Movement Disorders
Vol. 14, No. 5, 1999, pp. 790–799

Motor Cortex Activation in Parkinson's Disease: Dissociation of Electrocortical and Peripheral Measures of Response Generation

*Peter Praamstra, MD, *Erik M. Plat, MS, †Antje S. Meyer, PhD, and *Martin W. I. M. Horstink, MD

**Departments of Neurology and Clinical Neurophysiology, University Hospital Nijmegen; and †Max Planck Institute for Psycholinguistics, Nijmegen, The Netherlands*

Summary: This study investigated characteristics of motor cortex activation and response generation in Parkinson's disease with measures of electrocortical activity (lateralized readiness potential [LRP]), electromyographic activity (EMG), and isometric force in a noise-compatibility task. When presented with stimuli consisting of incompatible target and distractor elements asking for responses of opposite hands, patients were less able than control subjects to suppress activation of the motor cortex controlling the wrong response hand. This was manifested in the pattern of reaction times and in an incorrect lateralization of the LRP. Onset latency and rise time of the LRP did not differ between patients and control subjects, but EMG and response force developed more slowly in patients. Moreover, in patients but not in control subjects, the rate of development of EMG and response force decreased as reaction time increased. We hypothesize that this dissociation between electrocortical activity and peripheral measures in Parkinson's disease is the result of changes in motor cortex function that alter the relation between signal-related and movement-related neural activity in the motor cortex. In the LRP, this altered balance may obscure an abnormal development of movement-related neural activity. **Key Words:** Parkinson's disease—Motor cortex—Movement-related potentials—Movement preparation.

The motor symptoms of akinesia and bradykinesia in Parkinson's disease (PD) have often been attributed to dysfunction at a premotor level of movement organization. Convincing evidence for this view is the observation that relevant premotor areas show a partial return to normal levels of activation after the administration of dopaminergic medication,[1,2] stereotaxic pallidotomy,[3] and internal pallidum or subthalamic nucleus stimulation.[4]

There is, however, also evidence for involvement of the primary motor cortex in bradykinesia, for instance, from the observation that monkeys with MPTP-induced parkinsonism show a disruption of movement-related cortical activity in the primary motor cortex.[5,6] Ridding and colleagues studied motor cortex function in patients with PD using transcranial magnetic stimulation (TMS) and found abnormal cortical excitability, which they attributed to reduced inhibitory activity within the motor cortex.[7] They suggested that changes in motor cortex excitability compromised the selectivity of cortical discharge during movement, but they cautioned that bradykinesia was not likely to result solely from these changes at the motor cortex level. However, on the basis of a different experimental approach with the TMS technique, Pascual-Leone and coworkers have linked akinesia and bradykinesia to changes in the regulation of motor cortical excitability.[8,9] They applied subthreshold TMS during reaction time tasks and thereby obtained information about the development of motor cortex activity in the interval between the presentation of a reaction signal and the motor response. Their findings suggest that in patients with PD the motor cortex takes more time than in healthy subjects to become sufficiently activated to generate a motor command.[8–10]

To investigate the development of motor cortex activation more directly, we recorded movement-related cortical potentials derived from the scalp-recorded electroencephalogram (EEG). The movement-related potential suited for use in reaction time tasks is the lateralized readiness potential (LRP). The LRP measures the voltage difference between recordings ipsilateral and contralat-

Received November 6, 1998; revision received March 9, 1999. Accepted June 4, 1999.

Address correspondence and reprint requests to Peter Praamstra, MD, Department of Neurology, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

eral to the movement by a procedure designed to isolate lateralized motor cortex activity from overlapping stimulus-evoked activity in other cortical areas.[11,12] The LRP starts approximately 50–150 msec before the onset of movement and corresponds to the motor potential (MP) component of the readiness potential, which originates in the primary motor cortex contralateral to the side of movement.[13–15] In earlier studies of movement preparation in PD, we have used the onset time of the LRP as an index for the timing of response choice and as a measure for the onset of motor cortex activation.[16,17] One goal of this study was to replicate earlier results in the noise-compatibility task.[17] The main goal was to investigate the development of motor cortex activity and compare the central activation with motor output measures derived from electromyography (EMG) and isometric force recordings. This study therefore extended the application of the LRP by examining the rate of rise of the LRP as an index for the rate of growth of neural activity in the motor cortex.

METHODS

Subjects

The participants were 10 patients with PD (eight men, two women; age 60 ± 10 yrs) and nine control subjects (seven men, two women; age 60 ± 9 yrs). One additional control subject was tested, but later excluded when we discovered that a hand injury had influenced his performance. The subjects participated on the basis of informed consent and the procedures were approved by the local ethics committee. All but one of the participants were right-handed and all had normal or corrected-to-normal vision. The patients fulfilled established criteria for diagnosis of the disease,[18] which was of mild to moderate severity with slowness of movement present in all of them. Patients used anti-parkinsonian medication in various combinations (Table 1). They were tested after overnight withdrawal (>10 hrs after the last medication). Motor performance was determined during the state of medication withdrawal using the Unified Parkinson's Disease Rating Scale (UPDRS) motor section (mean 32 ± 6, range 24–40).[19] On the Hoehn & Yahr scale[20] patients were classified as 2, 2.5, or 3. Patients and control subjects completed the MMSE as a screening for dementia.[21] Performance ranged from 26–30 (mean 28) for patients and from 27–30 (mean 29) for the control subjects.

