Failed Suppression of Direct Visuomotor Activation in Parkinson's Disease

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Abstract

■ The response times in choice-reaction tasks are faster when the relative spatial positions of stimulus and response match than when they do not match, even when the spatial relation is irrelevant to response choice. This spatial stimulus–response (S–R) compatibility effect (i.e., the Simon effect) is attributed in part to the automatic activation of spatially corresponding responses, which need to be suppressed when the spatial location of stimulus and correct response do not correspond. The present study tested patients with Parkinson's disease and healthy control subjects in a spatial S–R compatibility task in order to investigate whether basal ganglia dysfunction in Parkinson's disease leads to disinhibition of direct visuomotor activation. High-density event-related brain potential recordings were used to chart the cortical activity accompanying attentional orientation and response selection. Response time measures demonstrated a failure to inhibit automatic response activation in Parkinson patients, which was revealed by taking into account a sequence-dependent modulation of the Simon effect. Event-related potential (ERP) recordings demonstrated that visuospatial orientation to target stimuli was accompanied by signal-locked activity above motor areas of the cortex, with similar latencies but an enhanced amplitude in patients compared to control subjects. The results suggest that inhibitory modulation of automatic, stimulus-driven, visuomotor activation occurs after the initial sensory activation of motor cortical areas. The failed inhibition in Parkinson's disease appears therefore related to a disturbance in processes that prevent early attention-related visuomotor activation, within motor areas, from actually evoking a response. ■

INTRODUCTION

Slowness in the initiation and execution of movements is a key feature of Parkinson's disease, but patients are not invariably slow or delayed in all components of a speeded response task. There are occasional observations of faster than normal shifts of visual attention from old to new locations or stimulus features, attributed to abnormally rapid disengagement or ''hyperreflexive'' orientation of attention (Jackson & Houghton, 1995; Filoteo et al., 1994; Wright, Geffen, & Geffen, 1993). The fact that attention is usually moved in concert with the eyes, head, and body raises the question whether such rapid shifts of attention in Parkinson's disease reflect a general impairment in the ability to inhibit automatic response tendencies. A failure to suppress automatic behavioral tendencies, however, is well-recognized in investigations of cognitive function in basal ganglia diseases (Hayes, Davidson, Keele, & Rafal, 1998; Rafal & Henik, 1994; Owen et al., 1993), but is not often considered relevant to the parkinsonian motor disturbance or perceived as a feature that may shed light on the role of the basal ganglia in motor control. Only recently have basal ganglia and motor cortical areas been discussed as jointly involved in the suppression of automatic behavioral tendencies (Wise, di Pellegrino, & Boussaoud, 1996; Wise, Murray, & Gerfen, 1996). More specifically, Wise et al. proposed that basal ganglia and motor cortex have a role in suppressing direct visuospatially guided movements in order to allow control by nonspatial stimuli or stimulus attributes. Against this background, we investigated in this study whether basal ganglia dysfunction in Parkinson's disease leads to disinhibition of direct visuomotor activation.

The notion of automatic response tendencies and the inhibitory modulation of automatic processes are common elements in current models of the effects of spatial stimulus–response (S–R) compatibility, as investigated in the Simon task (for a review, see Simon, 1990). In this choice-reaction task, subjects typically respond faster when the relative spatial positions of stimulus and response match (compatible condition), than when the positions do not match (incompatible condition). To explain the Simon effect, ''dual route'' models assume that a direct and an indirect route mediate between stimulus and response, with the direct route subserving automatic, stimulus-driven, response tendencies and the indirect route mediating controlled response selection (De Jong, Liang, & Lauber, 1994; Kornblum, Hasbroucq, & Osman, 1990; Frith & Done, 1986). The automatic response activation supports the selection of the re-

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sponse demanded by the stimulus, thus producing short reaction times, when the spatial positions of stimulus and response correspond. In contrast, when the spatial relation between stimulus and response does not match, the automatic response tendency toward the stimulus must be inhibited, yielding longer reaction times. To elucidate the covert process of direct response activation, recent studies on spatial S–R compatibility have used event-related brain potentials (ERPs) to complement reaction times as a measure of the overt response (Wascher & Wauschkuhn, 1996; Eimer, 1995; De Jong et al., 1994). Further evidence on the neurophysiological basis of spatial S–R effects comes mainly from research in the monkey (Zhang et al., 1997; Riehle, Kornblum, & Requin, 1997; Shen & Alexander, 1997; Wise, di Pelligrino, et al., 1996; Crammond & Kalaska, 1994; Alexander & Crutcher, 1990), and from positron emission tomography studies in humans (Iacoboni, Woods, & Mazziotta, 1998).

The spatial S–R compatibility task was used in the present study to investigate automatic activation of motor responses and the adequacy of inhibitory mechanisms in visuomotor control in Parkinson's disease. During task performance, the event-related potentials (ERPs) were recorded with a dense array of scalp electrodes for optimal spatial definition of relevant ERP components. Especially relevant to the question how basal ganglia dysfunction affects visuomotor processes are lateralized ERPs associated with attention and sensorimotor processing, in particular the N2pc (**p**osterior **c**ontralateral) and the lateralized readiness potential (LRP) (Praamstra, Stegeman, Cools, & Horstink, 1998; Praamstra, Meyer, Cools, Horstink, & Stegeman, 1996; Wascher & Wauschkuhn, 1996; Wascher, Reinhard, Wauschkuhn, & Verleger, 1999; Coles, Smid, Scheffers, & Otten, 1995; Luck & Hillyard, 1994). One noteworthy feature of previous ERP studies on spatial S–R compatibility is that they used a vertical arrangement of reaction stimuli and response keys, instead of horizontally lateralized stimuli, in order to avoid overlap of attention- and movement-related potentials (e.g., De Jong et al., 1994; see also Eimer, 1998). Here, we deliberately used the conventional left–right S–R arrangement, in the expectation that a sufficiently dense spatial sampling of brain electrical activity should allow differentiation of overlapping components. Moreover, keeping track of lateralized attention-related activity, instead of preventing its occurrence, might provide clues to the neural mechanisms underlying automatic, stimulus-driven, response activation.

RESULTS

Response Measures

The overall response times, determined from the recorded force signals, were markedly faster for Parkinson patients than for healthy controls (427 vs. 483 msec), $F(1,14) = 8.39, p < .05$. In contrast, the time from force onset to peak force was almost twice as long for patients than for control subjects, $F(1,14) = 37.33$, $p < .001$, consistent with the patients' manifest slowness and clinical ratings of their motor performance. As a result, the peak-force latencies were later for patients than for control subjects (623 vs. 590 msec), though this difference was not significant. Force amplitude did not differ between the groups, $F(1,14) < 1$.

