Reliance on external cues for movement initiation in Parkinson’s disease
Evidence from movement-related potentials

P. Praamstra,1,2 D. F. Stegeman,2 A. R. Cools3 and M. W. I. M. Horstink1

Departments of 1Neurology, 2Clinical Neurophysiology and 3Neuro-psychopharmacology, University of Nijmegen, The Netherlands

Correspondence to: P. Praamstra, Department of Neurology, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands

Summary
The aim of this study was to investigate the neurophysiological mechanisms underlying Parkinson’s disease patients’ increased reliance on external cues for the initiation of movement. Lateralized movement-related cortical potentials were recorded in a noise-compatibility task with seven patients and seven age-matched control subjects. In this two-choice task, visual stimuli containing incompatible target and distractor elements, which simultaneously instructed for responses from both hands, initially caused activation of the motor cortex controlling the wrong response hand. The incorrect response activation was of higher amplitude in patients than in control subjects, causing a longer response delay relative to response times when target and distractors instructed the same hand. In addition, hand-specific motor cortex activation started earlier in patients than in control subjects. These results indicate that visual stimuli exerted an earlier and stronger influence on movement initiation in patients than in control subjects. We hypothesize that information from sensory stimuli relevant for the generation of a response can have rapid access to motor structures in Parkinson’s disease patients, thereby facilitating the initiation of movement. The findings may reflect a compensatory mechanism, but could also be related to excitability changes in the motor cortex intrinsic to the pathophysiology of Parkinson’s disease.

Keywords: Parkinson’s disease; movement-related potentials; lateralized readiness potential; motor cortex; movement preparation

Abbreviations: CNV = contingent negative variation; LRP = lateralized readiness potential; UPDRS = United Parkinson’s Disease Rating Scale

Introduction
It is a common observation that slowness and poverty of movement in Parkinson’s disease can be improved by providing external stimuli for the guidance of movement (Martin, 1967). To explain this observation and related experimental results, it has been proposed that Parkinson’s disease patients rely on external cues as a compensatory strategy that bypasses the basal ganglia (Dick et al., 1989; Glickstein and Stein, 1991; Cunnington et al., 1995). The available neurophysiological evidence on movement preparation in Parkinson’s disease, however, mostly relates to deficits in internally generated movements, while there is relatively little evidence on the physiology of externally cued movements (Cunnington et al., 1995; Jahanshahi et al., 1995; Praamstra et al., 1996). Neurophysiological evidence for compensatory changes in the use of external cues would be valuable as confirmation of adaptive changes in movement preparation and might also contribute to our understanding of the nature of the motor impairments in Parkinson’s disease. In addition, the reliance on external cues might be exploited to greater benefit in physical therapy if its underlying mechanism is better understood (Hömb erg, 1993). We therefore investigated Parkinson’s disease patients’ reliance on external cues in an experiment recording the lateralized readiness potential (LRP). Earlier movement-related potential studies of stimulus-induced movements in Parkinson’s disease concerned anticipatory activity preceding the stimulus (Cunnington et al., 1995; Jahanshahi et al., 1995). In contrast, the LRP enables the study of covert response tendencies.
Fig. 1 Derivation of the LRP, illustrated for Parkinson’s disease patients responding to compatible stimulus arrays. The left part of panel A shows that a movement of the left hand is accompanied by a voltage difference between electrodes C3 and C4. The voltage difference is due to motor cortex activity contralateral to the response hand, which is superimposed on the prominent P300 component elicited by the reaction stimulus. The same movement-related activity is shown as a right–left difference potential (C4 – C3) in B, demonstrating a steep rise at about 250 ms. The right part of A shows that with right hand movements the amplitude relation between C3 and C4 is reversed. The movement-related activity is now isolated by the left–right difference potential (C3 – C4) in B. Note that in the time window before 250 ms the difference potentials in B are still contaminated by stimulus-related activity that is not associated with the movements. As these deflections are caused by a fixed asymmetry of the stimulus-evoked potentials, they are cancelled by averaging the difference potentials for left- and right-hand movements, yielding the LRP shown in C.