Task and Stimuli

A noise-compatibility task was used in which the participants made a choice reaction with the left or right hand on the presentation of visual stimuli on a computer screen. A stimulus consisted of a central target which was a leftward or rightward pointing arrow that in-

TABLE 1. *Summary of the age, sex, disease duration, disease severity, and medication of the patients with Parkinson's disease*

Patient no.	Age (yrs)	Sex	Disease duration (yrs)	H & Y*	UPDRS†	Medication (per day)‡
1	71	M	7	2.5	29	450 mg L-dopa
2	49	F	6	2	29	250 mg L-dopa 1.25 mg Pergolide 150 mg L-dopa
3	54	F	4	2.5	40	3 mg Pergolide 200 mg Amantadine
4	51	M	7	2	30	2.25 mg Pergolide 10 mg Selegiline
5	75	M	8	2.5	31	800 mg L-dopa 200 mg Amantadine 150 mg L-dopa
6	55	M	3	2	35	10 mg Selegiline 200 mg Amantadine
7	60	M	6	3	40	10 mg Selegiline
8	49	M	9	3	37	400 mg L-dopa 200 mg Amantadine 150 mg L-dopa
9	67	M	3	2	25	200 mg Amantadine 10 mg Selegiline
10	68	M	3	2	24	200 mg Amantadine 10 mg Selegiline

* Hoehn and Yahr scale (off medication for at least 10 hrs).
† Unified Parkinson's Disease Rating Scale (off medication for at least 10 hrs).
‡ L-Dopa was given with a peripheral decarboxylase inhibitor.

structed for a response of the left or right hand, respectively. The target was surrounded by arrows pointing in the same direction as the target (compatible condition), arrows pointing in the opposite direction (incompatible condition), or bars (neutral condition). We have previously found that similar stimuli with incompatible target and distractor elements caused initial activation of the motor cortex controlling the wrong response hand.[17] This incorrect response activation (expressed in the LRP) had a higher amplitude in patients than in control subjects. While the stronger incorrect response activation of patients with PD demonstrated that they were hindered more by incompatible distractors than control subjects, the study did not answer conclusively whether patients benefited more from compatible distractors than control subjects. Therefore, a neutral condition was included in the present study.

Subjects were seated at a viewing distance of approximately 1 m from the computer screen. They held manipulanda in both hands for the registration of hand grip strength (isometric force). Subjects were instructed to squeeze their right (or left) hand when the central arrow in the stimulus array pointed to the right (left). The stimuli were white against a gray background and subtended 2.0° × 1.4° of visual angle. Target fixation was guided by a fixation dot in the center of the screen. Stimuli were presented for 100 msec and intertrial intervals varied randomly between 3 and 4 seconds. There were six experimental blocks of 121 trials which contained equal numbers of trials for each condition (the first trial was always discarded), presented in random order. Before the experimental session, subjects received written instructions emphasizing response speed and they carried out one block of training trials.

Data Acquisition and Processing

EEG was recorded with Ag/AgCl electrodes from standard locations above the motor cortex (C3 and C4) and along the midline (Fz, Cz, and Pz) referred to linked mastoids. Only the movement-related activity recorded at C3 and C4 is considered in this report. Eye movements were monitored by bipolar horizontal and vertical EOG derivations. The band pass was 0.016–100 Hz. Digitization rate was 250 samples/s. EMG (filter 20–100 Hz) was recorded from the flexor side of both forearms. The EEG, EMG, and force signals were averaged off-line in an epoch from 250 msec before to 1000 msec after stimulus onset for stimulus-locked averages, and from −750–500 msec for response-locked averages. We rejected trials on which the subject made an error and trials that contained artifacts resulting from eye movements. Trials with eye blinks were removed when the blinks occurred during the first 500 msec of the trial. Later eye blink artifacts were corrected by applying an EOG correction algorithm. The number of remaining trials for each response side within a condition was always larger than 90, except for one patient who had a smaller number for one response side (>60).

The analysis of movement-related activity involved the computation of the LRP. This computation removes non-lateralized activity such as visual-evoked potentials and cognitive potentials that overlap with movement-related brain electrical activity. The LRP was derived after digital low-pass (8 Hz) filtering of the EEG according to the formula $LRP = (\text{Mean } (C4 - C3)_{\text{left-hand movement}} + \text{Mean } (C3 - C4)_{\text{right-hand movement}})/2$. For further background concerning the LRP, refer to recent reviews.[11,12]

Response devices were manipulanda for the measurement of isometric hand grip strength (one for each hand). Force was recorded by means of strain gauges attached to each hand grip (sensitivity 0.03 N) and was digitized at 250 samples/s. The criterion force for a response was 50 N, representing a threshold level that was easily exceeded with a modest hand squeeze. The participants learned when they reached this threshold by means of an auditory feedback signal presented only during the practice block.

Data Analyses

The analyses included the following variables:

1. *Reaction time:* Mean reaction times per subject and condition were determined from the force signals of each correct trial and defined as the time from stimulus onset until the point at which the force level reached a 25 N threshold.
2. *Errors:* As determined from the force signal, errors were defined as trials in which the wrong response alternative was chosen (choice errors), trials with reaction times below 200 msec (anticipation errors), and trials without response or reaction times above 1000 msec (missing responses). Trials were also discarded as errors when the force signal from the incorrect side surpassed the threshold level (double responses).
3. *LRP latency:* The latency of the LRP was defined as the moment at which 50% of the maximum amplitude was reached, which represents the best estimate of the mean latency in single trials.[22]
4. *LRP amplitude:* The amplitude of the LRP was measured at peak latency. In the incompatible condition, incorrect lateralization of the LRP was quantified by the amplitude of the incorrect lateralization measured

at peak latency, scaled as a percentage of the LRP amplitude in the compatible condition. Incorrect lateralization of the LRP was the only variable also measured in response locked averages.

