Movement preparation in Parkinson’s disease
Time course and distribution of movement-related potentials in a movement precueing task


Summary
Investigations of the effects of advance information on movement preparation in Parkinson’s disease using reaction time (RT) measures have yielded contradictory results. In order to obtain direct information regarding the time course of movement preparation, we combined RT measurements in a movement precueing task with multi-channel recordings of movement-related potentials in the present study. Movements of the index and middle fingers of the left and right hand were either precued or not by advance information regarding the side (left or right hand) of the required response. Reaction times were slower for patients than for control subjects. Both groups benefited equally from informative precues, indicating that patients utilized the advance information as effectively as control subjects. Lateralization of the movement-preceding cerebral activity [i.e. the lateralized readiness potential (LRP)] confirmed that patients used the available partial information to prepare their responses and started this process no later than controls. In conjunction with EMG onset times, the LRP onset measures allowed for a fractionation of the RTs, which provided clues to the stages where the slowness of Parkinson’s disease patients might arise. No definite abnormalities of temporal parameters were found, but differences in the distribution of the lateralized movement-preceding activity between patients and controls suggested differences in the cortical organization of movement preparation. Differences in amplitude of the contingent negative variation (CNV) and differences in the way in which the CNV was modulated by the information given by the precue pointed in the same direction. A difference in amplitude of the P300 between patients and controls suggested that preprogramming a response required more effort from patients than from control subjects.

Keywords: Parkinson’s disease; movement-related potentials; movement preparation; motor cortex, premotor cortex

Abbreviations: CNV = contingent negative variation; CRT = choice reaction time; EOG = electrooculogram; LRP = lateralized readiness potential; MANOVA = multivariate analysis of variance; RP = readiness potential; RT = reaction time; SMA = supplementary motor area; SRT = simple reaction time; TMS = transcranial magnetic stimulation

Introduction
An influential view on the slowness of movement in Parkinson’s disease attributes this phenomenon to deficient preparation of movement. According to this view, motor programming is one of the major functions of the basal ganglia (Marsden, 1982). An important source of evidence for a programming deficit has been the investigation of voluntary movements by means of RT paradigms. A number of studies have reported that Parkinson’s disease patients are more impaired in simple reaction time (SRT) than in choice reaction time (CRT) tasks (Evarts et al., 1981; Bloxham et al., 1984; Sheridan et al., 1987; Pullman et al., 1988, 1990; Goodrich et al., 1989; for a critical review, see Jahanshahi et al., 1992). In SRT tasks the response type is known before the reaction signal occurs. Hence, the response can be preprogrammed. By contrast, in CRT tasks the response depends on the identity of the stimulus. Therefore, the response can be programmed and initiated only after presentation of the reaction stimulus. A selective or differentially greater impairment of SRT compared with CRT tasks in Parkinson’s disease may be observed because Parkinson’s disease patients do not take advantage of the opportunity to preprogramme the response in the SRT task.
Longer RTs in SRT than in CRT tasks is a pattern repeatedly observed in Parkinson's disease patients. But the reverse pattern of greater impairment in CRT tasks has also been reported (Wiesendanger et al., 1969; Lichter et al., 1988; Reid et al., 1989; Jahanshahi et al., 1992). The contradictory findings in RT studies invite the use of other methods for investigating movement preparation. An inherent limitation of RT paradigms is that the information they provide on the processes preceding movement must be inferred from events that occur only after movement has started. Stronger evidence might be provided by measures that reflect the ongoing process of movement preparation. Movement-related potentials derived from the scalp-recorded EEG represent such a measure.

Studies employing movement-related potentials in Parkinson's disease have mainly concerned investigations of the readiness potential (RP) (Deecke et al., 1977; Barrett et al., 1986b; Dick et al., 1987, 1989; Simpson and Khuraibet, 1987; Tarkka et al., 1990; Feve et al., 1992). The RP is a slowly rising potential of negative polarity with an onset between 1000 and 2000 ms before movement-onset. It is typically recorded with self-paced voluntary movements that subjects are instructed to repeat with intervals of a few seconds. In Parkinson's disease, the initial part of the RP is often flatter and of lower amplitude than in control subjects, whereas the late rise shows a steeper slope. The abnormal configuration has been attributed to reduced activity of the supplementary motor area (SMA) (Dick et al., 1987, 1989; Simpson and Khuraibet, 1987; Feve et al., 1992). Task-related modulations of the RP amplitude, present in normal subjects, may be reduced or absent in Parkinson's disease, which has also been attributed to the SMA (Vidalilhet et al., 1993; Touge et al., 1995; Praamstra et al., 1995, 1996a, b).

