Response slowing in Parkinson’s disease
A psychophysiological analysis of premotor and motor processes

Kathy A. Low, Jeff Miller and Esther Vierck

1University of Illinois, Urbana, IL, USA and 2University of Otago, Dunedin, New Zealand

Correspondence to: Kathy Low, Beckman Institute, University of Illinois, Urbana, IL 61821, USA; or Jeff Miller, Department of Psychology, University of Otago, Dunedin, New Zealand
E-mail: lowka@uiuc.edu or miller@otago.ac.nz

Summary
The mechanisms responsible for reaction time slowing in Parkinson’s disease were investigated using movement-related potentials in a choice reaction time task. Parkinson’s disease patients and control subjects were required to respond with the left or right hand to indicate whether a visual stimulus was relatively large or small. The difficulty of the size discrimination was manipulated, as was the complexity of the manual response (single key press versus sequence of three key presses). Behavioural responses of Parkinson’s disease patients were slower than those of control subjects, especially when complex responses were required. Moreover, the timing of movement-related potentials indicated that motor processes clearly required extra time, relative to control subjects, for Parkinson’s disease patients making complex responses. In addition, delayed onset of the movement-related potentials indicated that one or more premotor processes are also slowed in these patients.

Keywords: Parkinson’s disease; lateralized readiness potential; response slowing; stimulus discrimination; sequential movement

Abbreviations: ERP = event-related potential; LRP = lateralized readiness potential; MT = movement time; R-LRP = response-locked lateralized readiness potential; RT = reaction time; S-LRP = stimulus-locked lateralized readiness potential

Introduction
Across a wide variety of experimental paradigms, people with Parkinson’s disease tend to have slower reactions compared with healthy adults of a similar age (e.g. Rafal et al., 1987; Brown and Marsden, 1988; Daum and Quinn, 1991; Wascher et al., 1997). Within an information processing framework, the slowing associated with Parkinson’s disease is usually conceptualized in terms of the processing stages that must occur between the time a stimulus is presented and the subsequent response is performed. For example, a choice reaction time task might include identifying and evaluating the stimulus, selecting the appropriate response, and programming and executing the movement. Thus, when Parkinson’s disease patients are slower to respond, any one or all of these stages may be contributing to the delayed reaction time (RT).

The processing stages related to motor function are perhaps the most obvious stages in which to expect some degree of slowing in Parkinson’s disease. After all, impaired motor activity is a defining feature of the disease. Even in tasks with minimal perceptual and decision requirements (e.g. simple RT task), Parkinson’s disease patients tend to have slower reactions than control subjects (Heilman et al., 1976; Evarts et al., 1981; Bloxham et al., 1987). In addition, Parkinson’s disease patients are especially slow and inaccurate at executing more complex movements (e.g. simultaneous or sequential movements), which presumably pose greater demands on motor processing compared with single element movements (Benecke et al., 1987; Agostino et al., 1992; Martin et al., 1994; Low, 1999). There is also evidence from transcranial magnetic stimulation studies to suggest that, in Parkinson’s disease, a longer time is needed for the motor
Response slowing in Parkinson’s disease

Parkinson’s disease patients show a selective deficit in preparation of a to-be-executed response—a hypothesis suggested among other things by evidence that Parkinson’s disease patients are usually slowed more in simple RT tasks than in choice RT tasks (Praamstra et al., 1996). To elucidate the hypothesized preparation deficit using the LRP, Praamstra and colleagues studied the development of motor potentials during a 1 s interval following a cue that indicated which hand would be required to make a subsequent speeded response. Somewhat surprisingly, they found only minor differences between the preparatory motor potentials of patients and controls, and they concluded that Parkinson’s disease patients are indeed able to prepare responses if sufficient time is allowed for that preparation (cf., Stelmach et al., 1986). Secondly, Wascher and colleagues also used a variety of psychophysiological measures, including the LRP and response force, to check for abnormal motor preparation in Parkinson’s disease patients (Wascher et al., 1997). In one experiment, the to-be-prepared response was required at unpredictable times, and in a second experiment the to-be-prepared response was required with varying probabilities. They also found comparable preparatory LRPs for Parkinson’s disease patients and control subjects, supporting the idea of reasonably normal response preparation in Parkinson’s disease. Thirdly, Praamstra and colleagues used the LRP to check for another type of abnormality in response preparation (Praamstra et al., 1998). Specifically, they examined the automatic build-up of response activation resulting from response-related but irrelevant distractor stimuli in a version of the flankers task (Eriksen and Eriksen, 1974). They found Parkinson’s disease patients more susceptible than control subjects to motor influences of the distractors, which they interpreted as evidence of greater reliance on external response cues in Parkinson’s disease.

The present study also investigated motor preparation in Parkinson’s disease using the LRP, but we used a different technique—described below—that allows the RT interval to be partitioned into premotor and motor components. That is, rather than assessing preparation in advance of stimulus onset, like Praamstra and colleagues (Praamstra et al., 1996) and Wascher and colleagues (Wascher et al., 1997), we used the LRP to monitor response preparation during the crucial interval between the onset of a reaction stimulus and the speeded response. This is precisely the interval often observed to be prolonged in Parkinson’s disease. In particular, we sought to isolate the interval consumed by motor processes so that we could establish their duration and study the motor delays thought to be characteristic of Parkinson’s disease. In addition to measuring the interval consumed by motor processes, this technique also allows measurement of the interval consumed by premotor processes, including sensory registration, perceptual discrimination and response selection. Thus, this study was designed to assess both premotor (cognitive) and motor contributions to the response slowing observed in Parkinson’s disease.