Compatibility of stimulus location and response side influenced response times according to the typical pattern in the Simon task, with spatially compatible responses being more than 30 msec faster than spatially incompatible responses (main effect of compatibility, $F(1, 14) = 31.81, p < .001$; Table 1). The size of this compatibility effect was larger for Parkinson patients than for control subjects (38 vs. 27 msec), but the difference was not significant (Group × Compatibility interaction, $F(1, 14) < 1$). However, while comparable measures of intraindividual variability of response times indicated a consistent task performance in both groups, the variability was relatively larger for control subjects in the compatible condition (Group × Compatibility interaction, $F(1, 14) = 13.70, p < .01$), suggesting a difference in behavior not captured in the mean response times (Table 1).

An explanation for the different response variability and specific evidence for inappropriate release of automatic response tendencies in Parkinson's disease were revealed by reaction time analyses that took the sequential dependencies between successive trials into account. When each trial was classified as preceded by a trial with compatible or incompatible S–R locations, it emerged that control subjects adjusted their performance from

Table 1. Response Measures (Mean ± 1 *SD*)

	Compatible Condition	*Incompatible Condition*
Response time (msec)		
Control subjects	470 ± 38	496 ± 52
PD patients	408 ± 32	446 ± 47
Response variability (msec)		
Control subjects	93 ± 18	74 ± 17
PD patients	72 ± 13	72 ± 13
Time-to-peak force (msec)		
Control subjects	107 ± 11	106 ± 10
PD patients	195 ± 39	196 ± 40
Errors (%)		
Control subjects	1.3 ± 1.1	3.1 ± 2.2
PD patients	2.8 ± 1.5	7.2 ± 3.4

PD = Parkinson's Disease.

Table 2. Sequence-Dependent Modulation of Simon Effect in msec (Mean Reaction Times ± 1 *SD* [in msec])

	Preceding Trial Compatible		*Preceding Trial Incompatible*	
Condition	*Compatible*	*Incompatible*	*Compatible*	*Incompatible*
Control subjects	453 ± 41	505 ± 55	482 ± 43	484 ± 48
PD patients	397 ± 37	450 ± 43	416 ± 42	439 ± 40

PD = Parkinson's Disease.

trial to trial, whereas the spatial S–R correspondence within a current trial had an overriding influence in Parkinson patients. Thus, in the control subjects, the Simon effect was 52 msec for the subset of trials preceded by a trial with compatible S–R locations, but only 2 msec for the subset with incompatible S–R locations in the preceding trial. In Parkinson patients, these effect sizes were 53 and 23 msec, respectively (Group × Compatibility × Sequence interaction, $F(1,14) = 5.30$, $p < .05$; Table 2).

Like the reaction time results, the error pattern indicated that Parkinson patients were more sensitive than control subjects to the spatial relation of stimulus and response side (Table 1). Errors were made more frequently with incompatible than with compatible S–R locations, $F(1,14) = 27.99$, $p < .001$, and Parkinson patients made significantly more errors than control subjects, $F(1,14) = 9.06$, $p < .05$, especially with incompatible S–R locations (Group × Compatibility interaction, $F(1,14) = 5.32$, $p < .05$). Patients also tended to be more prone to error following a trial with compatible S–R relation, but this failed to reach significance (Group × Sequence interaction, $F(1,14) = 3.07$, $p = 0.107$). The erroneous responses included a negligible number (0.03% across all participants) of anticipation errors (responses < 200 msec), and a very low number of missing responses (0.3%), with no differences between the groups.

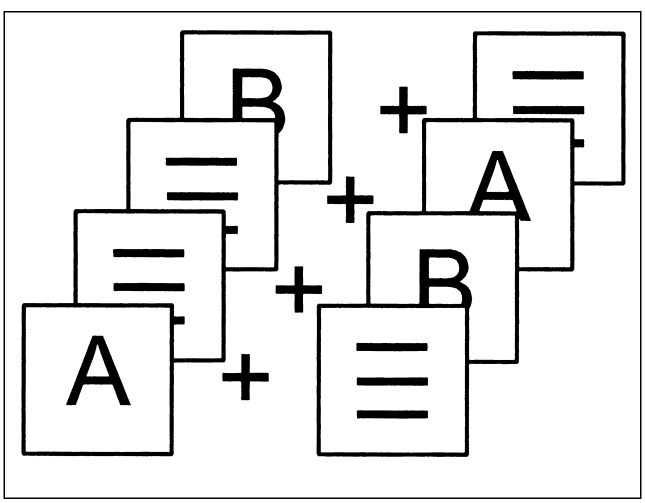

Figure 1. The four stimuli used in the spatial S–R compatibility task. The letters "A" and "B" always instructed for a left and right hand response, respectively, independent of whether they appeared to the left or to the right from the fixation cross.

Event-Related Potentials

Figure 2 illustrates the ERP waveforms averaged across conditions, emphasizing a difference in amplitude of the centrally distributed N2 component between Parkinson patients and control subjects. The distribution suggests that the difference is due to reduced activity in fronto-central midline structures in the Parkinson group. An analysis of the N2 amplitude encompassing all electrode sites yielded a group effect that approached significance, $F(1,14) = 3.99$, $p = 0.066$. Compatibility did not affect the N2 amplitude, $F(1,14) < 1$, nor were there significant interactions involving the group and compatibility variables. Given its unambiguous distribution with a central maximum, an additional analysis was performed on a subset of electrodes along and directly beside the midline (Fz, FCz, Cz, CPz, Pz, FC1, C1, CP1, FC2, C2, CP2). This analysis produced similar results and yielded only a slightly stronger group difference, $F(1,14) = 4.60$, $p < .05$. The discrepancy between the marginal statistical significance and the size of the group difference as reflected in the ERP waveforms, shown in Figure 2, was due to large variability between subjects.