The RP cannot be considered an important source of information regarding the time course of movement preparation. Given its extended duration and the fact that the potential is obtained by response-locked averaging of the EEG, it can only provide relevant temporal information if it can be divided into separate components with well-defined meanings. While a division of the RP into separate components has been proposed (Shibasaki et al., 1980; Barrett et al., 1986a), their identification is often difficult. Investigators have, therefore, used fixed latency criteria for the components, to the effect that any temporal information they might carry is lost (e.g. Dick et al., 1987, 1989; Vidalilhet et al., 1993; Touge et al., 1995). Moreover, the proposed components seem not to have distinct generators (Ikeda et al., 1992; Rektor et al., 1994).

In order to probe the time course of motor preparation with premovement potentials, it seems more useful to record movement-related activity with externally instructed instead of self-paced movements. In a warned RT task, in which each trial begins with a warning signal, premovement activity similar to the RP develops in the interval between the warning stimulus and the reaction stimulus. This negative-going potential is known as the CNV. The CNV is mostly viewed as a generalized event-preceding negative potential upon which the movement-related RP is superimposed (e.g. Kutach and Donchin, 1980; Brunia, 1993; Tecce and Cattanach, 1993; but for a different view, see Rohrbaugh and Gaillard, 1983). Similar to the contralateral predominance of the RP, the lateral distribution of the CNV is modulated in a predictable way by the side of movement if the warning stimulus specifies the hand with which to respond after the reaction stimulus (e.g. Syndulko and Lindsley, 1977). The modulation reflects the differential involvement of the two hemispheres following a decision to move one limb. In recent years, it has become a common procedure to isolate the lateralized movement-related activity by subtracting the potentials recorded over the left and right sides of the scalp, yielding the so-called LRP (for reviews, see Coles, 1989; Coles et al., 1995). The onset of the LRP has been shown to be a sensitive measure of response preparation, indexing the time at which response preparation becomes selective with respect to response hand (De Jong et al., 1988; Gratton et al., 1988; Osman et al., 1992).

Given the inconclusive evidence from RT studies on movement preparation in Parkinson's disease, the present study combined RT measurements with recordings of movement-preceding potentials in order to assess the cerebral events preceding movement. A straightforward way to address the preparation of movement in Parkinson's disease and explore the feasibility of LRP recordings in Parkinson's disease patients is the use of a movement precueing paradigm. This paradigm has previously been used in RT studies in Parkinson's disease (Stelmach et al., 1986; Jahanshahi et al., 1992) and also in LRP studies of normal subjects (e.g. De Jong et al., 1988). In both of the RT studies, it was found that Parkinson's disease patients, though they were slower than control subjects, used advance information to programme a motor response. Jahanshahi et al. (1992) also found, however, that Parkinson's disease patients needed a longer interval between precue and reaction signal than control subjects before a fully cued response was equally fast as responses in an SRT task. We expected that differences in the temporal development of movement-preceding cerebral activity might elucidate the slower utilization of advance information in Parkinson's disease, which was suggested by these findings. We used a version of the movement precueing task in which the effect of a precue which gave partial information about a forthcoming response was compared with the effect of a non-informative precue. Whether patients were slow in evaluating the advance information was assessed by means of the latency of the P300. The onset of the LRP provided information on the subsequent processing step in which advance information is translated into central motor activity. In addition to the onset of the LRP, focused on by most earlier LRP studies, we studied its topography and topographical changes over time as another source of information on the development of preparatory cortical activity preceding movement. The LRP measures were interpreted against the background of related CNV measures,
given that the LRP is derived from the CNV. Finally, EMG measures were included to help interpret any prolongation of the time between initial activation of the motor cortex and movement.

Methods

Task and design

A mixed between-groups and within-subjects design was used. Parkinson's disease patients and control subjects were investigated in a movement precueing experiment using a four-choice task. The response alternatives were realized by four response keys, assigned to the index and middle fingers of the two hands. Following a precue that was neutral in 50% of the trials and validly specified the hand to be moved on the other trials, the reaction signal specified hand and finger. Thus, on half the trials the precue provided partial information on the required response, allowing subjects to prepare for movement of the left or right hand. The effects of informative versus neutral precues on RTs, error rates, EMG onsets and movement-related potentials were evaluated.