To partition the RT interval and thereby estimate the durations of the motor and premotor components, researchers have used the procedure of time-locking the LRP to two different events, the onset of the stimulus and the onset of the response (e.g. Miller and Ulrich, 1998). When the LRP is aligned with respect to the moment of stimulus onset (stimulus-locked LRP or S-LRP), the interval between stimulus onset and LRP onset can be used as an estimate of the duration of premotor processes (i.e. cognitive processes which occur prior to the activation of the motor system). In contrast, when the LRP is aligned with respect to the moment
of the behavioural response (response-locked LRP or R-LRP), the interval from the onset of the LRP to the onset of the response can be used to estimate the duration of motor processes (Smulders et al., 1995; Leuthold et al., 1996; Miller and Ulrich, 1998). Thus, the S-LRP latencies and R-LRP latencies observed in a speeded RT task can be used to assess the separate contributions of premotor versus motor processes to the overall RTs. Then, by comparing the onset latency of the S-LRP for Parkinson’s disease patients versus control subjects, we can assess group differences in the durations of premotor processes. Analogously, by comparing the onset latencies of the R-LRPs, we can assess group differences in the durations of motor processes.

One virtue of this partitioning method is that R-LRP onset latency includes the time needed for fairly central motor processes. In contrast, partitioning the RT interval with respect to EMG onset (e.g. Praamstra processes. In contrast, partitioning the RT interval with respect to EMG onset (e.g. Praamstra et al., 1996) limits the estimate of motor time to only the relatively peripheral motor processes following the moment of EMG onset.

A second virtue of this partitioning method is its generality. Separate time-locking of EEG to stimuli and responses can be used in almost any task with an overt response to a presented stimulus. The present study, for example, used a choice RT paradigm in which participants were asked to respond with either the right or the left hand depending on the size of a visual stimulus. Of course, the durations of both motor and premotor processes must depend on the task requirements, and so too may the group differences (cf., Brown et al., 1993b). In particular, group differences may be especially pronounced when the stages affected by Parkinson’s disease are challenged by difficult processing requirements. Moreover, the effects of different types of task difficulty manipulations (e.g. perceptual, motor) can be used to help isolate the processing stages responsible for slowing in Parkinson’s disease (e.g. Stelmach et al., 1989).

We varied the difficulty of the task in two ways in order to explore the generality of the results, to help identify the processes responsible for slowing and to maximize the chances of finding group differences. First, in an effort to challenge a premotor processing stage, we manipulated the difficulty of the size discrimination (e.g. Sternberg, 1969; Sanders, 1980). Secondly, to challenge the motor processing stage, we manipulated the difficulty of the response (e.g. Sanders, 1980; Rosenbaum et al., 1984). We chose to manipulate these two particular factors because of their selective effects on the S- and R-LRP latencies. In healthy young adults, increasing the difficulty level of either the discrimination or the response tends to result in slower responses. Moreover, manipulations of stimulus discriminability affect the latency of the S-LRP, but have no influence on the R-LRP. This is consistent with the notion that harder discriminations require more time for cognitive operations, such as stimulus evaluation, but do not affect later motor processing (Osman et al., 1992; Smulders et al., 1995). In contrast, manipulations of response complexity affect the timing of the R-LRP but not the S-LRP, suggesting that more complex reactions require more time for motor processing without affecting the duration of earlier cognitive operations. By including manipulations that are known to challenge premotor and motor processes independently in healthy adults, we can determine whether Parkinson’s disease patients show a qualitatively similar pattern of results as task difficulty increases, and whether these patients have any selective deficits in either discrimination or response processes.

In sum, the LRP can be useful in the study of Parkinson’s disease because it can be used to separate the premotor and motor components comprising the RT interval. By including this measure along with more traditional measures (i.e. P300, EMG, RT and movement time), we can more directly assess how much of the RT slowing typically seen in Parkinson’s disease patients is due to cognitive deficits arising before the motor system has been engaged and how much is due to subsequent motor deficits.

Methods
Participants
Twelve patients with mild Parkinson’s disease (six females and six males) and 12 healthy control subjects (seven females and five males) participated in this study. Participants were recruited through a local Parkinson’s disease support group and from the general community. The average age of the patients was 66.5 years (range 55–76 years) while the average age of the control group was 64.8 years (range 58–74 years). All were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Neither group demonstrated signs of dementia or depression; scores on both the Geriatric Depression Inventory Short Form (Sheikh and Yesavage, 1986) and the Mini-Mental State Examination (Folstein et al., 1975) were within the normal range for all participants. Control participants had no known neurological disorders and had not been prescribed any neurological medications.

All the patients were under their normal medication routine at the time of testing. Seven of the patients were taking levodopa as their only form of parkinsonian therapy. Three others were taking some combination of levodopa plus selegiline and bromocriptine, or amantadine. One patient was on selegiline and bromocriptine, and one other patient was tested prior to being placed on any parkinsonian medication. The motor subscale of the Unified Parkinson’s Disease Rating Scale (Lang and Fahn, 1989) was used to measure the level of motor impairment on the day of testing. Scores ranged from 4 to 19 with a mean of 11 (postural instability was not assessed). This research was approved by the Human Ethics Committee of the University of Otago, New Zealand, and all participants provided written informed consent in accordance with the Declaration of Helsinki.
Apparatus and stimuli
Subjects were seated ~60 cm from the display monitor in a dimly lit room. The stimulus set consisted of four squares varying in size. The squares were white outline images on a black background and were presented at fixation with the visual angle of one side measuring ~0.85°, 0.96°, 1.2° or 1.6°. Responses consisted of either a single key press (simple response) or a three-finger key press sequence (complex response). For complex responses, subjects were required to press with the index, ring and middle fingers, in that order, using the c, z and x keys of a standard computer keyboard for left-hand responses and the comma, slash and period keys for right-hand responses. For simple responses, only the index finger of each hand was used to press either the c or the comma key. Feedback was provided following incorrect responses and consisted of a visual presentation of the word ‘wrong’ in the centre of the screen and ~3 cm below fixation. Stimulus presentation and recording of behavioural and electrophysiological responses were controlled by an IBM-PC compatible microcomputer (PC General Corp., Dunedin, NZ).