The LRP is a measure of movement-related brain activity that is derived from the EEG and indexes the preferential preparation for moving one hand or the other. It is computed by subtracting brain potentials recorded over the hemisphere ipsilateral to the response side from those recorded contralateral to the movement. These difference potentials are obtained for left- and right-hand movements and averaged to yield the LRP (Coles et al., 1995; see Fig. 1 for details of the derivation procedure). The LRP has played a prominent role in experimental work investigating chronometric properties of human information processing. One compelling result from this work is the LRP-supported analysis of the so-called noise-compatibility task (Eriksen and Eriksen, 1974). In this task, subjects perform a choice reaction on two letter stimuli (e.g. H and S) associated with left- and right-hand responses, respectively. The target letters (in the centre) are surrounded by distractor letters that can be identical to the target (compatible condition, e.g. HHHHH) or by distractor letters that call for a response of the opposite hand (incompatible condition, e.g. SSHSS). A consistent finding is that response times are longer with incompatible than with compatible arrays. Indirect evidence already existed for an explanation of this effect, i.e. that it is partially due to a response conflict (Coles et al., 1985). This response conflict, however, is directly manifested in the LRP as a short-lasting initial positive deflection of the waveform, which arises because the ‘wrong’ motor cortex is temporarily activated more strongly than the motor cortex controlling the correct response hand (Gratton et al., 1988). The early activation of the incorrect response in incompatible trials is considered important evidence for a mode of information transmission that allows response preparation to begin before stimulus analysis has been completed (Gratton et al., 1988; Smid et al., 1990; Coles et al., 1995). In a slightly different approach that involved similar recordings of movement-related potentials, Goodin et al. (1996) also found evidence supporting the notion that there can be considerable temporal overlap between stimulus- and response-related processes. Importantly, the occurrence of early response activation based on partial stimulus information, seems to be influenced by subjects’ strategies (Gratton et al., 1992; Coles et al., 1995; Smid et al., 1996).

Against this background, we considered that if Parkinson’s disease patients rely more on visual cues for movement...
preparation and initiation than healthy subjects, this might be manifested in the noise-compatibility task. More specifically, Parkinson’s disease patients might be more sensitive to the response conflict induced by stimuli that contain target and distractor elements cueing responses of opposite hands. This greater sensitivity should be expected in particular when Parkinson’s disease patients are, more than control subjects, inclined to make a fast response based on the earliest available information from the stimulus array. Thus, we hypothesized that Parkinson’s disease patients should be more strongly influenced by incompatible distractors and should demonstrate stronger incorrect lateralization of the LRP in the incompatible condition than for control subjects. Conversely, in the compatible condition, the stronger reliance on external cues may be reflected in a shorter latency of the LRP for patients than control subjects. These hypotheses were tested with seven Parkinson’s disease patients and an equal number of control subjects in an adapted noise-compatibility task using arrows instead of letter stimuli (Fig. 2).

Methods

Subjects

The participants were seven Parkinson’s disease patients (six male, one female; age 59 ± 9 years) and an equal number of control subjects (six men, one woman; age 60 ± 10 years), participating on the basis of informed consent. The study was approved by the ethics committee of The University Hospital of Nijmegen. All the participants were right-handed. The patients fulfilled established criteria for diagnosis of the disease (Hughes et al., 1992), which was of mild to moderate severity with slowness of movement present in all of them. Since the derivation of the LRP combines right- and left-hand responses, only patients with a fairly symmetrical distribution of motor symptoms were included in the study. Patients used anti-parkinsonian medication (amantadine, l-dopa, orphenadrine, pergolide, selegiline) in various combinations (Table 1). They were tested after overnight withdrawal (>10 h after the last medication, apart from one patient who was tested 6 h after the last medication). Motor performance was determined during the state of medication withdrawal, using the United Parkinson’s Disease Rating Scale (UPDRS) motor scale (mean 31 ± 8, range 23–45) (Lang and Fahn, 1989). On the Hoehn and Yahr scale patients were classified as 2, 2.5 or 3 (Hoehn and Yahr, 1967).