Subjects

Ten patients with a clinical diagnosis of Parkinson's disease and 10 healthy control subjects participated in the study. The mean age of the patients (nine men, one woman) was 53.6 years (range 42–67 years; SD 7.3 years). The mean age of the control subjects (eight men, two women) was 54.2 years (range 40–67 years; SD 9.0 years). All patients and control subjects were right-handed, as assessed by the Edinburgh Inventory (Oldfield, 1971). They gave informed consent for the study, which was approved by the local ethics committee.

Patients had bilateral Parkinson's disease of mild to moderate severity. They fulfilled the criteria of the UK Parkinson’s Disease Society Brain Bank for the diagnosis of Parkinson's disease (Hughes et al., 1992) and were all L-dopa responsive. All but two patients were treated with L-dopa (plus decarboxylase inhibitor) and some also with deprenyl. One of the two patients not using L-dopa used amantadine and deprenyl, and the other used no medication. The mean disease duration was 5.8 years (range 3–12 years; SD 2.5 years). Motor disability was evaluated by means of the motor subscale of the United Parkinson’s Disease Rating Scale (Lang and Fahn, 1989) and ranged between 15 and 43 (mean 27.5±10.2), whilst on medication at the time of the study, which was approved by the local ethics committee.

Electrophysiological recordings

The EEG was recorded with Ag/AgCl electrodes placed at the midline site Cz and at 26 lateral sites according to the extended International 10–20 System (American Electroencephalographic Society, 1994), i.e. F3 and F4, F1 and F2, FC5 and FC6, FC3 and FC4, C3 and C4, C1 and C2, CP5 and CP6, CP3 and CP4, CP1 and CP2, P3 and P4, P1 and P2. All electrodes were referenced to the right mastoid. Vertical and horizontal electrooculograms (EOGs) were recorded bipolarly from above/below the right eye and from locations at the outer canthi of each eye. Electrode impedance was kept below 5 kΩ. EMG activity was recorded bipolarly with electrodes attached 8 cm apart to the flexor side of each forearm. EEG activity was amplified using a bandpass of 0.016–35 Hz (EMG 10–70 Hz) and digitized at a rate of 200 samples per s. Trials contaminated by artefacts were removed prior to averaging. This was done by visual inspection of each individual trial, with EOG, EEG and EMG channels displayed simultaneously. Trials with EOG activity exceeding 100 μV within a time frame of 2000 ms following the precue were excluded, as were trials contaminated by artefacts due to movement or amplifier blocking. Electrical activity was averaged with respect to the occurrence of the precue (i.e. stimulus-locked) for an analysis period of 2750 ms starting...
250 ms before the precue. The baseline was calculated from these first 250 ms.

**Data analyses**

The RT data were analysed by multivariate analyses of variance (MANOVA) with group (Parkinson’s disease patients versus control subjects) as between-subjects variable, and block (six levels), cue (informative versus neutral), hand (left versus right) and finger (index versus middle) as within-subjects variables (Vasey and Thayer, 1987; Norusis, 1992).

For the analysis of the electrophysiological data, subject averages were computed after pooling the responses with the index and the middle finger. This yielded averages per subject for cued and uncued movements of the left and right hand, respectively. These averages comprised visual-evoked potentials elicited by the onset of the precue and by the onset of the reaction signal, and the CNV in the interval between the visual responses. The visual-evoked responses consisted of a sequence of a negative (N1), a positive (P1) and a negative (N2) peak. These were followed by a smaller positive–negative sequence (containing the P2) on the rising slope of a broadly distributed positive wave with a centroparietal maximum. Given its distribution and latency, this wave represented the endogenous P300. Latency and amplitude of the main visual-evoked responses (P1 and N2) following precue onset were quantified as the mean of the values measured at the most posteriorly located electrode sites P1 and P2. The P1 and N2 responses were identified by searching the highest positive and negative peaks in the time window of 100–200 ms (P1) and in the window from 150 to 250 ms (N2). The amplitude of the P1 was measured with respect to the pre-stimulus baseline, whereas the N2 amplitude was measured peak-to-peak with respect to the P1. The latency and amplitude of the P300 were measured at Cz as the highest positive peak within a search window of 280–500 ms. The visual-evoked responses following the reaction signal were analysed in the same way as the responses elicited by the precue. In some subjects, the P300 following the reaction signal was difficult to identify. In these cases, the index channel Cz was compared with the neighbouring central and parietal channels in order to choose the peak that most likely represented the P300. The CNV was quantified as the mean amplitude in the interval from 1000 to 1100 ms after onset of the precue. This interval occurred after the reaction signal but still before the first visual-evoked response. We chose this interval because, especially in the normal controls, the CNV continued to rise during this time frame. For the same reason, this interval instead of the 100 ms preceding the reaction signal was chosen as baseline for the P1 amplitude measures.