Procedure
On each trial, a fixation cross was presented for 500 ms followed by a blank period of 700 ms before the appearance of one of the four squares. The reaction stimulus remained on the screen until a response was made or 3000 ms had elapsed, whichever came first. The four square sizes were presented randomly and with equal probability. Following trials with an incorrect first key press, the word ‘wrong’ would appear for 2 s. There was ~2.5 s between the response and the onset of the next stimulus.

Prior to the experimental blocks, participants were first shown the complete stimulus set of four different sizes of squares, which were referred to as extra-small, small, large and extra-large. Subjects were then told to try to remember the stimulus set because only one of the four squares would appear on a given trial. The task was to determine whether the presented square was relatively small or relatively large (i.e. one of the smaller two versus one of the larger two) and to indicate this decision by making a right- or left-hand response, respectively (counterbalanced across subjects). Clearly, however, the ease of identifying whether a given square was large or small depended on its particular size. The extra-small and extra-large squares were ‘easy’ to identify as small and large (respectively), whereas the two intermediate sized squares were ‘hard’ to classify as small or large.

After familiarizing themselves with the stimulus set, participants were given at least one 20-trial block of practice with both the simple and complex response requirements. All but two of the Parkinson’s disease patients required additional training on the complex response. Our procedure was to allow these individuals as many repetitions of the complex response sequence as necessary to feel comfortable with the order of the finger movements. This additional practice was performed in a self-paced fashion (i.e. without the reaction signals), but once comfortable, these individuals were given an additional block of practice with complex responding to the reaction signals. This was because performing this response under the moderate constraints of the timed reaction task (i.e. a reaction had to be made within 3000 ms or an error message would appear) sometimes posed additional difficulties.

Following the practice blocks, each subject performed 16 experimental blocks. Both speed and accuracy were emphasized, with subjects asked to respond as quickly as possible without making too many mistakes. The type of response (simple versus complex) alternated across the blocks, but remained consistent within a given block. Half of the subjects started with a simple response block, and the other half started with a complex response block. Each block consisted of 40 trials for a total of 320 trials with each response type. Subjects were encouraged to take rest breaks between blocks as needed to avoid fatigue.

Electrophysiological recording
Electrophysiological activity was recorded using Ag–AgCl electrodes attached to the scalp with EC-2 (Astro-Med Inc., Rhode Island) paste at sites 1 cm anterior and superior to positions C3 and C4 of the International 10–20 System (designated C3’ and C4’) and at the midline parietal site Pz. Horizontal eye movements were monitored with electrodes placed ~2 cm lateral to the left and right outer canthi. These electrodes were all referenced to an electrode clipped on the left earlobe and were recorded with a band pass of 0.01–100 Hz. Blinks and vertical eye movements were monitored with electrodes placed ~2 cm above and below the left eye referenced to one another using a band pass of 0.1–100 Hz. EMG activity from the muscles controlling finger flexion was also recorded bipolarly at sites that roughly bisected the wrist–elbow distance on the ventral forearm. A band pass of 0.1–100 Hz was used for the EMG recordings and these signals were then full-wave rectified off-line. All electrophysiological signals were digitized at a rate of 100 Hz. Electrode impedances were <5 kΩ on the scalp and face and <15 kΩ on the forearms.

Data reduction
The EEG recordings were first examined for artefacts (excessive EMG activity, amplifier saturation and slow linear drift) that occurred between the start of the baseline period and the 95th percentile of the participant’s RT distribution for the condition being tested on that trial. This resulted in the rejection of ~5% of the trials. The remaining EEG waveforms were then corrected for contamination due to blinks and eye movements using the procedure developed by Gratton and colleagues (Gratton et al., 1983). Trials with RTs <150 ms (0.03%) or >2000 ms (0.68%) were also excluded from further analyses.
Signal-averaged ERPs were computed for each subject and trial type with time-locking to the onset of the reaction signal (i.e. stimulus-locked) or to the moment of the key press (i.e. response-locked). The LRP was then computed using the average ERPs at C3' and C4' in a manner consistent with prior investigations (cf., Smid et al., 1987; Gratton et al., 1988). For each time point and trial type, the activity at the site contralateral to the responding hand was subtracted from that at the ipsilateral site (e.g. C3' was subtracted from C4' for trials in which the right hand was signalled). These difference waveforms were then averaged across right- and left-hand trial types for each subject separately. This derivation produces a positive deflection in the LRP waveform when there is relatively more negativity recorded at the scalp site contralateral to the responding hand.

Electrophysiological readings were scored relative to the average value during the 200 ms baseline interval immediately preceding the reaction stimulus. The ERP (including LRP) and EMG waveforms shown in the figures were digitally smoothed using a 12 Hz finite impulse response low-pass filter using weights from the program developed by Cook and colleagues (Cook et al., 1987; Cook and Miller, 1992). This filter attenuates the amplitude of an 8 Hz signal by ~2% and a 16 Hz signal by 98%. In all cases, however, peak and mean amplitudes used in statistical analyses were computed on unfiltered waveforms.

LRP onset latencies were analysed using the jackknifing procedure recommended by Miller and colleagues (Miller et al., 1998). For this analysis, the waveforms were digitally smoothed using a 4 Hz finite impulse response low-pass filter (attenuates 1 and 6 Hz signals by ~7.5 and 80%, respectively). The onset latency of the LRP is then taken as the point in time when the grand average LRP for a given condition reaches a criterion amplitude, in this case 0.50 μV. A jackknifing method was then used to estimate the standard error of the latency differences (Mosteller and Tukey, 1977; Efron, 1981). Based on extensive simulations, Miller and colleagues concluded that this procedure has lower bias and higher power than other measures of LRP onset latency used previously (Miller et al., 1998). Interested readers should consult that article for a more detailed description and evaluation of the procedure. In the present study, the criterion value of 0.50 μV was selected as the lowest cut-off that yielded small standard errors of estimate for each group and condition. Similar LRP latency results were also obtained with cut-offs of 0.40, 0.60 and 0.75 μV. A factorial analysis of variance (ANOVA) of the jackknifed LRP onset latencies was conducted using the extension developed by Ulrich and Miller (2001) of the analysis described by Miller and colleagues (Miller et al., 1998).