Lateralized ERPs (N2pc and LRP)

The lateralized ERP waveforms showed three successive lateralizations, representing lateralized visual-evoked activity (not further considered), lateralized attention-related activity, and lateralized movement-related activity. The scalp voltage distribution of the group-averaged attention-related N2pc was plotted at peak latency, as represented in Figure 3. For the control subjects, the scalp topography demonstrated an occipito-temporal maximum, consistent with earlier reports on the N2pc. In the patient group, the N2pc topography in the compatible condition showed a shift of the maximum amplitude to central scalp sites. However, for both groups, scalp current source density (CSD) maps resolved the scalp topography unambiguously in current extrema at occipito-temporal and central scalp sites overlying the motor cortex. The well-defined CSD topography, with

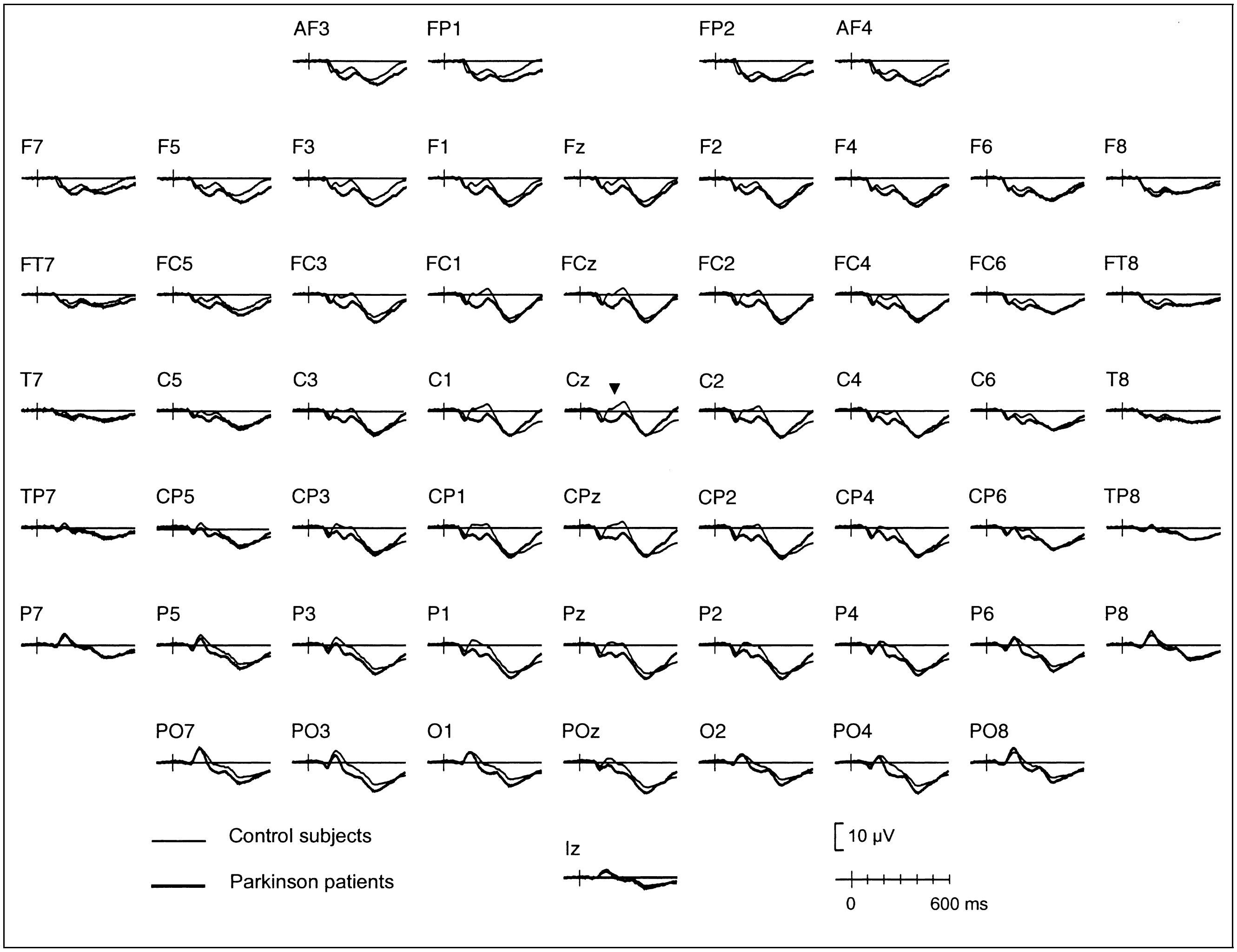

Figure 2. Group-averaged ERPs from control subjects and Parkinson patients. Superimposed are waveforms averaged across compatible/incompatible and left/right hand conditions. The arrow head at Cz marks the central N2 difference between patients and control subjects.

identically located current extrema in patients and control subjects, justified the selection of waveforms recorded at scalp sites nearest to these current extrema for further analyses (C3/C4 and PO7/PO8).

The peak latency of the N2pc was, for both groups, close to 250 msec and did not differ at occipito-temporal and central electrodes. Thus, effects of group, compatibility, and electrode, as well as their interactions were not significant, $F(1,14) < 1$. However, the amplitude relation of the two CSD extrema diverged between the groups. At the central location, but not at occipito-temporal sites, the attention-related N2pc was enhanced for patients relative to controls in the compatible condition (Group × Compatibility × Electrode interaction, $F(1,14) = 23.55$, $p < .001$; Figure 4). That the enhancement was specific for the central electrode site and the compatible condition was confirmed in analyses of simple effects, yielding a significant Group × Compatibility interaction at the central location, $F(1,14) = 15.76$, $p < .001$, but not occipitally, $F(1,14) < 1$. The specificity is underscored by the fact that the group difference at the occipital location, suggested in Figure 4, did not even approach significance, $F(1,14) < 1$. There were no significant main effects for the variables group, compatibility, or electrode.

The Parkinson patients' focal enhancement above the motor cortex, in the compatible condition, was not due to a normal N2pc "riding" on an unusually early LRP immediately following the N2pc. This explanation was ruled out by the fact that the same enhancement was present in a comparison of the four slowest Parkinson patients and the four fastest control subjects, who had comparable reaction times (Group × Compatibility × Electrode interaction, $F(1,6) = 11.83, p = 0.014$). Neither could the enhancement be attributed to horizontal eye movements towards the target stimuli, because the recording channel for eye movements showed activity of the same amplitude (albeit opposite polarity) in compatible and incompatible conditions $F(1,7) = 1.16$, $p = 0.318$; Figure 4). The exclusion of these two interpretations provides support for an interpretation of the focal enhancement as a neural correlate of the patients' altered behavior in the Simon task.