The measurements of the visual-evoked responses were performed on averages across all conditions, in order to eliminate irrelevant differences due to physical differences between the visual stimuli. The subject groups were compared using t tests. The P300 and CNV data at electrode Cz were entered into MANOVAs with group (Parkinson’s disease patients versus control subjects) as between-subjects variable, and cue (informative versus neutral) and hand (left versus right) as within-subject variables. An analysis of the CNV distribution was performed on averages across left- and right-hand data, since the lateralization of the CNV related to the response side was studied by means of the LRP derivation. Thus, the analysis included the within-subjects variables cue, hemisphere (left and right) and electrode. The levels of electrode were reduced from 13 to 3 by grouping the electrodes in rows from anterior to posterior. Over the left hemisphere the following electrodes were grouped together: FC5, C5, CP5 (the most lateral row); F3, FC3, C3, CP3, P3 (the middle row); F1, FC1, C1, CP1, P1 (the most medial row). The same grouping was applied to the right hemisphere electrodes. The grouping was applied to keep interactions involving the variable electrode interpretable and to focus the analysis on the dimension of the scalp distribution most likely to reveal differential contributions from medial premotor versus lateral premotor and motor cortex.

To isolate the lateralized movement-related activity from the CNV complex, we computed the voltage differences between homologous electrodes over the left and right side of the head, and averaged the left–right difference for right-hand movements with the right–left difference for left-hand movements (Coles, 1989). This computation creates 13 waveforms, i.e. one for each pair of homologous electrodes. The computation of the LRP can be expressed as:

\[
[(X_i - X_{i+1})_{\text{right-hand movement}} + (X_{i+1} - X_i)_{\text{left-hand movement}}]/2,
\]

where \(X_i\) and \(X_{i+1}\) are homologous electrodes over the left and right scalp, respectively.

The peak amplitude of the LRP was identified in the grand averaged waveforms. This provided the basis for a quantification in individual subjects as the mean amplitude between 1350 and 1450 ms (cued movements) and between 1550 and 1650 ms (uncued movements), after precue onset. These data were analysed by a MANOVA with group as between-subjects variable and cue and electrode (13 levels) as within-subjects variables. From the LRP for cued movements, additional amplitude measures were taken at 450–550 ms and at 900–1000 ms. These measures were analysed by a MANOVA with group as between-subjects variable and electrode as within-subjects variable. In the analyses of the LRP and the CNV distributions, interactions with the variable electrode were checked by performing an analysis on normalized data, as suggested by McCarthy and Wood (1985). The F values of this second analysis are reported.

The onset of the LRP was determined in the waveform recorded at C3/C4 by taking for each subject the first point in time at which the LRP was consistently above a criterion of \(3.5 \times SD\) was derived from the variability (in voltage over time) of the baseline in the averaged LRP waveforms of each subject (at electrode C3/C4). The onset was defined as the first timepoint at which the LRP exceeded this criterion for a duration of at
least 50 ms (for a similar procedure, see Osman et al., 1992).

The procedure was applied after low-pass (8 Hz) digital filtering. For determining EMG onsets the same procedure was used on the rectified EMG, without prior filtering. Onsets were analysed by MANOVAs with group as between-subjects variable and hand and cue as within-subjects variables.

To avoid false positive results, some investigators adjust the degrees of freedom for within-subjects variables, following Greenhouse and Geisser (1959). This adjustment only affects the results for variables with two or more degrees of freedom. Hence, for our variables hand, finger and cue, application of the Greenhouse–Geisser correction has no consequences. For block and electrode we report unadjusted and adjusted degrees of freedom and significance levels.