EMG onset was scored on individual trials for each subject separately. To estimate the onset latency, we first calculated the mean and standard deviation of EMG activity during the baseline period for each trial and set the criterion amplitude at 3.5 SD above the baseline mean. EMG onset was then defined as the first point in time during which the EMG amplitude reached the criterion and persisted such that the average amplitude during the next two 50 ms epochs also exceeded this criterion. Because EMG activity must start before the key press, trials that failed to reach the criterion amplitude within the RT interval were excluded from the analysis of EMG latency.

**Results**

**Behavioural measures**

Mean RTs and percentage correct for each group are displayed in Table 1. Preliminary analyses indicated that the only significant effect of practice was a reduction in RTs for the control subjects following the first two blocks (i.e. one block with each response requirement), so the main ANOVAs were conducted collapsing across practice levels. A mixed ANOVA was conducted with group (Parkinson’s disease versus control subjects) and order of response requirements as within subjects factors. Responses were reliably slower for complex compared with simple movements \(F(1,20) = 66.70, P < 0.001\), and for hard relative to easy discriminations \(F(1,20) = 224.31, P < 0.001\). Parkinson’s disease patients were 111 ms slower overall, but the difference only approached statistical significance \(F(1,20) = 3.43, P = 0.08\). There was, however, a

**Table 1 Mean reaction time and percentage of correct responses as a function of discrimination difficulty and response complexity for Parkinson’s patients and control subjects**

<table>
<thead>
<tr>
<th>Discrimination</th>
<th>Simple response</th>
<th>Complex response</th>
<th>Simple response</th>
<th>Complex response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy</td>
<td>Parkinson’s patients</td>
<td>638</td>
<td>875</td>
<td>773</td>
</tr>
<tr>
<td></td>
<td>Control subjects</td>
<td>585</td>
<td>686</td>
<td>742</td>
</tr>
<tr>
<td>Hard</td>
<td>Parkinson’s patients</td>
<td>98.6</td>
<td>98.4</td>
<td>87.9</td>
</tr>
<tr>
<td></td>
<td>Control subjects</td>
<td>99.2</td>
<td>99.4</td>
<td>90.4</td>
</tr>
</tbody>
</table>

For each time point and trial type, the activity at the site contralateral to the responding hand was subtracted from that at the ipsilateral site (e.g. C3’ was subtracted from C4’ for trials in which the right hand was signalled). These difference waveforms were then averaged across right- and left-hand trial types for each subject separately. This derivation produces a positive deflection in the LRP waveform when there is relatively more negativity recorded at the scalp site contralateral to the responding hand.

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ANOVA was computed for the intervals between the first and second key presses (MT-1 and the second and third key presses (MT-2). As can be seen in Table 2, Parkinson’s disease patients were slower on both MT-1 and MT-2 $\[F(1,22) = 9.37 \text{ and } 6.31, P < 0.05\]$. The sequence was generally performed faster with the right hand $\[F(1,22) = 5.71 \text{ and } 7.56, P < 0.05\]$. An unexpected effect of stimulus discriminability was found for MT-2. Initiation of the final key press was 5 ms faster following a hard compared with an easy discrimination trial $\[F(1,22) = 7.78, P < 0.01\]$, and we suspect that this is a Type I error.

**Psychophysiological measures**

**LRP**

The effects of stimulus discriminability and response complexity on the LRP waveforms are shown separately for each group in Fig. 1. In both groups, S-LRP onsets were later for hard discriminations than for easy ones, and R-LRP onsets were earlier for complex responses than for simple ones. Thus, both task–difficulty manipulations appear to have affected the expected stages of information processing.

Group differences for each condition, however, can be seen more easily in Fig. 2. This figure suggests a delay in the onset of the S-LRP for the Parkinson’s disease group (solid line) compared with the control group (dashed line), and this delay appears to persist under all conditions. Furthermore, when performing the complex response the Parkinson’s disease patients also seem to show an increase in the duration of the R-LRP.

These observations were tested statistically using the jackknife procedure (see Methods) in a factorial design that included the between-subjects factor of group and the within-subjects factors of stimulus discriminability and response complexity. In the analysis of S-LRP waveforms, there was a robust effect of stimulus discriminability $\[F(1,22) = 52.59, P < 0.001\]$, with lateralization beginning 44 ± 12 ms earlier in the easy compared with the hard stimulus condition. This suggests that at least a portion of the RT difference between easy- and hard-to-discriminate stimuli can be attributed to premotor processes. In contrast, response complexity had no effect on the interval between stimulus onset and S-LRP onset.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mean movement times and percentage of correct movement sequences in blocks with complex responses for Parkinson’s patients and control subjects</th>
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<tbody>
<tr>
<td></td>
<td>Discrimination</td>
</tr>
<tr>
<td></td>
<td>Easy</td>
</tr>
<tr>
<td>Mean movement time from the first to second key press MT-1 (ms)</td>
<td>Parkinson’s patients</td>
</tr>
<tr>
<td></td>
<td>Control subjects</td>
</tr>
<tr>
<td>Mean movement time from the second to third key press MT-2 (ms)</td>
<td>Parkinson’s patients</td>
</tr>
<tr>
<td></td>
<td>Control subjects</td>
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<tr>
<td>Percentage of correct responses</td>
<td>Parkinson’s patients</td>
</tr>
<tr>
<td></td>
<td>Control subjects</td>
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</tbody>
</table>

highly reliable group by response complexity interaction $\[F(1,20) = 10.91, P < 0.005\]$. On complex response trials, Parkinson’s disease patients were 180 ms slower than control subjects $\[F(1,22) = 7.70, P < 0.01\]$, but the 41 ms group difference on simple trials was not statistically significant, $F < 1$. The difference between Parkinson’s disease patients and control subjects was somewhat larger when the discrimination was easy (121 ms) than when it was hard (101 ms), but this interaction was not significant.