In the time frame immediately following the attention-related N2pc, movement-related activity (i.e., the LRP)

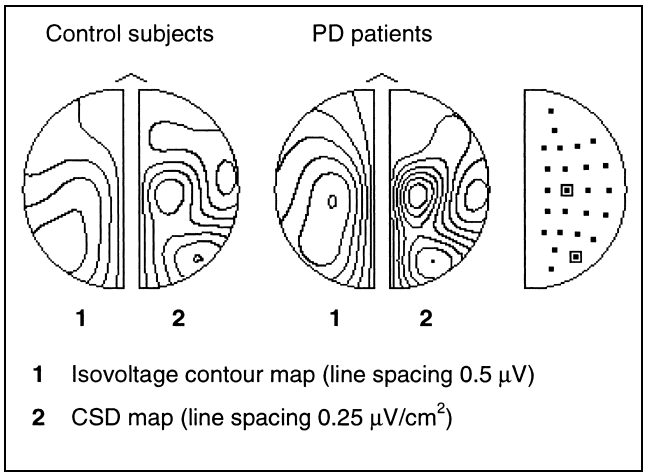

Figure 3. Scalp distribution of the attention-related N2pc in the compatible condition, plotted at peak latency (255 msec). Projected on the left side of each head are isovoltage maps (1) and on the right side CSD maps (2). Whereas the voltage maps indicate different maxima for patients and control subjects, the CSD maps show the same underlying topography with current extrema at occipito-temporal and central locations. The electrode positions nearest to these extrema (C3/C4 and PO7/PO8) are marked in the representation of electrode positions overlying one hemiscalp.

developed at central scalp sites overlying the motor cortex. The LRP peak latency reflected, consistent with the reaction time results, a significant compatibility effect, $F(1,14) = 20.94$, $p < .001$, though group differences were not significant. The LRP was of higher amplitude in the Parkinson group than in control subjects, $F(1,14) = 12.28$, $p < .01$, which is evident in Figure 4. The equal enhancement of the LRP in compatible and incompatible conditions contrasts with the selective enhancement of the N2pc in the compatible condition only. Note, however, that in the incompatible condition an N2pc enhancement at central electrode sites would involve increased activation of motor areas corresponding to the wrong response hand, thereby increasing the likelihood of an incorrect response. This mechanism fits the error pattern reported above and implies for the electrophysiological data that trials with an enhanced N2pc in the incompatible condition were filtered out as error trials. The possible operation of such a mechanism received support from an analysis of the averaged waveforms constructed from all errors committed in the incompatible condition (Figure 5). Thus, in control subjects, the movement-related activity accompanying erroneous responses clearly succeeded an N2pc that had the same amplitude as in correct trials. In patients, by contrast, the N2pc recorded at C3/C4 overlapped with movement-related activity accompanying the execution of erroneous responses. This resulted in a significant amplitude difference between patients and control subjects at the latency where the N2pc peaked in correct trials, $F(1,14) = 4.85$, $p < .05$. We will argue in the Discussion that, rather than a selective enhancement of the N2pc and/or component overlap of N2pc and LRP, the observed waveform morphology may be due to abnormal interaction of attention- and movement-related activity. Together, the enhancement of the N2pc in the compatible condition (for correct trials) and its enhancement or confluence with movement-related activity in the incompatible condition (for error trials) support that this signal-locked attention-related activity, as measured above the motor cortex, not merely precedes the movement-related LRP, but may contribute to the initiation of movement-related activity.

Subaverages for Trials Preceded by Compatible and by Incompatible Events

The role of the focal N2pc enhancement above the motor cortex was further investigated by creating se-

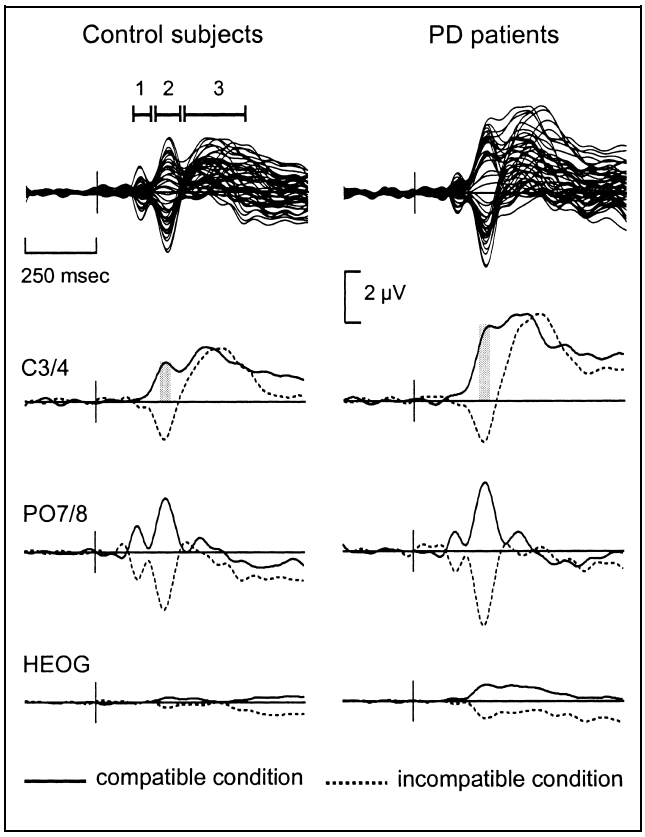

Figure 4. Lateralized ERPs. The upper panel shows a superimposition of waveforms from all electrode sites for compatible and incompatible condition. The second and third panels display the potentials recorded at C3/C4 and at PO7/PO8, respectively, i.e., the electrodes marked in Figure 3. Movement-related activity (the LRP) is indicated by the horizontal bar (3) and plotted upwards for both conditions. It is preceded by the N2pc (2), which in the compatible condition has the same polarity as the LRP, but has opposite polarity in the incompatible condition where direction of attention and response side differ. Lateralized visual-evoked potentials (1) have for both conditions the same polarity as the subsequent N2pc. The vertical bars emphasize the focal enhancement of the N2pc above the motor cortex for patients in the compatible condition. The lowest panel shows the horizontal EOG channel. Note the higher amplitude activity in the Parkinson group, the onset of which is closely synchronized to the N2pc.

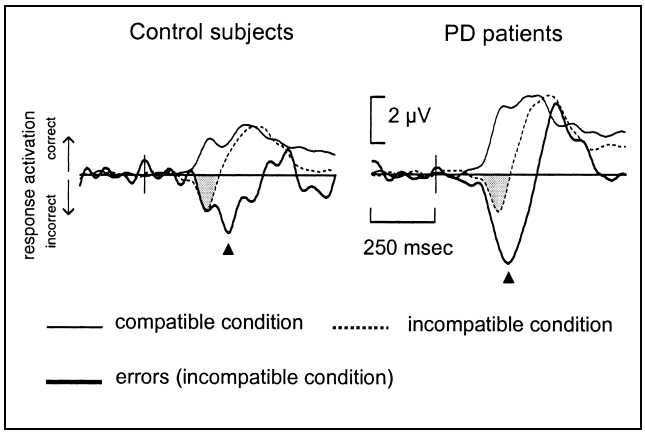

Figure 5. Averaged waveforms of error trials in the incompatible condition recorded above the motor cortex (electrode sites C3/C4). The waveforms are superimposed on the waveforms of correct trials, also represented in the second panel of Figure 4. The arrow heads indicate the incorrect motor activation that succeeds the N2pc in control subjects, but merges with the N2pc in Parkinson patients. Note that in the waveforms of correct trials the groups have comparable N2pc amplitudes in the incompatible condition (marked in gray), as if this amplitude defines a threshold level beyond which an incorrect response cannot be suppressed by patients.