Results

Behavioural measures

The analysis of RTs (see Table 1) showed that advance information about the side of movement shortened the response times by ~200 ms: main effect of cue \( F(1,18) = 668.77, P < 0.001 \). Patients were significantly slower than control subjects \( F(1,18) = 4.93, P < 0.05 \). However, the slowness of patients was not specifically related to either cued or uncued movements. The difference in response speed between patients and control subjects was 48 ms for cued and 59 ms for uncued movements. The interaction of group by cue was not significant \( F(1,18) = 0.69 \).

Probably due to the fact that subjects were right-handed, left-hand responses were significantly slower than right-hand responses: main effect of hand \( F(1,18) = 8.01, P < 0.05 \). Middle finger responses were slower than index finger movements \( F(1,18) = 9.73, P < 0.05 \). The right-hand advantage was ~50 ms for patients and control subjects. The difference between index and middle finger was 20 ms for controls and 42 ms for patients, but the interaction of finger by group was not significant. Interestingly, there were significant interactions of hand by cue \( F(1,18) = 6.79, P < 0.05 \) and finger by cue \( F(1,18) = 5.51, P < 0.05 \). The first interaction arose because the slowest hand gained most by advance information. This is consistent with findings by Hackley and Miller (1995), who found that when the time for preparing a response is increased, the disadvantage of the left hand is reduced. By contrast, the second interaction was related to a stronger precueing effect for the (faster) index finger than for the middle finger. This might be related to the fact that isolated flexion is a more natural movement for the index than for the middle finger.

There were no significant effects related to the block variable. The mean RT across blocks was stable in control subjects. In patients it decreased considerably across the first three blocks. The interaction of block by group was not significant, however.

The error rates were 2.3% and 3.4% for control subjects and patients, respectively. These errors include anticipatory responses, defined as responses with a latency of \( \leq 300 \) ms. Such responses only occurred for patients and only in the precued condition (on 0.1% of the trials). We also counted as error the trials in which subjects failed to give a response within 1500 ms. This occurred on 0.3% of the trials for the normal subjects and on 0.8% of the trials for patients. Given that the error rates were very low, they were not analysed statistically.

Electrophysiological data

Visual-evoked responses, P300 and CNV

The visual-evoked responses elicited by the precue were characterized by a very small negative deflection (N1), followed by a prominent positive component (P1), and again a smaller amplitude negative deflection (N2). The visual responses were recognizable at all electrode sites (see Fig. 2), but were best defined at the most posterior sites (electrode sites P1 and P2) from which measurements were taken (see Fig. 1 and Table 2). There were no significant amplitude differences between patients and control subjects for either the P1 or the N2 response. The latency of the P1 was longer for patients than for control subjects. The difference was ~10 ms for the P1 following the precue \( \tau(18) = 2.55, P < 0.05 \), and a non-significant 5 ms for the response elicited by the reaction signal \( \tau(18) = 0.68 \). The N2

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Table 1 Reaction times and EMG onsets for control subjects and patients

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<th>Reaction time</th>
<th>EMG onset</th>
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<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Patients</td>
</tr>
<tr>
<td>Noncued</td>
<td>844±52</td>
<td>902±74</td>
</tr>
<tr>
<td>Noncued</td>
<td>903±51</td>
<td>963±117</td>
</tr>
<tr>
<td>Cued</td>
<td>645±60</td>
<td>694±51</td>
</tr>
<tr>
<td>Cued</td>
<td>690±49</td>
<td>737±107</td>
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Measurements are relative to the onset of the reaction signal and expressed in ms (±SD).

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Fig. 1 Grand average movement-related potentials recorded from the midline Cz electrode (left) and (averaged) from P1 and P2 (right). For the traces on the right, the time scale is expanded to show the latency difference of the P1 between control subjects and patients. The thick traces are from the control subjects. The thin lines refer to recordings from the Parkinson's disease patients. Data are averaged across left and right hand, and across cued and uncued movements. Abbreviations P1, N2, P300 and CNV refer to event-related potential components discussed in the text.
following the precue was also later in patients, but the difference between control subjects and patients was not significant \((t(18) = 1.26)\).

The amplitude of the P300 elicited by the precue was higher in patients than in normal subjects \([F(1,18) = 4.48, P < 0.05]\). The latency showed no difference between the groups. Following the reaction signal the amplitude and latency were of comparable magnitude in both groups. Remarkably, no significant differences in amplitude or latency between the cued and uncued conditions were found in either patients or control subjects.