Accuracy for the first key press was fairly high overall with correct responses on 93% and 95% of trials for the Parkinson’s disease and control groups, respectively $\[F(1,20) = 1.36, P > 0.25\]$. Trials involving easy stimulus discriminations were more accurate than trials with hard discriminations $\[F(1,20) = 58.55, P < 0.001\]$, but this factor did not interact with group, $F = 1$. Thus, both groups were quite accurate with the initial key press. However, because the complex response condition provided more opportunity for error, a further exploration of sequence accuracy was conducted on these trials. Accuracy for performing all three key presses of the sequence was substantially higher for the control group (98.8%) than for the Parkinson’s disease patients (90%) $\[F(1,22) = 12.00, P < 0.002\]$, indicating that the complex response requirement was especially difficult for the patients.

The complex trials also afforded the opportunity to investigate movement time (MT). We reanalysed initial RT using the more strict accuracy criterion (i.e. entire sequence correct). The average initial RT for Parkinson’s disease patients dropped by ~88 ms, suggesting that when Parkinson’s disease patients made mistakes with the sequence, they were also more likely to be delayed in initiating that sequence. The change in criterion did not alter the initial RT in the control group, but this is likely due to the fact that this group made very few sequence errors so a similar number of trials are contributing to both analyses. Despite this difference, Parkinson’s disease patients were still ~150 ms slower than control subjects for initial RT $\[F(1,22) = 7.11, P < 0.01\]$. Including only those trials for which the entire sequence was correct, a group by discriminability by hand-mixed ANOVA was computed for the intervals between the first and second key presses (MT-1) and the second and third key presses (MT-2).
This pattern of S-LRP effects for stimulus discriminability and response complexity is consistent with that found by Smulders and colleagues (Smulders et al., 1995), and therefore extends their findings to include older adults.

The group difference in S-LRP onset that is apparent in Fig. 2 was also confirmed \( F(1,22) = 5.01, P < 0.05 \). Relative to control subjects, Parkinson’s disease patients showed a delay in onset of \( 66 \pm 59 \) ms. However, the group factor did not interact with either stimulus discriminability or response complexity for the S-LRP waveforms \( (P > 0.15) \). The lack of interaction of group with stimulus discriminability suggests that, although Parkinson’s disease patients appear to have a delay in some premotor process, the speed of stimulus discrimination processes is normal.

In the analysis of R-LRP waveforms, there were reliable main effects of both stimulus discriminability and response complexity \( F(1,22) = 7.46 \) and \( 46.79 \), respectively, \( P < 0.02 \). The LRP-to-key press interval lasted \( 45 \pm 33 \) ms longer in the hard relative to the easy discrimination condition and was \( 169 \pm 49 \) ms longer prior to complex compared with simple responses. Whereas the effect of response complexity on the R-LRP is consistent with prior research (e.g. Smulders et al., 1995), the effect of stimulus discriminability on the duration of motor processes is unexpected because it has not been observed in previous studies with normals (e.g. Smulders et al., 1995). Moreover, the effect was not simply produced by the inclusion of the Parkinson’s disease patients, because it is present in the control group as well (cf., Fig. 1). The reasons for and implications of this unexpected finding are considered in the Discussion.

Although there was not a main effect of group on the duration of the R-LRP \( (F < 1) \), there was a reliable group by response complexity interaction \( F(1,22) = 6.94, P < 0.025 \). Fig. 2 suggests that the duration of motor processes prior to the complex response was longer for patients compared with control subjects, whereas for the simple response the duration of motor processes was approximately the same for the two groups. To test this observation statistically, we compared the groups at each level of response complexity using the jackknife procedure. For complex responses, the duration of the R-LRP was \( 121 \pm 102 \) ms longer in the Parkinson’s disease compared with the control group, and this difference was statistically reliable \( F(1,22) = 5.62, P < 0.05 \). In contrast, the groups did not differ with simple responses \( (F < 1) \). So, the increased disadvantage in RT for Parkinson’s disease patients performing the complex response can be attributed in large part to the additional time needed by the central motor system to reach a level of activation sufficient to generate the initial key press in this condition.

**EMG**

As described above, the mean latency of EMG onset was based on single trial measurements. The group means for each condition are presented in Table 3. A mixed ANOVA
was conducted on these latency estimates with group as a between-subjects factor and stimulus discriminability, response complexity, and responding hand as within-subjects factors. The results were redundant with those obtained for RT. EMG onset occurred earlier for easy compared with hard discriminations and for simple compared with complex key presses \[F(1,22) = 161.71 \text{ and } 60.66, P < 0.001\]. Furthermore, there was a statistically reliable group by complexity interaction \[F(1,22) = 12.23, P < 0.001\], with group comparisons indicating a delay in EMG onset for Parkinson’s disease patients performing the complex, but not the simple response \[F(1,22) = 5.83, P < 0.025 \text{ and } F < 1, \text{ respectively}\].