parate averages for trials preceded by compatible and trials preceded by incompatible trials, thus allowing a comparison with the sequence effect in the reaction time analysis. The separation of the original set of trials for each condition into smaller subsets resulted in a reduction of the signal-to-noise ratio. Nevertheless, there was evidence that the variable sequence affected N2pc amplitude, with higher amplitudes following compatible than following incompatible trials (main effect of sequence, $F(1,14) = 6.92$, $p < .05$). For Parkinson patients, this modulation of the N2pc amplitude was slightly more pronounced than for controls, but this failed to reach significance (Group × Sequence interaction, $F(1,14) = 3.00$, $p = 0.105$). Consistent with the focal enhancement of the N2pc above the motor cortex, in the PD group, the variable sequence tended to have a stronger effect on the N2pc amplitude at the C3/C4 sites than at PO7/PO8 (Sequence × Electrode interaction, $F(1,14) = 3.97$, $p = 0.066$). However, the three-way Group × Sequence × Electrode interaction did not reach significance, although the modulation of the N2pc amplitude at C3/C4 appeared to be more pronounced in patients than in control subjects. Together, the results of these analyses do not contradict the view that the central N2pc enhancement in patients may be related to their abnormal performance, but the results do not add additional support for this interpretation.

Response-Locked Averages

Lateralized ERPs averaged with respect to response-onset will not be extensively reported, but selected channels are shown in Figure 6. The figure demonstrates that at recording sites above the motor cortex, in the compatible condition, the N2pc is smoothly integrated in movement-related cortical activity. In the incompatible condition, the N2pc is generated in the hemisphere opposite to the one that generates the motor command. It is therefore not closely time-locked to the resulting response and still visible as a "dip" in the waveforms, just preceding the movement-related LRP. The broader appearance in comparison to the brief phasic lateralization of the N2pc in stimulus-locked averages supports the signal-locked nature of this activity recorded above the motor cortex.

A second feature that is worth noting concerns reafferent potentials following force onset. Lateralized reafferent potentials are clearly present in the control subjects, but are absent in Parkinson patients, as shown in Figure 6. This absence is not likely explained by imperfect time-locking of brain potentials to the force signal, as the force-onset detection yielded reliable onsets with a low variability of onset-times. The absence therefore represents evidence for abnormal function of sensorimotor areas in Parkinson's disease.

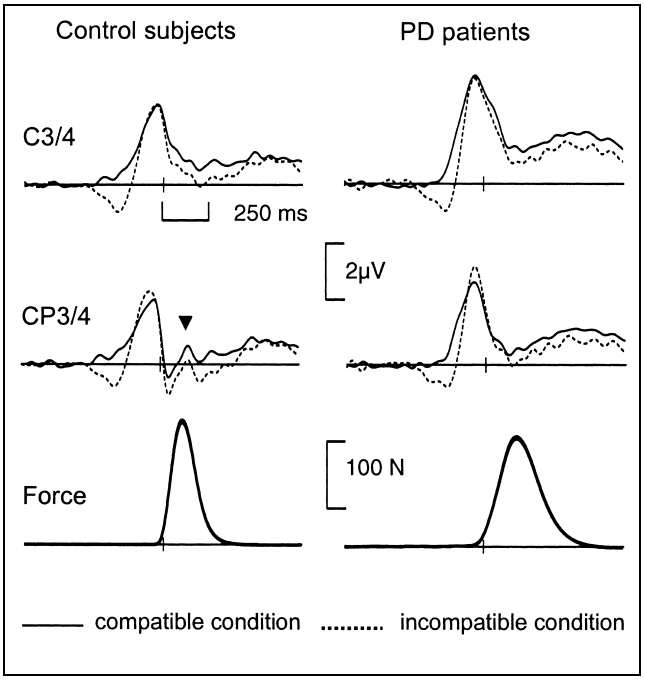

Figure 6. Response-locked lateralized potentials recorded between C3/C4 and between CP3/CP4. In the compatible condition, averaging with reference to the response instead of to the stimulus has made the signal-locked N2pc disappear in the movement-related activity of the motor command. The arrow head indicates the reafferent (movement-evoked) potentials recorded at the postcentral electrode site. These reafferent potentials are absent in Parkinson patients.

DISCUSSION

The present study investigated automatic activation of motor responses in Parkinson's disease. The results confirm a disinhibition of automatic response activation evidenced in the reaction time measures and error rates, which are evaluated below. Subsequent sections describe how specific differences of lateralized brain potentials between Parkinson patients and control subjects provide a possible explanation for the disinhibition. Finally, we will discuss relationships with previous work on cognition and motor function in Parkinson's disease.

Spatial S–R Compatibility

The difference in reaction time between trials with spatially compatible and trials with spatially incompatible S–R relation, i.e., the Simon effect, was not significantly larger for patients than for control subjects in the initial analysis of the data. The Simon effect was expected to be larger, based on the assumption that a stronger influence of automatic response activation entails larger performance benefits in the compatible condition, but also leads to larger costs in the incompatible condition. This assumption is in line with the proposed role of automatic response activation in the dimensional overlap model of S–R compatibility effects (Kornblum et al., 1990). According to the dimensional overlap model, the presence of shared features in stimulus and response sets elicits an automatic response activation process. When an automatically activated response coincides with the required response according to task instructions, the automatic activation produces facilitation. When task-relevant stimulus information requires another response, automatic activation produces interference with the controlled response selection and delays the execution of the correct response. The evidence obtained in previous ERP studies of spatial S–R correspondence have supported the operation of a direct activation route that interacts with controlled response activation processes (Eimer, 1995; De Jong et al., 1994).

In recent refinements that have been proposed for the interaction of direct and indirect response activation routes, it has been noted that the Simon effect is strongly dependent on the structure of the trial sequence. The Simon effect appears to be large in the subset of trials preceded by a trial with compatible S–R relation, while it is small or absent in the subset of trials preceded by a trial with incompatible S–R relation (Stürmer & Leuthold, 1999; Stoffels, 1996). This observation has been interpreted to suggest that the direct response activation route is normally inhibited, but temporarily released from inhibition after a trial with spatially compatible S–R locations.