Task and stimuli

As mentioned above, we adapted the noise-compatibility paradigm by replacing the customary letters by arrows that pointed to the left or right (see Fig. 2). Subjects were seated in a comfortable chair at a viewing distance of 1 m from a computer screen. They were instructed to press the response key under their right (or left) index finger when the central arrow in the stimulus array pointed to the right (or left). The stimuli were arrays of white arrows against a grey background (Fig. 2). The stimulus array subtended 2.0° × 1.4° of visual angle. Stimuli were presented for 100 ms in six blocks of 101 trials, of which the first was always discarded. Target fixation was guided by a fixation dot in the centre of the screen. The intertrial intervals varied randomly between 3 and 4 s. Before the experimental session, subjects received a written instruction emphasizing response speed and performed one practice block. Reaction time was measured to the nearest millisecond and expressed the time from stimulus-onset until switch-closure, which occurred when the response key was fully depressed.

Data acquisition and analysis

The EEG was recorded with Ag/AgCl electrodes from standard locations overlying the motor cortex (C3 and C4) and along the midline (Fz, Cz and Pz), referred to linked mastoids. Eye movements were monitored by bipolar horizontal and vertical EOG derivations. The bandpass was 0.016–35 Hz, and digitization rate was 200 samples per second. The EMG (bandpass filter 10–70 Hz) was recorded from the flexor side of both forearms. The EEG was averaged off-line in an epoch from 250 ms before to 1000 ms after stimulus onset, rejecting trials in which the subject made an erroneous response and trials that contained artefacts due to eye movements. Trials with eye blinks were removed when the blinks occurred early (latency <500 ms) and compromised identification of the P300 latency. The elimination of error trials and artefacts never resulted in a loss of more than 20% of the trials from a subject. For the analysis of the slow negative potential shift before the stimulus, i.e. the contingent negative variation (CNV), the EEG was averaged from −1750 ms before stimulus onset to 250 ms after it, using the first 250 ms as baseline. The mean amplitude from −100 to 0 ms was measured to quantify the CNV. For the construction of these averages, eye blink artefacts were corrected by

![Fig. 2](image-url) The four stimuli used in the adapted noise-compatibility task. Stimuli instructed either the left or the right hand by a central target, surrounded by task-irrelevant arrows that were either compatible or incompatible with the target.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Disease duration (years)</th>
<th>Hoehn and Yahr</th>
<th>UPDRS†</th>
<th>Medication (per day)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>M</td>
<td>8</td>
<td>3</td>
<td>45</td>
<td>L-dopa, 400 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amantadine, 200 mg</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>M</td>
<td>4</td>
<td>2</td>
<td>23</td>
<td>Selegiline, 10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amantadine, 200 mg</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>F</td>
<td>10</td>
<td>3</td>
<td>38</td>
<td>L-dopa, 1000 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Selegiline, 10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Orphenadrine, 150 mg</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>M</td>
<td>2</td>
<td>2</td>
<td>24</td>
<td>Selegiline, 10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amantadine, 200 mg</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>M</td>
<td>6</td>
<td>2</td>
<td>30</td>
<td>Selegiline, 10 mg</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>M</td>
<td>2</td>
<td>2</td>
<td>29</td>
<td>L-dopa, 150 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Selegiline, 10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amantadine, 200 mg</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>M</td>
<td>6</td>
<td>2.5</td>
<td>28</td>
<td>L-dopa, 500 mg</td>
</tr>
</tbody>
</table>

*Hoehn and Yahr score (off medication for ≥10 h). †United Parkinson’s Disease Rating Scale (off medication for ≥10 h). ‡L-dopa was given with a peripheral decarboxylase inhibitor.

Amplitude and latency of visual-evoked responses and P300 were measured for each subject at midline electrode sites by searching the maximum amplitude in specified time windows. The evaluation of these evoked responses might reveal differences between the groups or between experimental conditions in terms of early visual processing or cognitive evaluation of the stimuli. For the visual-evoked response the N1, P1 and N2 components were identified in time windows of 50–150 ms, 100–200 ms, and 150–250 ms, respectively. Since the search window for the P300 component (300–600 ms) contained two positive peaks, both peaks were quantified and analysed separately. They were labelled as P300-1 and P300-2, since they did not fit the subdivisions of the P300 that have earlier been proposed (for a recent discussion of different subdivisions, see Falkenstein et al., 1994). A negative-going wave which separated the P300-1 and P300-2 waves, was quantified by taking the mean amplitude in the interval from 400 to 500 ms. The LRP was derived after digital low-pass (8 Hz) filtering of the EEG, according to the formula: $LRP = \frac{\text{mean potential difference (C4 – C3) for left-hand movement} - \text{mean potential difference (C3 – C4) for right-hand movement}}{2}$.