The amplitude of the CNV, measured at Cz, was smaller for patients than for the normal controls \([F(1,18) = 6.44, P < 0.05]\), and higher for left- than for right-hand movements \([F(1,18) = 12.74, P < 0.01]\). Analyses of the CNV distribution demonstrated a significant main effect of electrode \([F(1,18) = 82.79, P < 0.001]\), and a significant group\(\times\)electrode interaction \([F(1,18) = 5.98, P < 0.05]\). However, there was no main effect for group. The interaction is explained by the fact that the difference is pronounced near the midline, but declines steeply from medial to lateral electrode locations \((see Fig. 3)\). Analyses of simple effects demonstrated no significant difference at any electrode row. When performed on the single electrodes, simple effect analyses showed a significant difference of the CNV amplitude between patients and controls at electrodes C1 and C2 \([F(1,18) = 4.09, P < 0.05]\).

Cued movements were preceded by a higher amplitude CNV than uncued movements. This was revealed by the analysis on the Cz recorded potential \([F(1,18) = 11.15, P < 0.05]\), as well as the analysis of the CNV distribution \([F(1,18) = 7.81, P < 0.05]\). Figure 2 suggests that the cued/uncued difference is much stronger in patients than in control subjects. This impression was confirmed by analyses of simple effects, yielding an effect of cue in the Parkinson’s disease group \([F(1,18) = 7.71, P < 0.05]\), but not in the normal controls \([F(1,18) = 1.38]\). The absence of a significant interaction of cue\(\times\)electrode \([F(1,18) = 0.46]\), showed that the cue effect was equally strong at lateral electrode sites as at locations near the midline \((see Fig. 2B)\). The different distributions of the CNV amplitude difference between the groups and between cued and uncued movements (for Parkinson’s disease patients) are represented graphically in Fig. 4.

### LRP and EMG measures

The LRPCs for patients and control subjects are represented in Fig. 5. For both groups the LRP preceded the onset of EMG activity accompanying uncued movements by \(~150\) ms \((see Table 3)\). Before cued movements, lateralized movement-related activity already started in the interval between precue and reaction signal, i.e. \(400-450\) ms after the precue. For normals as well as patients, the LRP for cued movements had a biphasic configuration with a first maximum at \(~500\) ms. This can be most clearly appreciated in the traces at C3/4. The difference in LRP onset between cued and uncued movements was significant \([main effect of cue: F(1,18) = 910.74, P < 0.001]\). There was no significant effect of the group variable or an interaction of group\(\times\)cue.

As illustrated in Fig. 6 \((iso-potential maps 3 and 4)\), the distribution of the LRP at peak latency was not different between the two groups. Only in map 2, representing the mean amplitude of the LRP preceding cued movements in the interval from 900 to 1000 ms, was there a difference between control subjects and patients. Whereas the lateralized preparatory activity had a very focal distribution in the control subjects, it was more extended and more frontally located in patients. The main effect of electrode was significant \([F(12,216) = 7.99, P < 0.001\) without Greenhouse–Geisser correction; \(F(1,18) = 7.99, P < 0.025\) with correction]. The group\(\times\)electrode interaction was
FIG. 2 (A) Superimposition of grand average movement-related potentials preceding uncued movements (thin line) and cued movements (thick line); control subjects. (B) Grand average movement-related potentials preceding uncued movements (thin line) and cued movements (thick line) in Parkinson's disease patients. Data are averaged across right- and left-hand movements. The layout of the traces reflects the arrangement of electrodes on the subjects' heads. HEOG and VEOG refer to horizontal and vertical EOG channels, respectively.

significant without the correction applied \([F(12,216) = 2.02, P < 0.01; F(1,18) = 2.02, P > 0.05\) with correction]. When the electrode sites were evaluated separately by analyses of simple effects, significant differences between the groups emerged at sites FC3/FC4 \([F(1,18) = 4.60, P < 0.05]\), FC1/FC2 \([F(1,18) = 4.58, P < 0.05]\) and F3/F4 \([F(1,18) = 4.20, P = 0.05]\).

The EMG onset data displayed largely the same pattern as the RT data. The main feature of the data was the earlier EMG onset for cued than for uncued movements [see Tables 1 and 3; main effect of cue: \(F(1,18) = 387.98, P < 0.001\)]. In contrast to the RT data, there was no main effect of hand \([F(1,18) = 1.47]\). Importantly, the group differences were not as pronounced as in the RT data. Whereas the RT differences between control subjects and patients were 59 and 48 ms in the noncued and the cued condition, the
Fig. 3 Superimposition of grand average movement-related potentials recorded from Parkinson’s disease patients (thin line) and control subjects (thick line). Data averaged across left- and right-hand movements, as well as cued and uncued movements.