Figure 3 displays the grand average response-locked EMG activity recorded from the responding and non-responding arms (top and bottom panels, respectively). To evaluate whether the groups differed with respect to EMG amplitude, for each subject and condition we calculated the mean amplitude of the response-locked EMG during four consecutive 200 ms epochs (from 700 ms prior to 100 ms after the initial key press). A mixed ANOVA was then conducted on these mean amplitudes with the between-subjects factor of group and the within-subjects factors of stimulus discriminability, response complexity, response hand and epoch. Overall, EMG amplitude on the responding arm was greater for Parkinson’s disease patients than for control subjects (17.4 and 12.3 \(\mu\)V, respectively), with this difference approaching statistical significance \[F(1,22) = 3.64, P < 0.07\]. Also for the responding arm, there was a reliable effect of epoch \[F(3,66) = 100.05, P < 0.001\], with mean

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**Fig. 2** Comparisons of Parkinson’s patients (PD, solid lines) and control subjects (CTL, dashed lines) on S-LRPs and R-LRPs for each level of stimulus discriminability and response complexity.
amplitudes increasing across the four epochs. EMG mean amplitude was greater on complex compared with simple responses [\( F(1,22) = 14.43, \ P < 0.001 \)] and this effect interacted with epoch [\( F(3,66) = 6.31, \ P < 0.02 \)]. Figure 3 shows that EMG amplitude began to increase much earlier preceding complex responses compared with simple responses. Although this difference appears to be more pronounced in the Parkinson’s disease group, the three-way interaction of group, complexity and epoch was not significant (\( F < 1 \)). There was an interaction between stimulus discriminability and epoch [\( F(3,66) = 4.53, \ P < 0.05 \)], but pairwise comparisons during each epoch failed to reveal any consistent pattern. During epochs 1 and 4, there was no difference in EMG amplitude for easy versus hard stimuli. During epoch 2 (±500 to ±300 ms), EMG mean amplitude was 0.2 μV larger on hard trials, and during epoch 3 (±300 to ±100 ms) this pattern reversed with larger (0.6 μV) mean amplitude on easy trials. Finally, there was a reliable three-way interaction of group, hand and epoch [\( F(3,66) = 4.54, \ P < 0.05 \)]. Inspection of the means indicated that during the last epoch (±100 to 100 ms), the Parkinson’s disease group tended to have larger EMG activity on the left hand while the control group showed more activity on the right hand.

A parallel analysis was conducted on the EMG activity of the non-responding hand. Again, Parkinson’s disease patients produced greater levels of EMG activity compared with the

Table 3 Mean latency of EMG as a function of discrimination difficulty and response complexity for Parkinson’s patients and control subjects

<table>
<thead>
<tr>
<th>Discrimination</th>
<th>Easy</th>
<th>Hard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simple response</td>
<td>Complex response</td>
</tr>
<tr>
<td>Parkinson’s patients</td>
<td>554</td>
<td>764</td>
</tr>
<tr>
<td>Control subjects</td>
<td>495</td>
<td>587</td>
</tr>
</tbody>
</table>

Fig. 3 Grand average response-locked EMG activity for Parkinson’s patients (PD patients) and control subjects. Time 0 corresponds to the moment of the initial key press. Responding arm (top panels) refers to the muscle corresponding to the hand indicated by the reaction stimulus, whereas non-responding arm (bottom panels) refers to the muscle activity of the hand opposite to that indicated by the reaction stimulus.
control group \[F(1,22) = 4.48, P < 0.05\]. This effect interacted with epoch \[F(3,66) = 3.28, P < 0.05\], such that the difference between groups was most pronounced in the 200 ms epoch surrounding the key press (i.e. movement of the opposite hand). This difference between groups was slightly more pronounced for complex movements as indicated by a trend towards the three-way interaction of group, epoch and complexity \[F(3,66) = 2.41, P = 0.09\]. Thus, it appears that Parkinson’s disease patients were not able to fully inhibit motor activity on the non-responding hand, especially when performing complex movements.

**P300**

Figure 4 displays the grand-average ERP waveforms recorded at Pz for patients (left panel) and control subjects (right panel), separately. These waveforms show a positive peak at ~125 ms followed by a negative component that peaks ~200 ms after the onset of the reaction signal. Scrutiny of the individual subject averages indicated that this P1–N2 complex varied considerably across subjects, with some individuals showing peak-to-peak amplitude changes as great as 14 μV while others showed no detectable change during the interval between 50 and 250 ms. This rather high variability may be due to the fact that our recording locations were not ideal for investigating these early components. When stimuli are presented visually, these components are typically largest at sites overlying the occipital cortex (Hillyard *et al*., 1990). Furthermore, there were no systematic differences between the two groups in terms of this variability. Although previous research has reported differences in these components in Parkinson’s disease patients compared with controls (e.g. Bodis-Wollner and Yahr, 1978; Wright *et al*., 1993), we were unable to investigate these potential group differences adequately due to the large variability across subjects in identifying these early components in the present study.

All subjects displayed a prominent P300 component that peaked ~500 ms after the onset of the reaction signal. For each subject and condition, the maximum amplitude recorded at Pz between 400 and 800 ms was identified, and the amplitude and corresponding latency of this maximum was scored. A mixed ANOVA was then conducted on both peak latency and peak amplitude with the factors of group, stimulus discriminability and response complexity. We failed to find any statistically reliable effects on P300 peak latency (all \(P > 0.10\)). The lack of an effect of stimulus discriminability was particularly surprising given the number of studies which have reported that P300 peaks earlier for easy compared with hard discriminations (e.g. Ritter *et al*., 1972; McCarthy and Donchin, 1981; Duncan-Johnson, 1981; Ford *et al*., 1982). We have since twice replicated the null effect in this paradigm with independent samples of young adults, and we have some evidence that it is caused by varying discriminability within blocks rather than between blocks as is more commonly done. Furthermore, a comparison of these young adults with our healthy older control group provided evidence that P300 latency was at least sensitive to the effects of age. Consistent with numerous studies on aging (e.g. Mullis *et al*., 1985; Barrett *et al*., 1987; Pfefferbaum and Ford, 1988; Verleger *et al*., 1991), P300 peaked earlier for the young adults than the older ones.