The latency of the LRP was defined as the time point at which 25% of the maximum amplitude was reached. Incorrect lateralization of the LRP was quantified by the amplitude of the positive LRP deflection measured at peak latency. The incorrect lateralization was compared between groups after scaling the absolute amplitude as a percentage of the amplitude of the LRP in the compatible condition. A direct analysis of the absolute amplitudes yielded similar results, though.

For the analysis of the behavioural responses, errors were initially classified as anticipation or reaction-time errors (reaction time <200 ms), decision errors (wrong responses), delayed (reaction time >1500 ms) or missing responses, and double responses (incorrect–correct and correct–incorrect sequences). Because errors occurred infrequently and had a similar distribution over the different error types for both groups, only the total error percentage is reported.
Reliance on external cues in Parkinson’s disease

Fig. 4 Group-averaged LRP for Parkinson’s disease (PD) patients and control subjects (uppermost waveforms). In all traces, the cursor indicates stimulus onset. The positive deflection of the LRP, indicated by arrow heads, is caused by incorrect response activation, i.e. a brief activation of the motor cortex ipsilateral to the correct response hand. The horizontal EOG below the LRP waveforms (obtained by the same derivation procedure as the LRP) demonstrates that the initial positive deflection in the LRP is not caused by eye movements. The lower part of the figure shows the rectified EMG from the response side (upper traces) and the inactive side (lower traces). The latter traces demonstrate that the incorrect central activation, measured by the LRP, can be dissociated from motor output, since the EMG activity on the incorrect response is approximately the same in the incompatible and compatible conditions. The EMG from the response side clearly shows the same pattern as the reaction times, with a larger difference between onset latencies for compatible and incompatible conditions in patients than in control subjects.

The reaction times from correct trials were analysed with repeated measures analysis of variance as implemented in the MANOVA procedure of the SPSS package (Norusis, 1992), evaluating the effect of Group (Parkinson’s disease patients versus control subjects) as between-subjects variable and Compatibility (compatible versus incompatible flankers) as the within-subjects variable. The latency of the P300 event-related potential at electrode Pz was analysed in the same way, while the analyses of the P300 amplitude, visually-evoked responses, the CNV, and the negative wave overlapping the P300 included Electrode as an additional variable. The incorrect lateralization of the LRP was evaluated with a $t$ test on the difference between groups.

Results

Reaction-time analysis

Analyses of reaction times showed that patients reacted just as fast as normal subjects in the compatible condition (mean ± SD for patients 502 ± 74 ms; for control subjects 503 ± 92 ms), but they were slower in the incompatible condition (586 ± 81 ms versus 557 ± 91 ms), which resulted in a significant interaction of Group × Compatibility [$F(1,12) = 6.49, \ P < 0.05$; see Fig. 3]. The number of errors was low (3.5 and 4.1 % for control subjects and patients, respectively) and did not differ between groups [$F(1,12) < 1$]. Almost all errors (89%) occurred in the incompatible condition.

Movement- and event-related potentials

The measurement of central response activation by means of the LRP shows that in the incompatible trials, activation of the wrong response hand preceded activation of the correct response, as indicated by the initial positive deflection of the LRP in this condition. The amplitude of the initial positive deflection (indexing the incorrect activation) was higher in patients than in control subjects [$t(12) = 3.04, \ P < 0.01$, two-tailed; see Figs 4 and 5]. Thus, both the reaction times and the incorrect lateralization of the LRP indicate that Parkinson’s disease patients were influenced more strongly by the incompatible flankers than the control subjects. A positive correlation was found between the magnitude of incorrect LRP activation and the reaction-time delay in the incompatible condition, as measured across all participants (Pearson correlation coefficient $r = 0.75, \ P < 0.01$).
### Table 2 P300 amplitude and latency

<table>
<thead>
<tr>
<th></th>
<th>Compatible condition</th>
<th>Incompatible condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latency (ms)</td>
<td>Amplitude (µV)</td>
</tr>
<tr>
<td><strong>P300-1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control subjects</td>
<td>413 ± 31</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>Parkinson’s disease patients</td>
<td>408 ± 18</td>
<td>18 ± 7</td>
</tr>
<tr>
<td><strong>P300-2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control subjects</td>
<td>483 ± 58</td>
<td>19 ± 4</td>
</tr>
<tr>
<td>Parkinson’s disease patients</td>
<td>471 ± 58</td>
<td>18 ± 8</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD.

