psychological Corporation.

Benecke, R. (2002). Clinical features and laboratory findings for differentiating Parkinsonian symptoms. *Journal of Neurology, 249*(Suppl. 3), 6–14.

Bloxham, C. A., Dick, D. J., & Moore, M. (1987). Reaction times and attention in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 50,* 1178–1183.

Bradley, V. A., Welch, J. L., & Dick, D. J. (1989). Visuospatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 52,* 1228–1235.

Braver, T. S., Barch, D. M., Keys, B. A., Carter, C. S., Cohen, J. D., Kaye, J. A., et al. (2001). Context processing in older adults: Evidence for a theory relating cognitive control to neurobiology in healthy aging. *Journal of Experimental Psychology: General, 130,* 746–763.

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

Brown, R. G., & Marsden, C. D. (1991). Dual task performance and processing resources in normal subjects and patients with Parkinson's disease. *Brain, 114,* 215–231.

Brunia, C. H. M. (1993). Waiting in readiness: Gating in attention and motor preparation. *Psychophysiology, 30,* 327–339.

Brunia, C. H. M., & van Boxtel, G. J. M. (2001). Wait and see. *International Journal of Psychophysiology, 43,* 59–75.

Castner, S. A., Williams, G. V., & Goldman-Rakic, P. S. (2000, March 17). Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. *Science, 287,* 2020–2022.

Cools, R., Stefanova, E., Barker, R. A., Robbins, T. W., & Owen, A. M. (2002). Dopaminergic modulation of high-level cognition in Parkinson's disease: The role of the prefrontal cortex revealed by PET. *Brain, 125,* 584–594.

Cordes, M., Snow, B. J., Cooper, S., Schulzer, M., Pate, B. D., Ruth, T. J., & Calne, D. B. (1994). Age-dependent decline of nigrostriatal dopaminergic function: A positron emission tomographic study of grandparents and their grandchildren. *Annals of Neurology, 36,* 667–670.

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology, 50,* 873–880.

Dalrymple-Alford, J. C., Kalders, A. S., Jones, R. D., & Watson, R. W. (1994). A central executive deficit in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 57,* 360–367.

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). Amsterdam: Elsevier.

Dubois, B., & Pillon, B. (1997). Cognitive deficits in Parkinson's disease. *Journal of Neurology, 244,* 2–8.

Durstewitz, D., Seamans, J. K., & Sejnowski, T. J. (2000). Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. *Journal of Neurophysiology, 83,* 1733–1750.

Fahn, S., Elton, R. L., and Members of the UPDRS Committee. (1987). Unified Parkinson's disease rating scale. In S. Fahn, C. D. Marsden, M. Goldstein, & D. M. Calne (Eds.), *Recent developments in Parkinson's disease and Appendices I and II* (pp. 153–163). New York: Macmillan.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12,* 189–198.

Foltynie, T., Brayne, C., & Barker, R. A. (2002). The heterogeneity of idiopathic Parkinson's disease. *Journal of Neurology, 249,* 138–145.

Frith, C. D., & Done, D. J. (1986). Routes to action in reaction time tasks. *Psychological Research, 48,* 169–177.

Gasparoli, E., Delibori, D., Polesello, G., Santelli, K., Ermani, M., Battistin, L., & Bracco, F. (2002). Clinical predictors in Parkinson's disease. *Neurological Sciences, 23,* S77–S78.

Gibbon, J., Malapani, C., Dale, C. L., & Gallistel, C. R. (1997). Toward a neurobiology of temporal cognition: Advances and challenges. *Current Opinions in Neurobiology, 7,* 170–184.

Goldman, W. P., Batsy, J. D., Buckles, V. D., Sahrmann, S., & Morris, J. C. (1998). Cognitive and motor functioning in Parkinson's disease: Subjects with and without questionable dementia. *Archives of Neurology, 55,* 674–680.

Goldman-Rakic, P. S. (1990). Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates. *Progress in Brain Research, 85,* 325–335.

Goldman-Rakic, P. S. (1995). Cellular basis of working memory. *Neuron, 14*, 477–485.

Goodrich, S., Henderson, L., & Kennard, C. (1989). On the existence of an attention-demanding process peculiar to reaction time: Converging evidence from Parkinson's disease. *Cognitive Neuropsychology, 6,* 309–331.