Fig. 4 Lateral distribution of the CNV. The amplitude difference between control subjects and Parkinson’s disease patients (left panel) is most pronounced at the midline and very small at lateral electrode locations. The amplitude difference between the CNVs preceding cued and uncued movements of Parkinson’s disease patients (right panel) is more equally distributed. The different distributions suggest that different underlying neural generators are responsible for the effects. Electrode row on the horizontal axis refers to the grouping of electrodes applied also in the statistical analyses of the CNV distribution (see Methods). Row numbers 5, 3 and 1 designate the most lateral, the middle and the most medial electrode row over the left hemisphere, respectively; row numbers 6, 4 and 2 refer to the homologous electrode rows over the right hemisphere. The numbering derives from the International 10–20 System (see electrode labels in Figs 2 and 3).
Table 3  Mean LRP for control subjects and Parkinson patients precue

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<tr>
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<th>LRP onset</th>
<th>EMG onset</th>
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<tr>
<td></td>
<td>Controls</td>
<td>Patients</td>
</tr>
<tr>
<td>Noncued</td>
<td>1267±82</td>
<td>1287±60</td>
</tr>
<tr>
<td>Cued</td>
<td>460±123</td>
<td>415±89</td>
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Onset times: ms±SD. For comparison with the LRP onsets, the mean EMG onsets across left- and right-hand responses are also listed. Note that, in contrast to Table 1, all measures are referred to the onset of the precue.

Discussion

Origin of the response delay in Parkinson’s disease patients

As expected, Parkinson’s disease patients reacted more slowly than control subjects, but the difference between the two groups was smaller than the differences found in some earlier studies (e.g. Stelmach et al., 1986; Jahanshahi et al., 1992). This may be due to the fact that, compared with the aiming movements used in those studies, the movements required in our experiment were less difficult, as the subjects’ fingers rested on the response keys throughout the experiment. In addition, our precue and reaction signals were of a symbolic nature and, therefore, required more time to evaluate than the spatial cues (compatible with the required responses) used in the above studies. This may explain why the RTs were relatively slow for patients as well as for normal subjects. In addition, it may also be relevant to the relatively small group difference. In a recent study by Brown et al. (1993), the difference in response speed between Parkinson’s disease patients and normal subjects was smaller with symbolic reaction signals than with spatial signals containing intrinsic information about the required response.

The analyses of the electrophysiological measures provide evidence about the origin of the response delay in Parkinson’s disease patients. Replicating findings by Bodis-Wollner and Yahr (1978) and Bodis-Wollner et al. (1982), we found later visual-evoked responses in patients than in control subjects. However, differences in the exogenous visual-evoked potentials, such as the P1, are unlikely to be related to the slowness of movement investigated here. Although it cannot be excluded that the delayed visual responses indicate slower stimulus encoding, patients were not slower in extracting information from the stimuli. This is indicated by the fact that patients and control subjects did not differ in the latency of the P300, which is generally taken to be related to stimulus evaluation time (McCarthy and Donchin, 1981; Magliero et al., 1984).

The temporal information conveyed by the LRP, in relation to the question addressed in this section, will be discussed on the basis of the LRP for uncued movements. The LRP onset for uncued movements occurred 20 ms later for patients than for controls. There was a delay in the patients’ EMG

Fig. 5 Lateralized readiness potentials (LRPs) from control subjects (upper panel) and patients (lower panel). The traces are grouped as if recorded from electrodes over the left hemi-scalp. As indicated by the labels with each trace, however, it concerns activity recorded between homologous electrode sites over both hemispheres. Thin traces represent the lateralized movement-related activity associated with uncued movements, while the thick traces refer to the activity preceding cued movements.