For the analysis of peak amplitude, the P300 component was smaller on hard compared with easy discriminations and with complex as opposed to simple responses \[F(1,22) = 40.44\] and 20.01, respectively, \(P < 0.001\). Thus, as the overall difficulty of the task increased, the amplitude of P300 decreased (easy/simple > easy/complex > hard/simple > hard/complex). Moreover, there was a reliable interaction between stimulus discriminability and response complexity \[F(1,22) = 5.04, P < 0.05\]. Inspection of the means indicated that the amplitude difference between easy and hard discriminations was larger with simple responses than with complex ones.

Careful inspection of Fig. 4 also suggests differential activity for the two groups during the baseline window with the control group, showing a negative trend that was not apparent in the Parkinson’s disease waveforms. It is possible that this negative-going waveform represents the tail end of the contingent negative variation, a component that has been shown to be reduced in amplitude in Parkinson’s disease patients (e.g. Wascher *et al*., 1997; Cunnington *et al*., 1999a). To test whether this group difference in baseline activity was
reliable in our study, we calculated the slope of the linear trend of Pz amplitude over the interval from −200 to 0, and found that the slope was statistically greater in the control group compared with the Parkinson’s disease group \( [F(1,22) = 9.90, P < 0.005] \). Although the present study was not specifically designed to look at prestimulus preparatory differences, this finding is compatible with the notion of strategic differences in attention between Parkinson’s disease patients and control subjects reported by Cunnington and colleagues (Cunnington et al., 1999a). We would like to thank an anonymous reviewer for calling this difference to our attention.

**Discussion**

The present study used behavioural and psychophysiological measures—particularly the LRP—to investigate the RT slowing typically seen in Parkinson’s disease patients. In particular, we sought to isolate the slowing of motor processes and separate it from slowing due to cognitive deficits arising before the motor system has been activated by using a psychophysiological measure of motor preparation—the LRP. To that end, we also manipulated the difficulty of the choice reaction task both in terms of the processing required for stimulus identification (i.e. stimulus discriminability) and the processing required for performing the response (i.e. response complexity). We reasoned that increasing the difficulty of specific processes would be more likely to reveal any deficit in those processes present in Parkinson’s disease and that the differential effects of these manipulations on Parkinson’s disease patients versus control subjects would help to elucidate the specific processes affected by Parkinson’s disease.

Overall, Parkinson’s disease patients were slower to initiate responses than were age-matched control subjects: the electrophysiological data allowed us to explore the processes responsible for this slowing. Because LRP onset reflects the moment that one response hand becomes more activated than the other hand, the onset latencies of the LRP relative to the stimulus (i.e. S-LRP onset) and to the response (i.e. R-LRP) can be used as estimates of the duration of premotor and motor processes, respectively. In the present study, the stimulus-locked LRP began later for Parkinson’s disease patients relative to control subjects in all conditions. This indicates a deficit in some process or processes that occur prior to the engagement of the motor system when Parkinson’s disease patients are performing choice reactions. Thus, slower premotor processing contributed to the overall delay in RT for the Parkinson’s disease group. Given that the patients included in this study were in relatively early stages of the disease, this strongly suggests a cognitive component to Parkinson’s disease that is not attributable to a dementing process sometimes associated with the disease. Given the focused-attention nature of the task, it is also unlikely to reflect stringent attentional demands.

In contrast to their general premotor slowing, Parkinson’s disease patients showed a deficit in motor processing speed only when performing the complex movement. With simple responses (i.e. single key presses), motor processing time for the Parkinson’s disease patients was equivalent to that of the control group. Thus, deficits in motor processing only became apparent when the motor requirements of the task were stringent. This pattern is no doubt due in part to the fact that the patients were in the relatively early stages of the disease.

The effects of discriminability provide further clues about which premotor stages are affected by Parkinson’s disease. First, there was no interaction of group with stimulus discriminability for either RT or S-LRP onset latency. Secondly, P300 peak latency, which is often used as an estimate of the relative timing of stimulus evaluation processes, was approximately the same for Parkinson’s disease patients and control subjects across all conditions. Together, these findings suggest that Parkinson’s disease patients have no specific impairment in the perceptual processes responsible for size discrimination. Instead, it appears that the delay in premotor processing in Parkinson’s disease patients involves a deficit in some stage after stimulus evaluation but before hand-specific motor activation.

One plausible interpretation of the premotor slowing is that Parkinson’s disease patients were slower at mapping the stimuli to their associated responses. More specifically, Parkinson’s disease patients may be quite able to distinguish among the different sizes but then might be slow at retrieving the correct response hand. Consistent with this possibility, Brown and colleagues (Brown et al., 1993a) found that Parkinson’s disease patients were slowed more than control subjects by an incompatible assignment of stimuli to responses. Response selection may have been particularly difficult in the present experiment, because the assignment of stimuli to responses was arbitrary. There is evidence to suggest, however, that Parkinson’s disease patients are not selectively impaired in tasks with arbitrary stimulus-response mappings (Zimmermann et al., 1992; Brown et al., 1993b). Also contrary to the hypothesis of difficulties with response selection are findings that Parkinson’s disease patients are not selectively impaired by conflicting response-related information (e.g. Cope et al., 1996). Clearly, further research is needed to isolate exactly which premotor stages of processing are slowed in Parkinson’s disease.