5. *LRP slope:* The rate of development of cortical activity was estimated from the upward slope of the LRP by fitting a regression line through the data points between 20% and 80% of the maximum amplitude of the signal.

   Because the LRP combines the movement-related activity preceding the left and right hand movements, the following analyses of averaged EMG and force signals were also carried out on data collapsed across both hands.
6. *EMG and force peak latencies:* Latencies at maximum amplitude.
7. *EMG and force amplitude:* Amplitude of the averaged EMG (force) per subject and condition determined at peak latency.
8. *EMG and force slope:* In the averaged EMG (force) signals per subject and condition, the rate of EMG (force) development was determined in the same way as the slope of the LRP.
9. *Analyses on binned data:* To examine the relationship between motor cortex activation and peripheral motor output across different segments of the reaction time distribution, we partitioned the data on the basis of the reaction times. For each subject, three reaction time bins were defined. They collected the responses of three contiguous latency windows of 50 msec width, centered at the subject's mean response latency. LRP, EMG, and force were averaged separately for each bin. The binning procedure was only performed on the data from compatible and neutral conditions, because the slope of the LRP in the incompatible condition depends more than in the other conditions on the relative strength and timing of activity in ipsi- and contralateral motor cortex, rather than on contralateral motor cortex activity only.

Analyses of variance (MANOVA procedure of SPSS)[23] were conducted on the reaction times from correct trials, evaluating the effect of Group (PD versus control subjects) as between-subjects variable and compatibility (compatible, neutral, and incompatible flankers) as within-subjects (repeated measurements) variable. The latency of the LRP and the slopes of LRP, EMG, and force signals were analyzed in the same way. Analyses on the binned data were also performed for each measure, with latency bin (first versus third bin) as an additional variable. The incorrect lateralization of the LRP was evaluated with a *t* test comparing the difference between groups. Degrees of freedom of F-tests were adjusted according to the Greenhouse-Geisser procedure.

RESULTS

Reaction Time Analysis

The reaction times in the neutral condition were not intermediate between the compatible and incompatible conditions, as we had expected, but almost identical to those in the compatible condition. This result was not anticipated but can be explained within the theoretical framework developed around this task, as will be discussed later. Because there were no significant differences between the neutral and compatible conditions in either reaction time analyses or the analyses of electrophysiological data, analyses related to the compatibility effect were confined to a comparison of compatible and incompatible conditions.

As shown in Table 2, the reaction times were faster in the compatible than in the incompatible condition ($F[1,17] = 321.32$, $p < 0.001$). This compatibility effect was stronger in patients with PD than in control subjects ($F[1,17] = 4.98$, $p < 0.05$). The mean reaction time was slightly faster for the patients with PD than for the control subjects, but the difference was not significant ($F[1,17] < 1$).

Errors occurred in 4.6% of the trials for patients and in 3.8% of the trials for control subjects ($F[1,17] < 1$). Most of the errors (79%) occurred in the incompatible condition.

Lateralized Readiness Potential

Figure 1 shows stimulus-locked and response-locked averages of the LRP in the compatible and incompatible

TABLE 2. *Lateralized readiness potential (LRP) onset, force onset (RT), response variability,* and error rates for patients with Parkinson's disease (PD) and control subjects (means ± 1 standard deviation)*

	Condition		
	Compatible	Neutral	Incompatible
LRP onset (ms)			
Control subjects	293 ± 32	297 ± 35	378 ± 36
PD patients	279 ± 16	284 ± 21	379 ± 32
Reaction time (ms)			
Control subjects	439 ± 54	435 ± 49	506 ± 44
PD patients	409 ± 36	405 ± 36	496 ± 44
Response variability (ms)			
Control subjects	55 ± 14	52 ± 15	59 ± 14
PD patients	52 ± 13	49 ± 12	57 ± 10
Errors (%)			
Control subjects	1.7 ± 1.9	1.5 ± 1.3	8.3 ± 3.7
PD patients	1.2 ± 1.6	1.0 ± 1.5	11.7 ± 8.7

* Response variability is the mean standard deviation of the reaction times.