The present data revealed a difference between Parkinson patients and control subjects that was confined to the subset of trials following an incompatible trial. Like healthy subjects of younger age (Stürmer & Leuthold, 1999; Stoffels, 1996), our control group suppressed the Simon effect after incompatible trials. In Parkinson patients, however, the suppression was incomplete, such that a substantial Simon effect remained present. The different modulation of the Simon effect probably caused the larger trial-to-trial variability of response times of the control subjects in the compatible condition (Table 1). The Parkinson patients' increased sensitivity to the spatial position of reaction stimuli was also evidenced in the error rates. Together, the specific differences in response measures between Parkinson patients and control subjects lend support to the notion of a direct response activation route the influence of which is modulated through selective inhibition. Conversely, the sequence-dependent modulation of the direct response activation route provides an interpretation of the patients' behavior in terms of failed suppression of automatic response activation.

The abnormal sensitivity of Parkinson patients to the spatial relation of stimulus and response does not explain that they were generally faster than control subjects. While reaction times are not always prolonged in Parkinson's disease (for review, see Jahanshahi, Brown, & Marsden, 1992), a speed advantage is uncommon (Jackson & Houghton, 1995; Kingstone, Klein, Maxner, & Fisk, 1992). Possibly, patients benefited from the large number of trials in the present study and from a strong encouragement to generate fast responses, so as to ensure that automatic response tendencies came to expression. Of major significance is further that reaction times were measured from force signals instead of by response keys. Only force onset times differed, but peak latencies of the force signals did not differ between the groups, indicating that the faster reaction times in patients might have gone undetected with response buttons. In fact, our force-onset and peak-latency data are consistent with the view that a prolongation of reaction times is not a necessary feature of Parkinson's disease, and that movement time may capture their motor impairment more reliably (Harrison, Henderson, & Kennard., 1995).

Attention- and Movement-Related Lateralized Brain Potentials

Of particular interest in this study were two brain potentials related, respectively, to attentional selection (the N2pc), and to response selection and motor cortex activation (the LRP). The N2pc has been identified in visual selective attention tasks and accompanies the voluntary focusing (Luck & Hillyard, 1994) as well as automatic orienting (Girelli & Luck, 1997) of attention on a visual target. It has recently also been proposed to play a role in sensorimotor transmission (Wascher & Wauschkuhn, 1996). In the present study, the scalp

distribution of the N2pc was sampled with more electrodes than previous studies used, revealing a particularly interesting new feature. Whereas the N2pc is known to have maximum amplitudes at occipito-temporal electrode sites, scalp CSD maps demonstrated a second current source at central scalp sites overlying motor areas of the cortex (Figure 3). The observation of two electric current extrema in the distribution of the N2pc at peak latency indicates that there is simultaneous attention-related activity generated in disjunct brain areas. The possibility of (pre)motor cortex activation by shifts of spatial attention has been raised before on the basis of other EEG potentials (Eimer, 1995) and on the basis of cortical activation patterns measured with PET or fMRI (Gitelman et al., 1999; Rosen et al., 1999; Corbetta, Miezin, Shulman, & Petersen, 1993). The occipital activation is consistent with existing evidence for N2pc generation close to the location of attention effects on visual-evoked potentials at shorter latency (Heinze et al., 1994; Luck & Hillyard, 1994).

The observation of attention-related activity at electrode sites C3 and C4 does not prove that the activity is generated in motor areas of the cortex. However, these electrode sites are among the electrode locations in the international 10–20 system whose position relative to underlying brain structures is the most reliable (Steinmetz, Fuerst, & Meyer, 1989). This provides, in conjunction with the fact that scalp CSD analysis emphasizes the activity of superficial sources directly underneath the recording electrodes, a strong indication for the involvement of motor and/or premotor cortex. Note that the attention-related activity measured above the motor cortex might be better designated as, for instance, N2cc (**c**entral **c**ontralateral). Whatever the label, it is important to recognize that the focal activity at central electrode sites, coinciding in time with the posterior N2pc, represents stimulus-locked activity and should be equated neither with an early lateralization of the LRP (Zeef & Kok, 1993), nor with brain activity that is generated in posterior brain areas, visible at central electrode sites due to volume conduction (Eimer, 1998).

Failed Suppression of Direct Visuomotor Activation

Attentional orientation to a new location engages rapid visuomotor pathways linking extrastriate visual cortex with motor areas (Wise, Boussaoud, Johnson, & Caminiti, 1997; Tanné, Boussaoud, Boyer-Zeller, & Rouiller, 1995). Neither at posterior nor at central electrode locations, however, the latency of the N2pc differed between the groups. Hence, the altered behavior in the patient group was not due to earlier access of visual information to the motor system, as might be found if patients moved their attention faster than controls (Jackson & Houghton, 1995). The impaired performance may be explained instead by changes in sensory-to-motor translation within motor areas, giving rise to the central N2pc enhancement. Pathways for rapid visuomotor transmission target on dorsal premotor and primary motor areas and attention-related visuospatial neural activity has been documented in these areas (Shen & Alexander, 1997; Wise et al., 1997; Zhang, Riehle, Requin, & Kornblum, 1997). Subsequent movement-related activity in these areas can be recorded from the same neurons that exhibit visuospatial–attentional activity (Wise et al., 1997). This provides a basis for the hypothesis that disinhibition of direct visuomotor activation, evidenced in the reaction time data and error pattern of the Parkinson patients, is due to abnormal interaction of visuospatial–attentional with movement-related activity within motor areas. Possibly, this spurious interaction is related to the decreased selectivity of pallidal and motor cortex neuronal discharges (Doudet, Gross, Arluison, & Bioulac, 1990; Filion, Tremblay, & Bedard, 1988) that presumably underlies elementary motor symptoms like muscular cocontraction in Parkinson's disease. The decreased selectivity may yield an increase of neural activity in the motor cortex, which fits the topographically specific enhancement of the N2pc and the higher amplitude of the movement-related LRP in the Parkinson group. This construal of the focal N2pc and LRP enhancement is consistent with functional imaging observations of motor cortex overactivity in Parkinson's disease (Hanakawa, Fukuyama, Katsumi, Honda, & Shibasaki, 1999; Humberstone, Clare, Hykin, Morris, & Sawle, 1998). It is also tempting to speculate on a relation with recent demonstrations of abnormal motor cortical inhibitory mechanisms in patients with Parkinson's disease (Ridding, Inzelberg, & Rothwell, 1995), which we have tentatively linked to movement-related potential changes in Parkinson's disease (Praamstra et al., 1998).