Two aspects of our results are at odds with a previously suggested explanation of the fact that Parkinson’s disease patients are sometimes, but not always slower, than control subjects in choice RT tasks. Based on their findings with transcranial magnetic stimulation, Pascual-Leone and colleagues (Pascual-Leone et al., 1994a) suggested that ‘the main abnormality of Parkinson’s disease patients in a RT situation is the abnormally slow build-up of premovement excitability’ (Pascual-Leone et al., 1994a; for similar suggestions, see Cunnington et al., 1999b; Praamstra et al., 1998). Pascual-Leone and colleagues went on to suggest that...
this could account for differences in the effects of Parkinson’s disease on RT:

In a cRT situation, the influence of this process on the RT will depend on the difficulty of the go-signal discrimination. If the go-signal is difficult to discriminate, it will take longer to complete the stimulus-evaluation system and there will be enough time available for activation of the response channel, so that cRT will be normal. However, if the go-signal is easy to discriminate, the abnormally slow activation of the response channel will become the main determinant of the RT and the cRT will be prolonged. (Pascual-Leone et al., 1994a)

According to the model that they suggested, Parkinson’s disease patients should be much slower, relative to control subjects, when the discrimination is easy compared with when it is difficult. This was clearly not the case in our data, because the patient/control RT difference was essentially the same regardless of discrimination difficulty. Moreover, with simple responses, the R-LRPs were approximately equivalent for patients versus control subjects, suggesting that activation of the response channel was not prolonged in the present study. Thus, our data suggest that the complexity of the response is much more important than the difficulty of the stimulus discrimination in determining whether Parkinson’s disease patients will be slower than or equal to control subjects in a choice-RT situation.

**Stimulus discriminability**

As expected, it took longer for subjects to respond to the intermediate-sized squares (i.e. hard discrimination) compared with the more extreme, extra-small and extra-large squares (i.e. easy discrimination). This manipulation of stimulus discriminability, however, produced some surprising results for the electrophysiological data. Based on prior research, we expected to find an effect of discriminability on S-LRP onset latency and no effect on R-LRP duration—consistent with the notion that stimulus discriminability affects a relatively early premotor process (Smulders et al., 1995). Although we did find a later S-LRP onset on hard than on easy trials, this difference could only account for a portion of the total RT effect. The remainder of the RT difference showed up as an effect on the duration of motor processes, with the duration of the R-LRP being greater on hard compared with easy trials. As mentioned above, this pattern of LRP activity is not simply due to the inclusion of Parkinson’s disease patients because the effects were found in both groups. This unexpected result can most easily be interpreted in terms of a model in which preliminary partial output about stimulus size is transmitted from perceptual processes to motor processes so that motor activation can begin before perceptual analysis is finished (cf., Trevena and Miller, 1998). In that case, the duration of motor activation will be increased if the motor process must wait for final perceptual output before a response is actually made (cf., Osman et al., 1995; Miller and Ulrich, 1998). With the

difficult discrimination, it is easy to imagine that the final perceptual decision would be quite slow, perhaps due to rechecking, and that the response would be delayed even though preliminary motor preparation had been carried out. The main difficulty with this account is to explain why Smulders and colleagues (Smulders et al., 1995) did not find the same effect. One potentially important difference between the present study and that of Smulders and colleagues was that we intermixed easy and difficult discriminations randomly within each block, whereas they presented easy and difficult discriminations in separate blocks. This blocked versus mixed difference could cause various differences in processing, including strategy changes (Los, 1996). In the present case, it could be that participants transmit partial perceptual information when perceptual difficulty is mixed, but wait for full information when it is blocked.

The data indicate that early discrimination processes are normal in Parkinson’s disease patients tested while on medication, at least for discriminations based on object size. [There is evidence to suggest Parkinson’s disease patients may have problems discriminating small variations in contrast (e.g. Tebartz van Elst et al., 1997).] The RT difference between easy and hard trials was approximately equivalent for the two groups. Moreover, stimulus discriminability affected the LRP latencies similarly for patients and control subjects. The P300 component peaked at approximately the same time for the two groups as well, but this null result is somewhat difficult to interpret because P300 latency was also not affected by stimulus discriminability as was expected, and therefore calls into question the functional significance of P300 peak latency in the present experiment. Still, the RT and LRP data provide reasonable evidence that Parkinson’s disease patients do not have a specific deficit for stimulus discrimination processes.

**Response complexity**

The complexity of the response varied across blocks such that on some blocks subjects responded with a simple, one key press response and on the other blocks they responded with a more complex, three key press sequence. Consistent with prior research, RT for the complex response was longer than for the simple response (Henry and Rogers, 1960; Sternberg et al., 1978). The increase in RT on complex trials was related to an increase in the duration of motor-related processing. The duration of the R-LRP was longer prior to complex as opposed to simple movements. Moreover, the onset of the S-LRP occurred with the same latency for both levels of response complexity suggesting that response complexity had no effect on earlier premotor processing. This pattern of results extends the findings of Smulders and colleagues (Smulders et al., 1995) to include older adults and supports the notion that complex movements require more time for motor-related activity than is necessary for simple movements, and that these processes occur prior to the initiation of the first movement.
The complex response requirement clearly created greater difficulties for the Parkinson’s disease patients than for the control subjects. First, as noted in Methods, most of the patients required additional training to learn the sequential pattern adequately. Secondly, the group difference in RT was much more pronounced when subjects were performing the complex, three key press sequence than when performing the simpler one key press response. Thirdly, R-LRP data showed clearly that complex responses slowed motor processing to a much greater extent for patients than for controls. Finally, patients were slower, and more error prone, when executing the second and third key presses of the sequence—a finding that is consistent with one of the cardinal features of Parkinson’s disease known as bradykinesia or slowness of movement. Together, these results support previous reports indicating that Parkinson’s disease patients may have a selective impairment for performing sequential movements (Stelmach et al., 1987; Agostino et al., 1992; Weiss et al., 1997; Low, 1999; in contrast, see Rafal et al., 1987).

In conclusion, the motor-related potentials observed in this study clearly reveal increases in the duration of both premotor and motor processes in Parkinson’s disease patients performing a choice RT task, as compared with control subjects. These results provide clear evidence that previously observed RT slowing in Parkinson’s disease patients stems from both motor and premotor or cognitive components, even in early stages of the disease. The technique of partitioning the RT interval into components before as against after the onset of motor-related activity appears to be a very promising tool in the quest to understand the nature of this and other disease processes that affect RT.

Acknowledgement
This research was supported by an Otago Research Grant to J.M.

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