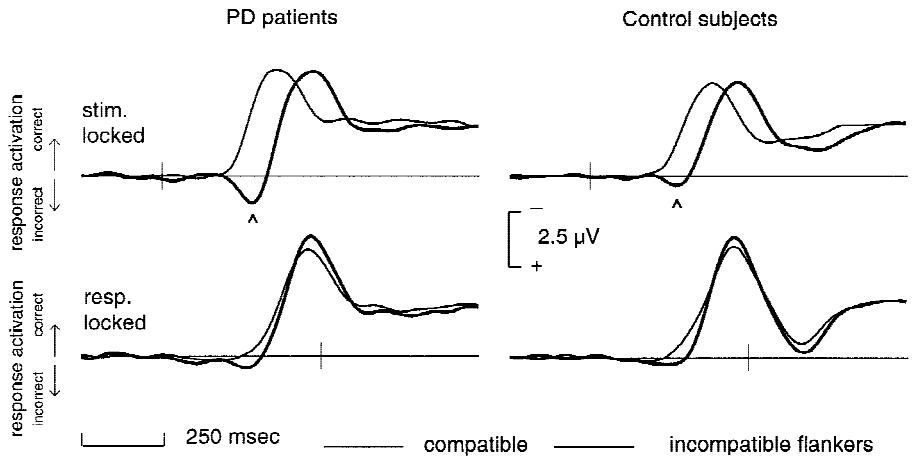

FIG. 1. Group-averaged LRPs for patients and control subjects. The uppermost waveforms represent LRPs that are averaged with reference to stimulus onset, which is indicated by the vertical line. The positive deflection of the LRP in the incompatible condition, indicated by arrowheads, is caused by initial activation of the incorrect response, that is, a brief activation of the motor cortex ipsilateral to the correct response hand. In the lower panel the LRPs averaged in a response-locked fashion are represented.

conditions. The initial positive (downward) deflection of the LRP in the incompatible condition demonstrates that in this condition, the wrong response side was initially activated more strongly than the correct side. In the stimulus-locked averages, the amplitude of this initial positive deflection was higher in patients than in control subjects ($t[17] = 2.36$, $p < 0.05$ two-tailed). Thus, both the reaction times and the incorrect lateralization of the LRP support the conclusion that patients with PD were influenced more strongly by the incompatible flankers than the control subjects.

Activation of the incorrect response was less conspicuous when the movement-related EEG activity was averaged relative to the response instead of to the stimulus. Moreover, the amplitude of the incorrect activation now no longer differed between the groups ($t[17] = 1.67$, $p > 0.05$), indicating that the surplus activity in patients was more closely synchronized to the stimulus than to the response.

TABLE 3. *Amplitude and slope of LRP, EMG, and force signals for patients with Parkinson's disease (PD) and control subjects (mean ± 1 standard deviation)*

	Condition		
	Compatible	Neutral	Incompatible
LRP amplitude (μV)			
Control subjects	8.9 ± 3.5	8.8 ± 3.7	9.2 ± 3.5
PD patients	10.6 ± 4.0	10.9 ± 4.1	11.8 ± 3.7
LRP slope (μV/s)			
Control subjects	41.7 ± 17.9	40.3 ± 17.8	49.1 ± 7.1
PD patients	46.8 ± 17.9	43.3 ± 21.3	66.9 ± 30.3
EMG amplitude (μV)			
Control subjects	122 ± 63	119 ± 64	125 ± 61
PD patients	124 ± 40	124 ± 37	135 ± 47
EMG slope (10^{-2}·μV/s)			
Control subjects	12.2 ± 6.6	12.1 ± 7.4	13.3 ± 7.4
PD patients	9.8 ± 5.8	10.4 ± 5.3	8.8 ± 4.6
Force amplitude (N)			
Control subjects	162 ± 51	163 ± 51	169 ± 58
PD patients	153 ± 38	153 ± 37	159 ± 37
Force slope (10^{-2}·N/s)			
Control subjects	12.8 ± 3.4	13.0 ± 3.4	13.7 ± 3.4
PD patients	9.5 ± 3.7	9.6 ± 3.4	9.8 ± 3.8

LRP, lateralized readiness potential; EMG, electromyography.

The latency of the LRP was shorter in the compatible than in the incompatible condition ($F[1,17] = 484.53$, $p < 0.001$) and the amplitude was lower ($F[1,17] = 7.40$, $p < 0.05$). The slope of the LRP was steeper in the incompatible condition ($F[1,17] = 9.66$, $p < 0.01$) (see Tables 2 and 3). No significant differences between patients and control subjects were found for any of these variables.

EMG and Force Measures

The force amplitude was higher in the incompatible condition than in the neutral and compatible conditions ($F[1,17] = 5.63$, $p < 0.05$). This effect approached significance for the EMG signal ($F[1,17] = 3.62$, $p < 0.10$). These differences are most likely an expression of the response competition induced by the incompatible stimuli. After the initial activation of the incorrect response, the correct response is a corrective response that is executed more forcefully than the responses in the compatible condition. The higher amplitude of the force signal in the incompatible condition corresponds to the higher amplitude of the LRP in this condition, as reported above. EMG and force amplitude did not differ between patients and control subjects.

Like the reaction times, EMG and force peak latencies were longer in the incompatible than in the compatible and neutral conditions (EMG: $F[1,17] = 73.69$, $p < 0.001$; Force: $F[1,17] = 291.80$, $p < 0.001$). However, while the reaction times were shorter in patients than in control subjects, the EMG and force peak latencies were slightly longer, although these differences were not significant. This reversal suggests, nonetheless, that response execution was slower in patients than in control

subjects. Quantitative analyses of the slope of the force signals confirmed this, because the slope was steeper in control subjects than in patients ($F[1,17] = 4.91$, $p < 0.05$). Probably as a result of a larger variability in this measure (see Table 3), the slope of the EMG signal was not significantly different between the groups.

LRP, EMG, and Force in Fast and Slow Response Latency Bins

The dissociation between a normal rate of development of cortical activity in patients and a slower than normal rate of force generation (see Fig. 2) was further explored by evaluating LRP, EMG, and force across different reaction time bins. Preliminary analyses established that the mean number of trials from earliest through latest bin were not different between groups. We contrasted the fast and slow bins, which included comparable numbers of trials. The mean number of trials (across response sides) was for control subjects 60 ± 8 versus 47 ± 6 and for patients 64 ± 6 versus 47 ± 7 in fast versus slow bins.