The proposed explanation is predicated on the view that motor cortical neurons are a site of convergence for sensorimotor input and have a role in processing visuospatial information relevant to a motor task. Their role in visuospatial processes is influenced by the basal ganglia (Kermadi & Boussaoud, 1995; Alexander & Crutcher, 1990). Thus, impaired basal ganglia output to motor areas of the cortex may be responsible for Parkinson patients' failure to keep early visuomotor activity from actually evoking a response or leaking activity to response-related neurons. Particularly important in the suppression of direct visuomotor activation is, according to Wise, di Pelligrino, et al. (1996) and Wise, Murray, et al. (1996), the dorsal premotor cortex. A support for this view, establishing, moreover, a link to the abnormal performance of Parkinson patients in the Simon task, was obtained in a recent experiment with repetitive transcranial magnetic stimulation of the dorsal premotor cortex. Temporary interference with dorsal premotor cortex function in neurologically intact subjects, which has previously been shown to disrupt movement selec-

tion (Schluter, Rushworth, Passingham, & Mills, 1998), induced a change of the Simon effect resembling the altered performance here observed in Parkinson patients (Praamstra, Kleine, & Schnitzler, 1999).

Relationships to Previous Work

With respect to the Simon effect in Parkinson's disease, there are not many studies available for comparison. Two studies manipulated spatial S–R compatibility, combined with an investigation into the effects of response uncertainty (Brown, Jahanshahi, & Marsden, 1993) and combined with an investigation of conditionality effects (Cope, Georgiou, Bradshaw, Iansek, & Phillips, 1996). In the tasks most closely resembling our two-choice S–R task, the Simon effect was in both studies of similar size in Parkinson patients and controls. These results agree with our findings, as we found a group difference only when serial dependencies between trials were taken into account. Sequence effects were either not examined (Cope et al., 1996) or were not present because of a blocked presentation of compatible and incompatible conditions (Brown et al., 1993). These studies therefore fail to provide data that can serve to confirm or disconfirm the disinhibition of automatic response activation reported here.

Another source of information regarding Parkinson patients' ability to suppress reflexive responses can be found in the oculomotor domain, in studies using the antisaccade task (for a review, see Everling & Fischer, 1998). Initial studies have reported a normal behavior of Parkinson patients in this task (e.g., Lueck, Tanyeri, Crawford, Henderson, & Kennard, 1990), but a recent report demonstrated an increased rate of erroneous reflexive saccades in patients with moderate to severe Parkinson's disease (Crevits & De Ridder, 1997). In our study, patients had more difficulty than control subjects to suppress eye movements towards the targets, as evidenced in the EOG recordings. This tendency seemed not related to the automatic activation of manual responses, however, as comparisons between EOG amplitude and the size of the Simon effect yielded not a consistent pattern or significant correlations. In conjunction with the fact that our study only included patients with mild to moderate disease severity, this suggests that the spatial S–R task and the antisaccade task may not tap into exactly the same processes.

Several recent neuroimaging studies provide information on the functional neuroanatomy relevant to spatial S–R processing and suppression of automatically triggered movements. Iacoboni et al. (1998) used PET to investigate sensorimotor integration in a spatial S–R task and found activation of dorsal premotor and posterior parietal areas. The requirement to inhibit a response or to withhold one of two competing responses has also been found associated with activity in the anterior cingulate cortex (Carter et al., 1998; Krams, Rushworth, Deiber, Frackowiak, & Passingham, 1998; Taylor, Kornblum, Minoshima, Oliver, & Koeppe, 1994). The involvement of medial frontal structures corresponds well with the reduced amplitude of the central N2 component exhibited by Parkinson patients in the present study, and is consistent with earlier neuroimaging and neurophysiological evidence for deficient function of mesial motor areas (e.g., Praamstra, Meyer, et al., 1996; Jahanshahi et al., 1995). Given their strong afferent input from the basal ganglia and their predominantly efferent interaction with the primary motor cortex (Picard & Strick, 1996; Aizawa & Tanji, 1994), the dysfunction of these mesial areas in Parkinson's disease might be causally related to the disinhibition of direct visuomotor activation that occurs in motor areas at the convexity, as suggested by our lateralized ERPs. However, motor areas at the lateral convexity are also targets of independent output channels from the internal pallidum (Hoover & Strick, 1993). In addition, reduced dopaminergic innervation from mesencephalic projections can affect the function of motor and lateral premotor areas (Gaspar, Duyckaerts, Alvarez, Javoy-Agid, & Berger, 1991). We therefore favor the view that disinhibition of direct visuomotor activation in Parkinson's disease represents a problem of sensorimotor function that is not necessarily dependent on dysfunction of mesial frontal areas in Parkinson's disease, which is generally associated with problems of internally generated movements (e.g., Jahanshahi et al., 1995).

Conclusions

The difficulties of Parkinson patients in making spontaneous voluntary movements are often contrasted with their less impaired performance when movements are elicited by a stimulus. This has led some researchers to the view that the latter type of movement is mediated by circuitry that bypasses the basal ganglia (e.g., Cunnington, Iansek, Bradshaw, & Phillips, 1995). The results of the present investigation shed a different light on the notion that external cues support movement performance in Parkinson's disease. We have shown that Parkinson patients are, detrimental to their performance, more strongly affected by task-irrelevant spatial properties of a reaction signal than control subjects. The disinhibition of direct, stimulus-driven, visuomotor activation underlying this altered behavior was manifested in a focal enhancement of attention-related lateralized potentials above motor areas of the cortex. Presumably, this attention-related visuomotor signal, which normally primes the generation of a spatially congruent motor response, more readily ignited movement-related activity in patients than in control subjects. The impaired inhibitory modulation of direct visuomotor activation, within motor areas of the cortex, implies that intact operation of basal ganglia motor circuits is a necessary requirement for the motor system to sustain competing

response tendencies. Impaired executive control, the heading under which an inability to sustain competition may be subsumed, thus seems more narrowly related to the motor system dysfunction in Parkinson's disease than is commonly realized.

METHODS

Subjects

The participants included eight patients with Parkinson's disease (eight men: age 58 ± 8 years), who fulfilled diagnostic criteria of the UK Parkinson's Disease Society Brain Bank (Hughes, Daniel, Kilford, & Lees, 1992). The disease was of mild to moderate severity with slowness of movement present in all, and dyskinesia in none of the patients. Patients and control subjects (eight men: age 57 ± 5 years) participated on the basis of informed consent and the study was approved by the Ethics Committee of the University Hospital Nijmegen. Both groups had seven right-handed and one left-handed participants. All patients used anti-Parkinson medication (Table 3). They were tested after overnight withdrawal (> 10 hr after the last medication), and their motor performance was tested in this state, using the UPDRS motor scale (mean 37 ± 9, range 24–50) (Lang & Fahn, 1989). On the H&Y scale patients were classified as 2, 2.5, or 3 (Hoehn & Yahr, 1967).