The LRP latency was shorter for patients than for the control subjects. In the compatible condition the mean latencies were 292 ± 40 ms and 255 ± 21 ms for control subjects and patients, respectively; in the incompatible condition they were 367 ± 33 ms and 352 ± 30 ms. As the difference between patients and control subjects was larger in the compatible than in the incompatible condition, a significant interaction of Group × Compatibility was obtained \([F(1,12) = 5.98, P < 0.05]\) (Fig. 3). Analyses of simple effects showed that patients had a shorter latency of the LRP than control subjects only in the compatible condition \([F(1,12) = 4.73, P < 0.05]\). Since the two groups had a remarkable difference in variance in this condition (Levene’s test: \(F = 11.68, P < 0.01\)), we also applied a \(t\) test after adjustment of the degrees of freedom. This analysis also confirmed a shorter onset latency for patients compared with control subjects \((t(9) = 2.17, P < 0.05, \text{one-tailed})\).

The visual-evoked responses were not significantly different between groups, nor was there a significant interaction involving the group variable. The P300 measures at electrode Pz are summarized in Table 2. Neither amplitude nor latency measures of the P300 differed significantly between groups. Thus, the higher amplitude of the P300 for patients than control subjects at electrodes Cz and Fz, suggested by Fig. 6, was not significant. Across groups, the amplitude of the P300-1 was smaller in the incompatible than in the compatible condition \([F(1,12) = 6.08, P < 0.05]\).

For both groups, P300-2 was found to increase in latency from the compatible to the incompatible condition, resulting in a marginally significant effect of Compatibility \([F(1,12) = 4.44, P < 0.057]\). This increase was slightly larger for control subjects than for patients, while a similar increase in latency of the P300-1 was found only in the control group. These differences did not yield a significant interaction of Group × Compatibility, although they might explain why, in Fig. 6, the increase of P300 latency appears larger in control subjects than in patients. The discrepancy between Fig. 6 and the quantitative evaluation of P300 latencies is related to the fact that the construction of group-averages for Fig. 6 blurred the distinction between the P300-1 and P300-2 components and made them virtually merge into one positive peak. For the
same reason, the negative component separating the P300-1 and P300-2 components became inconspicuous, although it can still be seen in the trace for the incompatible condition in the control group. The analysis of this component demonstrated a significant interaction of Compatibility × Electrode [\(F(1,12) = 7.06, P < 0.05\)]. Analyses of simple effects showed that the difference between conditions was significant only at Pz [\(F(1,12) = 6.25, P < 0.05\)]. The amplitude difference was not significantly larger for the control subjects than for patients, however, in spite of the considerable difference between the groups suggested by Fig. 6.

An analysis of the time window preceding stimulus presentation was motivated by the presence of a small negative shift in the prestimulus baseline of the control group (see Fig. 6). This shift could indicate that subjects developed preparatory activity anticipating the occurrence of a stimulus. This type of negative potential shift is related to the CNV, and probably reflects expectancy as well as motor preparation. As shown in Fig. 7, the analysis revealed a negative shift in the 1500-ms interval before stimulus presentation. The slow potential shift appears smaller in patients than in control subjects, especially at the Cz location where the CNV usually has its maximum amplitude, but the between-group difference was not significant [\(F(1,12) < 1\)].