In analyses of signal amplitudes, only EMG amplitude decreased from the earliest to the latest bin ($F[1,17] = 5.89$, $p < 0.05$), and tended to do so more in the patient group than in control subjects, as indicated by a marginally significant interaction of group by bin ($F[1,17] = 4.19$, $p < 0.06$) and subsequent simple effect analysis of bin within the patient group ($F[1,17] = 10.57$, $p < 0.01$; see Fig. 3).

Analyses of the slopes of EMG and force signals showed the same pattern as the earlier analyses of the unbinned data but were more sensitive to group differences. Thus, the slope of the EMG and force signals differed significantly between the groups (EMG: $F[1,17] = 4.58$, $p < 0.05$; force: $F[1,17] = 10.66$, $p < 0.01$). However, the group by bin interaction was not significant for force or for the EMG signal. The simple effects analyses of bin (fast versus slow) within group showed that the slope of the force signal decreased for patients ($F[1,17] = 5.37$, $p < 0.05$) but not for control subjects ($F[1,17] < 1$). Similarly, for the EMG slope, a difference was found between the earliest and the latest bin for the patient group ($F[1,17] = 5.46$, $p < 0.05$) but not for control subjects ($F[1,17] = 2.48$).

Whereas the slopes of EMG and force decreased with increasing response latency, the slope of the LRP increased. This increase was larger for patients than for control subjects, yielding a significant group by bin interaction ($F[1,17] = 5.56$, $p < 0.05$). Analyses of simple effects showed a significant increase across bins for patients ($F[1,17] = 14.51$, $p < 0.01$) but not for the control subjects ($F[1,17] < 1$).

The question of whether latency changes from first to third bin were similar for each measure and comparable for patients and control subjects was addressed by computing the difference between LRP peak latency and force peak latency. Comparing the first and third bin, this latency difference increased more strongly for the patient group than for the control subjects, as indicated by an interaction of group by bin ($F[1,17] = 5.58$, $p < 0.05$; see Fig. 4).

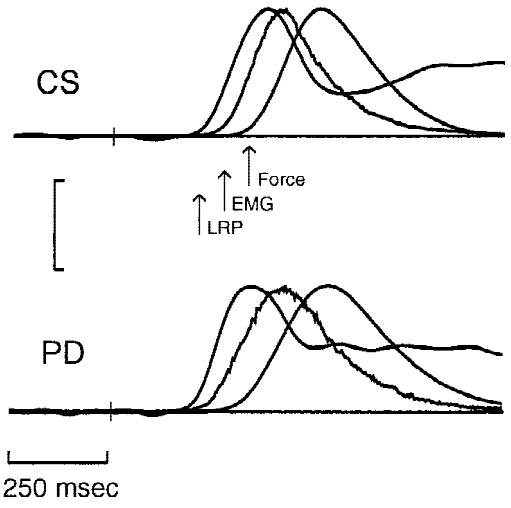

FIG. 2. LRP, EMG, and force signals averaged across compatible and neutral conditions normalized to the same (arbitrary) scale to illustrate the dissociation between central and peripheral measures in the patients with Parkinson's disease.

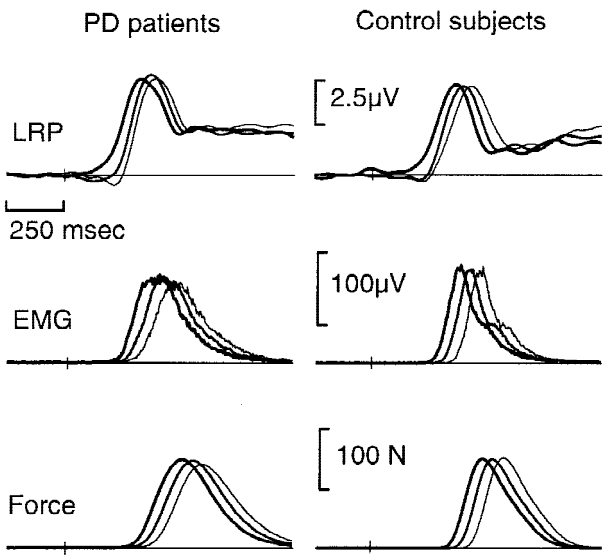

FIG. 3. From top to bottom: LRP, EMG, and force signals in fast, medium, and slow response latency bins. Note that from the fast to the slow latency bin, there is no decrease in the slope of the LRP for either of the groups. In the patient group, the slope of EMG and force signals decrease from the fast to the slow response latency bin.

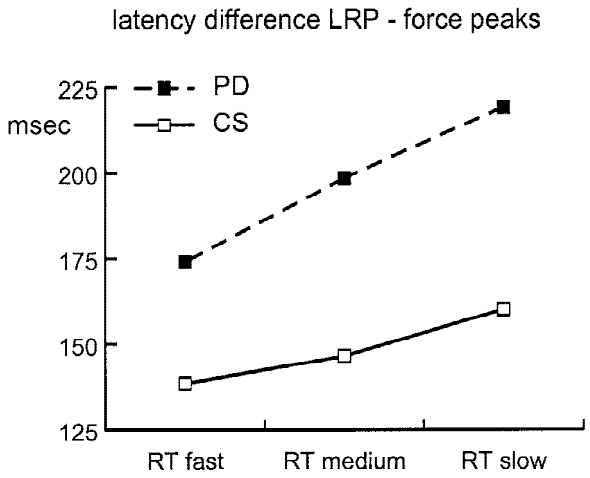

FIG. 4. The LRP peak latency increased less for patients than for control subjects across response latency bins, whereas the peak latency of the force signal showed a larger increase in the patient group. These tendencies add up to a significantly larger increase of the latency difference between LRP and force peaks for patients compared with control subjects.