Task and Stimuli

Stimuli were presented on a computer screen at 1-m viewing distance and consisted of two rectangular frames displayed permanently in white lines against a gray background (Figure 1). The frames subtended 0.7 × 0.7° of visual angle and were positioned at a distance of 1.0° from a central fixation cross. In each trial, a letter (''A'' or ''B'') was presented in one and a filler (three horizontal bars) in the other frame (cf. Wascher & Wauschkuhn, 1996). The letter ''A'' instructed for a left hand response and ''B'' for a right hand response, irrespective of the side of presentation. Stimuli were presented for 200 msec in six blocks of 121 trials, of which the first trial was always discarded. Each block contained an equal number of stimuli of each condition and the blocks were presented in a random order. The intertrial interval varied randomly between 2 and 3 sec. Before the experimental session subjects received a written instruction, emphasizing response speed, and performed one practice block. After the completion of the six trial blocks, the first two blocks were repeated with a passive viewing instruction. During the experiment subjects were seated upright in a comfortable chair and instructed to maintain eye fixation on a central fixation cross on the screen. Responses were made by squeezing the left or right hand on manipulanda recording isometric grip force.

Physiological Recording and Data Processing

The electroencephalogram was recorded continuously with Ag/AgCl electrodes from 58 standard locations according to the international 10–10 system, referred to the left mastoid. Eye movements were monitored by bipolar horizontal and vertical EOG derivations. Impedance was kept below 10 kΩ. Isometric handgrip force was recorded bilaterally and digitally stored with EEG and EOG signals.

EEG and EOG signals were amplified between 0.03 and 100 Hz by Nihon-Kohden 4421 amplifiers. The data were sampled at 250 Hz using a standard data acquisition system (NeuroScan, Herndon, VA, USA). For each subject and condition, the data were averaged off-line to form ERPs. Averages were constructed time-locked to stimulus onset, as well as response-locked. Trials where

Table 3. Patient Characteristics

Patient Number	*Age (year)*	*Sex*	*Disease Duration (year)*	*H&Y* [a]	*UPDRS* [b]	*Medication (per day)* [c]
1	72	M	5	2.5	31	L-Dopa, 500 mg
2	53	M	2	2	24	Pergolide, 0.75 mg; Amantadine, 200 mg
3	57	M	5	2	32	Amantadine, 200 mg; Selegiline, 10 mg
4	55	M	4	2	38	L-Dopa, 150 mg; Selegiline, 10 mg; Amantadine, 200 mg
5	51	M	7	3	50	L-Dopa, 425 mg; Pergolide, 4.5 mg
6	50	M	10	3	48	L-Dopa, 600 mg; Amantadine, 200 mg
7	55	M	9	2.5	40	Ropinirol, 16 mg; Amantadine, 200 mg; Selegiline, 10 mg
8	69	M	4	2	35	Amantadine, 200 mg; Selegiline, 10 mg

[a]Hoehn and Yahr scale (off medication for at least 10 h).
[b]Unified Parkinson's Disease Rating Scale (UPDRS; off medication for at least 10 h).
[c]L-Dopa was given with a peripheral decarboxylase inhibitor.

subjects made an error were averaged separately. Trials contaminated by eye-blink artifacts within a latency of 500 msec from stimulus-onset were removed prior to averaging in subjects with infrequent blinks. In three control subjects and three patients, blink artifacts were corrected using standard methods (Semlitsch, Anderer, Schuster, & Presslich, 1986). Averaged data were rereferenced to an off-line reconstructed linked mastoid reference.

The force signals were analyzed at the single trial level. Force onsets were determined with a threshold detection algorithm. The computed onsets were checked visually to ensure that tremor caused no spurious onsets. In addition, peak latency and peak amplitude were measured. The time between onset and peak of the force signal was defined as time-to-peak force. When both response hands were activated, a trial was counted as error whenever the wrong response channel crossed threshold earlier than the correct response side and reached an amplitude higher than 5% of the force amplitude on the correct side.

Data Analysis

Response accuracy and the reaction times of correct trials were analyzed with repeated measures analysis of variance, using the MANOVA procedure of SPSS. Additional variables that were evaluated included the within-subject response variability (i.e., the standard deviation of the reaction time), the force amplitude, the peak-force latency, and the time-to-peak force. The analyses evaluated the effect of group (Parkinson's disease subjects vs. control subjects) as between-subjects variable and compatibility (compatible vs. incompatible S–R relation) as within-subjects variable. In addition, for each trial was determined whether it had a compatible or an incompatible trial as predecessor, yielding the within-subjects variable sequence (compatible vs. incompatible S–R relation in preceding trial).

Analyses of the averaged ERP waveforms included the amplitude of the central N2 component determined as the mean amplitude in a fixed interval from 150 to 250 msec after stimulus-onset. Analyses of visual-evoked responses and the P300 contributed no relevant information and are not reported. The main analyses focused on lateralized ERPs, i.e., the attention-related N2pc and the movement-related LRP. These lateralized potentials were derived by, firstly, computing difference potentials between recordings contra- and ipsilateral of the side of movement and, secondly, averaging the potentials produced by left and right hand movements. For homologous electrodes over left and right motor cortex (C3 and C4), the LRP derivation reads LRP = [Mean $(C4 - C3)_{\text{left hand movement}}$ + Mean $(C3 - C4)_{\text{right hand movement}}$] / 2. The LRP derivation has been introduced to enable the analysis of movement-related electrical activity elicited in reaction time tasks (for reviews, see Eimer, 1998; Coles et al., 1995), and was applied also in previous studies of movement-related brain activity in Parkinson's disease (Praamstra, Meyer, et al., 1996; Praamstra et al., 1998).

The scalp distributions of N2pc and LRP were plotted as spline-interpolated isovoltage and CSD maps, using BESA software (BESA, 1996). For the computation of these maps, the lateralized waveforms were projected on both sides of the head following a procedure described earlier (Praamstra, Stegeman, Horstink, & Cools, 1996). Since the CSD maps showed for both groups the same distributions of current source extrema at N2pc and LRP peak latencies, further analyses were restricted to the potentials recorded between electrode sites PO7/PO8 (N2pc) and between C3/C4 (LRP and N2pc), which sites nearly coincided with the current extrema. Thus, the variable electrode had two levels in the analyses of lateralized potentials. Analyses on the N2pc amplitude were performed on absolute values.

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