**Discussion**

The present study sought to elucidate why Parkinson’s disease patients initiate movement more easily in response to an external cue than on the basis of an internal decision. One explanation is that externally cued and internally generated movements are subserved by neural systems that overlap only partially (Goldberg, 1985; Glickstein and Stein, 1991; Rascol et al., 1997), such that basal ganglia disease may affect one type of movement more than the other. This explanation only implies that externally cued movements are better preserved than internally generated movements, though it is compatible with a notion of compensatory reliance on external cues in Parkinson’s disease. In this study, we investigated the stronger hypothesis that the reliance on external cues in Parkinson’s disease involves exploitation of external stimuli for movement initiation in a way that differs from normal motor behaviour. To investigate this hypothesis we used a thoroughly tested experimental paradigm, which involves the induction of a response conflict (Coles et al., 1995). This was achieved by means of visual stimuli that contain target and distractor elements instructing for responses of opposite hands. Competition between an incorrect response (elicited by the distractors) and the correct response (instructed by the target) should lead to stronger interference with the execution of the correct response when subjects rely more strongly on external cues. Note that this interference effect is independent of the absolute response times and therefore not influenced by factors like weakness and rigidity, which impair response execution in Parkinson’s disease.

The reaction-time results support our hypothesis, as a significantly stronger increase in mean reaction time from the compatible to the incompatible condition was found in Parkinson’s disease patients than in the control subjects. Furthermore, the LRP results ascertain the operation of a response competition mechanism as a major contribution to this response delay in the incompatible condition. Since the LRP measures the voltage difference between left and right motor cortex, it provides a direct demonstration of response competition, evidenced by the brief positive deflection reflecting temporary activation of the motor cortex controlling the incorrect response hand (Figs 4 and 5). In addition, the incorrect lateralization of the LRP was of higher amplitude in Parkinson’s disease patients than in control subjects, which is consistent with the patients’ longer response delay and confirms our main prediction.

**Event-related potentials related to stimulus evaluation and response processing**

While the reaction-time differences between patients and control subjects are important as such, the LRP is pivotal for their interpretation. In tasks like the one used in this study, the LRP precedes EMG-onset by an interval as short as 25–100 ms. There is clear evidence that, even with such short intervals, the LRP is not tightly coupled to EMG or movement parameters, but is subject to central influences from the motor programming level and can be dissociated from motor output (Smid et al., 1990, 1996; Miller and Hackley, 1992; De Jong et al., 1994). It is important to stress that such a dissociation also occurred in our data, as the stronger incorrect lateralization of the LRP for patients compared with control subjects was not accompanied by a larger number of incorrect responses. As in other studies (e.g. Smid et al., 1990), the claim of a dissociation does not mean that the response conflict induced by incompatible stimuli remained confined entirely to the neurocortical level and was never transmitted to the neuromuscular apparatus. As shown in Fig. 4, in the patient group, the EMG of the incorrect response hand in the incompatible condition seems to be briefly activated to a level that slightly surpasses EMG activity of the incorrect
side in the compatible condition. This was due, however, to a single patient who displayed this incorrect EMG activity on only one response side. As the amplitude of the incorrect EMG activation (i.e. the amplitude of incorrect EMG activation in the incompatible relative to the incorrect EMG activation in the compatible condition) was very small compared with the magnitude of the incorrect lateralization of the LRP, there was no reason to use the EMG rather than the button-press responses for the separation of correct and incorrect trials.

Although the incorrect lateralization of the LRP confirms the occurrence of a response conflict in both groups, it does not exclude the possibility that differences in stimulus evaluation time for the compatible and incompatible stimuli also contributed to the slower reactions to incompatible stimuli. Given that the peak latency of the P300 component is a marker of stimulus evaluation time (McCarthy and Donchin, 1981), this possibility is suggested by the P300 latencies as they appear in Fig. 6, and confirmed by the (marginally significant) increase in P300-2 latency from the compatible to the incompatible condition. The further possibility that stronger incorrect lateralization of the LRP in patients compared with control subjects is related to a shorter period of time dedicated to the evaluation of the incompatible stimuli, was not confirmed statistically.

As already mentioned, the presence of two peaks in the P300 latency range, which we arbitrarily labelled as P300-1 and P300-2, was attributed to overlap of the P300 by a negative component. This component might be related to the negative component associated with efference monitoring and error detection that has recently been reported in related experimental paradigms (Gehring et al., 1993; Falkenstein et al., 1995; Kopp et al., 1996). For our data, this interpretation is supported by the fact that the overlapping negative component [labelled as error-related negativity (ERN), N2 or N2c by different groups], was more prominent in the incompatible condition, which fits the proposal that it reflects neural activity related to the detection of inappropriate responses that are inhibited before they are executed. If the negative component has the functional meaning which has been proposed, it might be exploited in further experiments to investigate to what extent the differences between patients and control subjects result from different strategies.