Grady, C. L. (2000). Functional brain imaging and age-related changes in cognition. *Biological Psychology, 54,* 259–281.

Green, J., McDonald, W. M., Vitek, J. L., Evatt, M., Freeman, A., Haber, M., et al. (2002). Cognitive impairments in advanced PD without dementia. *Neurology, 59,* 1320–1324.

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. C., & Curtis, G. (1993). *Wisconsin Card Sorting Test manual: Revised and expanded.* Odessa, FL: Psychological Assessment Resources.

Heilman, K. M., Bowers, D., Watson, R. T., & Greer, M. (1976). Reaction times in Parkinson's disease. *Archives of Neurology, 33,* 139–140.

Henze, D. A., Gonzalez-Burgos, G. R., Urban, N. N., Lewis, D. A., & Barrionuevo, G. (2000). Dopamine increases excitability of pyramidal neurons in primate prefrontal cortex. *Journal of Neurophysiology, 84,* 2799–2809.

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

Hornykiewicz, O. (1979). Brain dopamine in Parkinson's disease and other neurological disturbances. In A. S. Horn, J. Korf, & B. H. C. Westerning (Eds.), *The neurobiology of dopamine* (pp. 633–654). London: Academic Press.

Horvitz, J. C. (2002). Dopamine gating of glutamatergic sensorimotor and incentive motivational input signals to the striatum. *Behavioural Brain Research, 137,* 65–74.

Jahanshahi, M., Brown, R. G., & Marsden, C. D. (1992). Simple and choice reaction time and the use of advance information for motor preparation in Parkinson's disease. *Brain, 115,* 539–564.

Javoy-Agid, F., & Agid, F. (1980). Is the mesocortical dopaminergic system involved in Parkinson's disease? *Neurology, 30,* 1326–1330.

Jellinger, K. A. (1991). Pathology of Parkinson's disease. *Molecular and Chemical Neuropathology, 14,* 153–197.

Kimura, M. (1990). Behaviorally contingent property of movement-related activity in the primate putamen. *Journal of Neurophysiology, 63,* 1277–1296.

Krebs, H. I., Hogan, N., Hening, W., Adamovich, S. V., & Poizner, H. (2001). Procedural motor learning in Parkinson's disease. *Experimental Brain Research, 141,* 425–437.

Kulisevsky, J., Garcia-Sanchez, C., Berthier, M. L., Barbanoj, M., Pascual-Sedano, B., Gironell, A., & Estevez-Gonzalez, A. (2000). Chronic effects of dopaminergic replacement on cognitive function in Parkinson's disease: A two-year follow-up study of previously untreated patients. *Movement Disorders, 15,* 613–626.

Labutta, R. J., Miles, R. B., Sanes, J. N., & Hallett, M. (1994). Motor program memory storage in Parkinson's disease patients tested with a delayed response task. *Movement Disorders, 9,* 218–222.

Levy, G., Tang, M.-X., Cote, L. J., Louis, E. D., Alfaro, B., Mejia, H., et al. (2000). Motor impairment in PD. Relationship to incident dementia and age. *Neurology, 55,* 539–544.

Marchese, R., Bove, M., & Abbruzzese, G. (2003). Effect of cognitive and motor tasks on postural stability in Parkinson's disease: A posturographic study. *Movement Disorders, 18,* 652–658.

Mattay, V. S., Tessitore, A., Callicott, J. H., Bertolino, A., Goldberg, T. E., Chase, T. N., et al. (2002). Dopaminergic modulation of cortical function in patients with Parkinson's disease. *Annals of Neurology, 51,* 156–164.

McFadden, L., Mohr, E., Sampson, M., Mendis, T., & Grimes, J. D. (1996). A profile analysis of demented and nondemented Parkinson's disease patients. *Advances in Neurology, 69,* 339–341.

Minger, S. L., Esiri, M. M., McDonald, B., Keene, J., Carter, J., Hope, T., & Francis, P. T. (2002). Cholinergic deficits contribute to behavioral disturbances in patients with dementia. *Neurology, 55,* 1460–1467.

Niemi, P., & Naatanen, R. (1981). Foreperiod and simple reaction time. *Psychological Bulletin, 89,* 133–162.