DISCUSSION

The present study replicates the abnormal performance of patients with PD reported in an earlier study with a similar task.[17] The most important new finding is the dissociation between a normal rate of development of neural activity in the motor cortex, as measured with movement-related potentials recorded from the scalp, and a slower rate of force production. This dissociation will be our main concern in the following discussion.

Noise-Compatibility Effects

In noise-compatibility tasks, slower responses are observed when distractors are incompatible with the target than when they are neutral or compatible.[11,24,25] In the present study, this reaction time effect was substantial and significantly larger in patients than in control subjects. The delayed reaction in the incompatible condition has been attributed in part to a response conflict induced by incompatible target and distractors, which instruct for responses of opposite hands.[11,25] This response conflict was manifested in the LRP as an initial deflection of positive polarity caused by activation of the motor cortex controlling the wrong response hand.[11] Supporting the reaction time findings and consistent with our previous work, the incorrect lateralization of the LRP was of higher amplitude in patients than in control subjects.[17]

An unexpected finding was that the reaction times in the neutral condition were similar to those in the compatible condition. This result may be related to faster recognition of the arrow target amidst bars than amidst identical visual elements. In addition, because of the different shapes of target and distractors in the neutral condition, subjects only have to identify the target, whereas in the compatible condition, they have to process identity and location information. These effects may have canceled out any facilitation by redundant target information in the compatible condition.[26]

We found no overall reaction time delay for the patients with PD. The choice of stimuli, the large number of trials providing ample practice, and the strong emphasis on response speed in the instructions may have contributed to the short reaction times for the patients with PD. Normal rather than delayed reaction times in PD are uncommon although not unprecedented (for reviews, see references 27 and 28) and have also been found after pallidal inactivation.[29]

Comparison of Central and Peripheral Measures of Response Generation

The main analysis did not show any evidence for a slower rise of the LRP in patients with PD compared with control subjects. On the contrary, analyses comparing fast and slow response latency bins showed that the slope of the LRP increased, paradoxically, from fast to slow response bin for patients, whereas the EMG and force slopes decreased. As shown in Figure 3, there was an early and gradual rise of the LRP in the fast bin for both groups. In the slow response latency bin, there was an early lateralization in the opposite direction. These early effects reflect preactivation of either correct or false response side and have been attributed to response biases existing before the occurrence of the reaction stimulus.[30] This phenomenon influences the LRP slope and implies that the changes of the LRP slope across latency bins are not an entirely selective measure of changes in contralateral motor cortex activation and therefore have to be interpreted with caution. Notwithstanding this inherent limitation of the LRP, it can be concluded that the slope of the LRP was not decreased in patients with PD.

In contrast to the LRP, the rate of force development was significantly slower in patients than in control subjects, consistent with earlier studies that recorded isometric force in PD.[31,32] In addition to the overall difference in force slope between patients and control subjects, the analyses suggested a picture of impoverished EMG and force generation with increasing response latency. While this picture is not supported in the strongest possible way, coherent evidence is the observation that, from the fast to the slow response latency bin (spanning just 150 msec), EMG amplitude tended to decrease more for patients than for control subjects. It is also supported by the latency difference between LRP and force peaks which,

from fast to slow latency bins, increased more for the patient group (see Fig. 4). Finally, the slope of EMG and force decreased significantly from fast to slow latency bins in patients but not in the control subjects.

Together, the analyses of central and peripheral measures of response generation yield a dissociation between an apparently normal motor cortex activation and abnormal motor output in the PD group. In interpreting this dissociation, it must be acknowledged that the measured data represent averaged signals whose characteristics can be considerably influenced by intra-individual variability in response latencies. However, this does not provide an explanation for the dissociation, because there was no difference in the spread of response latencies (see Table 2) or in the number of averaged responses between the groups. It might also be argued that the LRP, while recorded at electrode sites overlying the motor cortex, is still an indirect measure of motor cortex activation. Although it is true that the LRP may pick up activity from other areas than only the primary motor cortex, its derivation from the MP (motor potential) component of the readiness potential establishes the primary motor cortex as its main generator.[12–15] Appropriate to a signal from the motor cortex,[33,34] the MP is sensitive to the rate of force production.[35] Thus, given that force production in our patient group was slower than in control subjects, the normal rate of development of motor cortex activity, as measured by the LRP, needs further explanation.

Motor Cortex Activation in Parkinson's Disease

As discussed at the beginning of this article, there is evidence for changes in primary motor cortex function in PD based on cell recordings in the motor cortex of monkeys with MPTP-induced parkinsonism.[5,6] In agreement with these data, transcranial magnetic stimulation studies of the motor cortex have suggested that the development of motor cortex activity is slower than normal in PD.[8–10] How should the findings of this study be interpreted against the existing evidence for impaired development of M1 neuronal activity in PD?