Reliance on partial stimulus information in Parkinson’s disease

Incorrect lateralization of the LRP, induced by incongruent stimulus configurations, has been attributed to an early, preliminary analysis of the stimulus configuration (Gratton et al., 1988, 1992; Smid et al., 1990; Coles et al., 1995). The stimulus analysis proceeds through an initial ‘parallel’ phase, in which the elements of the stimulus configuration (i.e. the arrows in our experiment) are processed independently of their location. Since distractor elements dominate the stimulus array, the incorrect response is activated before the correct one in this phase. In the subsequent ‘focused’ phase of stimulus analysis, subjects select the target location and inhibit the incorrect response while they activate the correct response (Gratton et al., 1992). From the initial activation of the incorrect response, it has been inferred that information is not always transmitted in an all-or-none fashion. Instead, it appears that partial stimulus information can reach the response system before stimulus analysis has been completed (Coles et al., 1995). Importantly, the early transmission of partial stimulus information has been shown to be influenced by subjects’ strategies and task requirements (Gratton et al., 1992; Coles et al., 1995; Smid et al., 1996). Given this background, the stronger incorrect lateralization of the LRP in patients than in control subjects, confirms changes in the utilization of visual information in Parkinson’s disease. These changes appear to involve an abnormal reliance on the early ‘parallel’ phase of visual analysis, which was not only manifested in the incorrect lateralization of the LRP in the incompatible condition, but also in the shorter onset latency of the LRP for patients than for control subjects in the compatible condition. This latency difference bears out the second prediction of this study.

What are the implications of these findings? The shorter latency of the LRP, the stronger incorrect response activation and the associated longer delay in reaction time indicate that visual information exerted an earlier and stronger influence on movement initiation in Parkinson’s disease patients than in control subjects. While this does not necessarily entail the existence of a compensatory strategy, there is a possible mechanism by which early transmission of partial stimulus information may facilitate movement initiation in Parkinson’s disease. A well-documented feature of motor cortex physiology in Parkinson’s disease is a slower development of activation, indicated for instance by a prolonged time interval between initial activation of motor cortex neurons and movement onset in MPTP-induced parkinsonism of macaque monkeys (Doudet et al., 1990; Watts and Mandir, 1992). In humans, changes in excitability of the motor cortex, as measured by transcranial magnetic stimulation, start earlier before movement in Parkinson’s disease than in control subjects (Hallett et al., 1991). The slower buildup of motor cortex activity can be speeded up in Parkinson’s disease by single-pulse or repetitive subthreshold transcranial magnetic stimulation, which is associated with increased response speed and normalization of electromyographic activity (Pascual-Leone et al., 1994a, b). Perhaps the facilitative effects of rapid information transmission to the motor cortex (i.e. reliance on preliminary perceptual output to the motor cortex) are not unlike the mechanism by which transcranial magnetic stimulation facilitates movement initiation. Recordings of single-neuron activity in the primary motor cortex have indicated that partial response activation due to preliminary perceptual output to the motor cortex consists mainly of signal-related activity of sensory and sensorimotor type neurons, but also of weak movement-related activity of
sensorimotor and motor neurons (Miller et al., 1992). Thus, early access to visual information by the motor cortex may support movement initiation due to the intimate relation between these different populations of neurons in the motor cortex. That sensory information can indeed energize the motor cortex in an almost pulse-like fashion is supported by the observation that the incorrect lateralization of the LRP was short-lived and tightly locked to stimulus presentation, as it almost vanished in response-locked averages (relative to switch-closure) of the activity preceding movement. Recent data from Goodin et al. (1996) suggested a similarly tight coupling between lateralized movement-related and auditory-evoked activity. In our data, the hypothesis is further supported by the significantly smaller variance of the LRP onset latency (compatible condition) for patients than for control subjects.