Oishi, M., Mochizuki, Y., Du, C., & Takasu, T. (1995). Contingent negative variation and movement-related cortical potentials in Parkinsonism. *Electroencephalography and Clinical Neurophysiology, 95,* 346–349.

Picciotto, M. R., & Zoli, M. (2002). Nicotinic receptors in aging and dementia. *Journal of Neurobiology, 53,* 641–655.

Praamstra, P., Meyer, A. S., Cools, A. R., Horstink, M. W., & Stegeman, D. F. (1996). Movement preparation in Parkinson's disease. Time course and distribution of movement-related potentials in a movement precueing task. *Brain, 119,* 1689–1704.

Pullman, S. L., Watts, R. L., Juncos, J. L., Chase, T. N., & Sanes, J. N. (1988). Dopaminergic effects on simple and choice reaction time performance in Parkinson's disease. *Neurology, 38,* 249–254.

Reeves, S., Bench, C., & Howard, R. (2002). Ageing and the nigrostriatal dopaminergic system. *International Journal of Geriatric Psychiatry, 17,* 359–370.

Rehman, H. U., & Masson, E. A. (2001). Neuroendocrinology of ageing. *Age and Ageing, 30,* 279–287.

Rektor, I., Bares, M., & Kubova, D. (2001). Movement-related potentials in the basal ganglia: A SEEG readiness potential study. *Clinical Neurophysiology, 112,* 2146–2153.

Robertson, I. H., Ward, T., Ridgeray, V., & Nimmo-Smith, I. (1994). *The Test of Everyday Attention.* Bury St. Edmunds, England: Thames Valley Test Company.

Romanides, A. J., Duffy, P., & Kalivas, P. W. (1999). Glutamatergic and dopaminergic afferents to the prefrontal cortex regulate spatial working memory in rats. *Neuroscience, 92,* 97–106.

Saint-Cyr, J. A. (2003). Frontal-striatal circuit functions: Context, sequence, and consequence. *Journal of the International Neuropsychological Society, 9,* 103–127.

Sawaguchi, T. (2001). The role of D1-dopamine receptors in working memory-guided movements mediated by frontal cortical areas. *Parkinsonism and Related Disorders, 7,* 9–19.

Sawaguchi, T., & Goldman-Rakic, P. S. (1991, February 22). D1 dopamine receptors in prefrontal cortex: Involvement in working memory. *Science, 251,* 947–950.

Scatton, B., Javoy-Agid, F., Rouquier, L., Dubois, B., & Agid, Y. (1983). Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. *Brain Research, 275,* 321–328.

Schultz, W., & Romo, R. (1988). Neuronal activity in the monkey striatum during the initiation of movements. *Experimental Brain Research, 71,* 431–436.

Sheridan, M. R., Flowers, K. A., & Hurrell, J. (1987). Programming and execution of movement in Parkinson's disease. *Brain, 110,* 1247–1271.

Smith, E. E., & Jonides, J. (1997). Working memory: A view from neuroimaging. *Cognitive Psychology, 33,* 5–42.

Stern, Y., Sano, M., Paulson, J., & Mayeux, R. (1982). Modified Mini-Mental State Examination: Validity and reliability. *Neurology, 37*(Suppl. 1), 179.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1986). Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. *Brain, 109,* 845–883.

Torstenson, R., Hartvig, P., Langstrom, B., Westerberg, G., & Tedroff, J. (1997). Differential effects of levodopa and dopaminergic function in early and advanced Parkinson's disease. *Annals of Neurology, 41,* 334–340.

Uekermann, J., Daum, I., Peters, S., Wiebel, B., Przuntek, H., & Muller, T. (2003). Depressed mood and executive dysfunction in early Parkinson's disease. *Acta Neurologica Scandinavica, 107,* 341–348.

Wascher, E., Verleger, R., Vieregge, P., Jaskowski, P., Koch, S., & Kompf, D. (1997). Responses to cued signals in Parkinson's disease. Distinguishing between disorders of cognition and of activation. *Brain, 120,* 1355–1375.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale—III.* San Antonio, TX: Psychological Corporation.

Woods, S. P., & Troster, A. L. (2003). Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease. *Journal of the International Neuropsychological Society, 9,* 17–24.

Received March 4, 2003
Revision received October 21, 2003
Accepted February 3, 2004 ■