The discrepancy between central and peripheral measures might be the result of coactivation of agonist and antagonist muscles, which can contribute to bradykinesia.[29] However, in the analyses of LRP, EMG, and force signals in separate response latency bins, EMG and force slopes demonstrated a significant group difference, which makes this explanation unlikely. Another possibility is that the slow rate of EMG and force development are related to changes in peripheral mechanisms mediating response execution. This cannot be ruled out with certainty and may contribute to the dissociation between cortical and peripheral measures.

An explanation that may reconcile the normal rate of rise of the LRP with the abnormal peripheral measures in the group of patients with PD is that impaired movement-related activity is concealed from view by abnormal neural activity of another kind. Unit recordings in the monkey motor cortex have shown that the LRP receives an early contribution from sensory and sensorimotor type neurons with signal rather than movement-related response properties.[36] This contribution might be stronger in patients than in control subjects. A relative increase of signal-related neural activity in the motor cortex of patients with PD is supported, in our data, by the fact that the incorrect lateralization of the LRP, in the incompatible condition, was of higher amplitude in patients than in control subjects when the LRP was averaged with respect to stimulus-onset, but not when it was averaged in response-locked fashion (see Fig. 1). A similar increase of signal-related activity should also be present in the compatible and neutral conditions and can be responsible for the normal appearance of the LRP, because it is likely to enhance its slope.

Like we have discussed in a previous report, increased signal-related neural activity in the motor cortex may be the result of a compensation mechanism.[17] It might be the case that as sensory-type neurons in the motor cortex are activated more strongly or in larger proportions, movement initiation improves, resulting from more effective activation of the corticospinal output neurons. Alternatively, increased signal-related neural activity may be the result of spurious activation of inappropriate populations of cortical cells in response to sensory input. Such spurious activation may underlie the enhanced long-latency stretch reflex in PD and a relation has been suggested to the decreased corticocortical inhibition demonstrated with transcranial magnetic stimulation by Ridding and coworkers.[7] Assuming a role of the basal ganglia in preparing motor cortical areas for a forthcoming movement, which is recognized as a process that includes a regulation of the motor cortex' susceptibility to sensory input,[37] decreased intracortical inhibition may lead to increased responsiveness to sensory stimulation. Results in healthy subjects, indicating that this responsiveness is influenced by the predictability of stimulus occurrence, also support such a mechanism.[38]

CONCLUSIONS

This report extends a previous study in which we found that stimuli inducing a response conflict between the two hands produce a stronger response of the wrong motor cortex in patients with PD than in control subjects. Evidence is provided here that this increased activation, expressed in an incorrect lateralization of movement-

related potentials, is the result of stimulus-synchronized rather than response-locked neural activity. A general increase of stimulus-locked neural activity in the motor cortex may be responsible for the normal LRP slope that was observed in the presence of impaired development of peripheral response measures in patients with PD. On this account, the intriguing dissociation between central and peripheral response measures, reported here for the first time, does not contradict the common view that the corticomotoneuron tract is normal in PD.[39] The dissociation does point, however, to changes in primary motor cortex function in PD, which may be related to the motor cortex dysfunction inferred from increased excitability to transcranial magnetic stimulation.[7] To assess the functional meaning of the dissociation, further research is needed into processes of sensory-to-motor translation in the motor cortex in PD.

Acknowledgments: The authors thank the patients and volunteers who participated in this study. D. Stegeman gave valuable comments on the manuscript and L. Haegens, C. Berenstein, and H. van Dijk provided technical and software support.