Relation with cortical excitability changes

Although it is attractive to interpret the present results in terms of a compensatory difference in the use of partial stimulus information involving the visuomotor system as a whole, it cannot be ruled out that the results could reflect a more ‘local’ difference between Parkinson’s disease patients and control subjects at the level of the motor cortex. Recent studies with transcranial magnetic stimulation have indicated a reduction in corticocortical inhibitory activity in the motor cortex of Parkinson’s disease patients, which may render the motor cortex more susceptible to sensory input (Ridding et al., 1995). The excitability changes are viewed as an inadequate ‘presetting’ of the motor cortex for a forthcoming movement and have been related to common features of parkinsonian pathophysiology, like enhanced long-latency stretch reflexes and dyskinesias (Ridding et al., 1995). Possibly, our findings point out the existence of a movement-related potential correlate of the reduced inhibitory cortical activity. In this context, the pre-stimulus CNV-like negative shift (Fig. 7) is of interest, given the supplementary motor area contribution to the generation of the CNV (Ikeda et al., 1996). The supplementary motor area is a major target for the output of the basal ganglia (Schell and Strick, 1984), and it has been suggested that it mediates an inhibitory influence of the basal ganglia on primary motor cortex (Rossini and Tecchio, 1996). Thus, in spite of the fact that the reduction of the CNV amplitude in Parkinson’s disease did not reach statistical significance in the present study, there may be a relation between CNV changes preceding the reaction stimulus and an abnormal LRP, related to changes in excitability, following the stimulus. Support for this proposal is suggested by the results of Goodin et al. (1996) that we referred to earlier. In a simple reaction-time task to auditory stimuli, they found a lateralization of tightly coupled auditory-evoked and movement-related activity to the hemisphere contralateral to the response hand. This lateralization was much stronger when the auditory stimuli were presented irregularly so as to reduce anticipation, indicating that anticipatory activity that ‘presets’ the motor cortex for an upcoming movement also involves a regulation of its susceptibility to sensory input.

An explanation of the LRP findings in terms of changes in cortical excitability need not exclude that, in certain stages of the disease, the alterations in cortical physiology are exploited in a compensatory strategy. Thus, one direction for further research is to investigate the extent the described effects can be influenced by patients’ strategies. However, if the effects indeed reflect a compensatory mechanism, this mechanism is not necessarily useful in a wide range of situations outside the laboratory. Whether or not partial stimulus information is used, for instance, may depend on the number of response alternatives in a task (Coles et al., 1995). This is in keeping with a previous study in which we found that the LRP following a precue signalling preparation of the left or right hand tended to have a shorter onset latency in Parkinson’s disease patients than in control subjects, while it tended to be later following the reaction signal, which instructed for one response out of four alternatives (Praamstra et al., 1996).

Conclusion

In conclusion, the present data suggest intricate changes in sensorimotor integration underlying Parkinson’s disease patients’ increased dependence on external cues for movement initiation. These changes may be related to a compensatory mechanism or strategy that evolves with the disease and incorporates the alterations in cortical physiology caused by the disease. In particular, we have shown that there are differences in the way Parkinson’s disease patients and control subjects utilize visual information for the initiation of hand movements. This was suggested, firstly, by the finding that hand-specific motor cortex activation can start at a shorter latency in Parkinson’s disease patients than in control subjects. Secondly, erroneous response tendencies elicited by task-irrelevant distractor elements in the reaction stimulus were more pronounced, and they delayed the correct response more, in Parkinson’s disease patients than in control subjects. The latter finding has an interesting resemblance to the observation by Angel et al. (1970) that Parkinson’s disease patients require more time to stop false moves than control subjects. These authors proposed that stop commands, issued at a central level, have a delayed transmission to the motor system in Parkinson’s disease. The approach taken in the present study, exploiting concepts and tools developed in recent psychophysiological research on processes of stimulus–response translation (Coles et al., 1995) suggests instead that the reason why in Parkinson’s disease an erroneous response tendency is checked more slowly has to do with the way it is initiated. Under the circumstances created in this experiment, the initiation of movement in Parkinson’s disease patients seemed to rely more strongly than in control subjects on a preliminary visual analysis.
whose output has rapid access to the motor cortex and facilitates the initiation of movement.

Acknowledgements
We wish to thank the patients and volunteers who participated in this study, also A. S. Meyer and J. Blok for comments on the manuscript, and H. van Dijk and L. Haegens for technical assistance.

References


Reliance on external cues in Parkinson’s disease


Schell GR, Strick PL. The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. J Neurosci 1984; 4: 539–60.