REFERENCES

1. Jenkins IH, Fernandez W, Playford ED, et al. Impaired activation of the supplementary motor area in Parkinson's disease is reversed when akinesia is treated with apomorhine. *Ann Neurol* 1992;32: 749–757.
2. Rascol O, Sabatini U, Chollet F, et al. Normal activation of the supplementary motor area in patients with Parkinson's disease undergoing long-term treatment with levodopa. *J Neurol Neurosurg Psychiatry* 1994;57:567–571.
3. Grafton ST, Waters C, Sutton J. Pallidotomy increases activity of motor association cortex in Parkinson's disease: a positron emission tomography study. *Ann Neurol* 1995;37:776–783.
4. Limousin P, Greene J, Pollak P, Rothwell J, Benabid AL, Frackowiak R. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Ann Neurol* 1997;42:283–291.
5. Doudet DJ, Gross C, Arluison M, Bioulac B. Modifications of precentral cortex discharge and EMG activity in monkeys with MPTP-induced lesions of DA nigral neurons. *Exp Brain Res* 1990; 80:177–188.
6. Watts RL, Mandir AS. The role of motor cortex in the pathophysiology of voluntary movement deficits associated with parkinsonism. *Neurol Clin* 1992;10:451–469.
7. Ridding MC, Inzelberg R, Rothwell JC. Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. *Ann Neurol* 1995;37:181–188.
8. Pascual-Leone A, Valls-Sole J, Brasil-Neto JP, Cohen LG, Hallett M. Akinesia in Parkinson's disease. I: shortening of simple reaction time with focal, single-pulse transcranial magnetic stimulation. *Neurology* 1994;44:884–891.
9. Pascual-Leone A, Valls-Sole J, Brasil-Neto JP, Cammarota A, Grafman J, Hallett M. Akinesia in Parkinson's disease. II: effects of subthreshold repetitive transcranial motor cortex stimulation. *Neurology* 1994;44:892–898.
10. Hallett M, Cohen LG, Bierner SM. Studies of sensory and motor cortex physiology: with observations on akinesia in Parkinson's disease. In: Levy WJ, Cracco RQ, Barker AT, Rothwell JC, eds. *Magnetic Motor Stimulation: Basic Principles and Clinical Experience. Electroencephalogr Clin Neurophysiol*, suppl 43. Amsterdam: Elsevier, 1991:76–85.
11. Coles MGH, Smid HGOM, Scheffers MK, Otten LJ. Mental chronometry and the study of human information processing. In: Rugg MD, Coles MGH, eds. *Electrophysiology of Mind: Event-Related Brain Potentials and Cognition.* Oxford: Oxford University Press, 1995:86–131.
12. Eimer M. The lateralized readiness potential as an on-line measure of central response activation processes. *Behavior Research Methods, Instruments, and Computers* 1998;30:146–156.
13. Deecke L, Scheid P, Kornhuber HH. Distribution of readiness potential, pre-motion positivity, and motor potential of the human cerebral cortex preceding voluntary finger movements. *Exp Brain Res* 1969;7:158–168.
14. Arezzo J, Vaughan HG. Intracortical sources and surface topography of the motor potential and somatosensory evoked potential in the monkey. *Prog Brain Res* 1980;54:77–83.
15. Neshige R, Lüders H, Shibasaki H. Recording of movement-related potentials from scalp and cortex in man. *Brain* 1988;111: 719–736.
16. Praamstra P, Meyer AS, Cools AR, Horstink MWIM, Stegeman DF. Movement preparation in Parkinson's disease: time course and distribution of movement-related potentials in a movement precueing task. *Brain* 1996;119:1689–1704.
17. Praamstra P, Stegeman DF, Cools AR, Horstink MWIM. Reliance on external cues for movement initiation in Parkinson's disease. Evidence from movement-related potentials. *Brain* 1998;121:167–177.
18. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–184.
19. Lang AET, Fahn AS. Assessment of Parkinson's disease. In: Munsat TL, ed. *Quantification of Neurologic Deficit.* Boston, MA: Butterworths, 1989:285–309.
20. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;17:427–442.
21. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
22. Smulders FTY, Kenemans JL, Kok A. Effects of task variables on measures of the mean onset latency of LRP depend on the scoring method. *Psychophysiology* 1996;33:194–205.
23. SPSS for Windows. *Advanced Statistics*, release 5. Chicago, IL: SPSS, 1992.
24. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception and Psychophysics* 1974;16:143–149.
25. Coles MGH, Gratton G, Bashore TR, Eriksen CW, Donchin E. A psychophysio-logical investigation of the continuous flow model of human information processing. *J Exp Psychol Hum Percept Perform* 1985;11:529–553.
26. Eriksen CW, Schultz DW. Information processing in visual search: a continuous flow conception and experimental results. *Perception and Psychophysics* 1979;25:249–263.
27. Jahanshahi M, Brown RG, Marsden CD. Simple and choice reaction time and the use of advance information for motor preparation in Parkinson's disease. *Brain* 1992;115:539–564.
28. Harrison J, Henderson L. Kennard C. Abnormal refractoriness in patients with Parkinson's disease after brief withdrawal of levodopa treatment. *J Neurol Neurosurg Psychiatry* 1995;59:499–506.
29. Mink JW, Thach WT. Basal ganglia motor control. III: pallidal ablation: normal reaction time, muscle contraction, and slow movement. *J Neurophysiol* 1991;65:330–351.
30. Gratton G, Coles MGH, Sirevaag EJ, Eriksen CW, Donchin E. Pre- and post-stimulus activation of response channels: a psychophysiological analysis. *J Exp Psychol Hum Percept Perform* 1988;14: 331–344.
31. Jordan N, Sagar HJ, Cooper JA. A component analysis of the

generation and release of isometric force in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1992;55:572–576.
32. Stelmach GE, Teasdale N, Phillips J, Worringham CJ. Force production characteristics in Parkinson's disease. *Exp Brain Res* 1989; 76:165–172.
33. Evarts EV, Fromm C, Kröller J, Jennings VA. Motor cortex control of finely graded forces. *J Neurophysiol* 1983;49:1199–1215.
34. Smith AM, Hepp-Reymond MC, Wyss UR. Relation of activity in precentral cortical neurons to force and of force change during isometric contractions of finger muscles. *Exp Brain Res* 1975;23: 315–332.
35. Slobounov SM, Ray WJ. Movement-related potentials with reference to isometric force output in discrete and repetitive tasks. *Exp Brain Res* 1998;123:461–473.
36. Miller J, Riehle A, Requin J. Effects of preliminary perceptual output on neuronal activity of the primary motor cortex. *J Exp Psychol Hum Percept Perform* 1992;18:1121–1138.
37. Rossini PM, Paradiso C, Zarola F, et al. Brain excitability and long latency muscular arm responses: non-invasive evaluation in healthy and parkinsonian subjects. *Electroencephalogr Clin Neurophysiol* 1991;81:454–465.
38. Goodin DS, Aminoff MJ, Ortiz TA, Chequer RS. Response times and handedness in simple reaction-time tasks. *Exp Brain Res* 1996; 109:117–126.
39. Dick JPR, Cowan JMA, Day BL, et al. The corticomotoneurone connection is normal in Parkinson's disease. *Nature* 1984;310: 407–409.