corresponding differences in EMG onset were both only 23 ms and not significant \( F(1,18) = 1.23 \). Note that this pattern of EMG onsets and RTs suggests that about half the difference in RTs between the groups originated from a slower initiation and execution of the movements by the Parkinson’s disease group.
The hypothesis that the response delay in Parkinson’s disease patients may be partly due to a central delay should be further tested by measuring LRP onsets in tasks that yield more pronounced differences between patients and control subjects. However, there is already some evidence about the initiation of motor cortex activity in Parkinson’s disease patients. Evidence for a delayed initiation was obtained by Pascual-Leone et al. (1994) on the basis of transcranial magnetic stimulation (TMS) studies. When applied shortly before or after the response signal, TMS of subthreshold intensity speeded responses in a warned RT task. Interestingly, this effect was stronger in Parkinson’s disease patients than in control subjects, resulting in similar response times for both groups. Pascual-Leone et al. (1994) proposed that TMS activates corticocortical connections, thereby enhancing information transfer between premotor cortices and the primary motor cortex. However, another physiological measure of central motor processes, i.e. the premotion silent period, appears not to be delayed in Parkinson’s disease (Kaneoke et al., 1989), while direct recordings of precentral cortex neurons in MPTP-treated monkeys did not find a delayed onset either (Doudet et al., 1990).

For uncued movements, the RT difference between Parkinson’s disease patients and control subjects seemed partly due to a later onset of the LRP, as discussed in the last paragraph, and to a longer interval between EMG onset and RT. A mechanism that might explain the latter finding is that motor cortex activity, once initiated, is slower to develop, resulting in a slower execution of movement. Pascual-Leone et al. (1994) hypothesized such a mechanism on the basis of TMS evidence for a longer pre-movement excitability buildup in Parkinson’s disease patients. Premovement excitability was measured by the probability of a subthreshold TMS pulse inducing a motor evoked potential. In normal subjects this probability increased from 0 to 1 in an interval from -95 to -30 ms before EMG onset of a voluntary movement, whereas it started at -135 ms in Parkinson’s disease patients. Additional support for abnormal development of motor cortex activity in Parkinson’s disease comes from studies of MPTP-induced parkinsonism in macaque monkeys (Doudet et al., 1990; Watts and Mandir, 1992), where prolonged latencies were found between the onset of motor cortex activity and the onset of movement. This prolongation was attributed to disrupted movement-
related neuronal activity in the primary motor cortex making agonist muscle activity less efficient.

In conclusion, the temporal information provided by LRP and EMG onsets does not allow a firm conclusion as to the origin of the longer RTs in Parkinson's disease patients, since the group differences were not significant. The LRP and EMG onset latencies displayed a plausible pattern, however, in the sense that they were consistent with existing evidence for normal corticomotor neuron transmission. The results encourage further use of the LRP as a temporal measure of central motor activation in the investigation of movement disorders.

**Use of advance information in Parkinson's disease**

Both groups of participants benefitted equally from informative precues. The cue effect amounted to 217 ms for patients and to 206 ms for control subjects. Thus, Parkinson's disease patients apparently used informative precues as efficiently as control subjects. Cue effects of comparable magnitude have been reported by De Jong et al. (1988), who studied normal subjects using a very similar experimental paradigm.

The results obtained for the electrophysiological measures support the assumption that patients and control participants used the precues to prepare the response. For cued movements, the LRP onset occurred even earlier in patients than in control participants. The difference of 45 ms was not significant, however. The more gradual onset of the LRP for cued (as compared with uncued) movements makes a reliable onset determination more difficult, and may be responsible for the difference.

It should be emphasized that the LRP preceding cued movements is a more complex phenomenon than the LRP preceding uncued movements. Whereas the latter mainly represents movement-related activity that is probably caused by discharge of pyramidal tract neurons, the former consists for a larger part (i.e. in the S1–S2 interval) of instruction-dependent neural activity preparing for a movement (cf. Miller et al., 1992). Only after the response signal, can a motor command be released, initiating movement-related activity. The fact that for both types of movement, EMG onset occurred 23 ms later in patients than in control subjects might indicate that in Parkinson's disease patients the initiation of movement-related activity was delayed to the same extent in cued movements as in uncued movements.

As mentioned, the EMG–RT interval was longer for patients than for control subjects. However, in both groups of participants, the EMG–RT interval was shorter after informative than after uninformative cues. The cue effect on this interval was 40 ms for patients and 29 ms for control participants. One effect of response preparation can be a reduction of the EMG–RT interval (Lecas et al., 1986; Hackley and Miller, 1995). The fact that this interval was shortened in both groups of our experiment further supports the hypothesis that Parkinson's disease patients are not necessarily impaired in the use of informative precues.

An interesting feature of the LRP preceding cued movements is its biphasic configuration, which in our data seems to be slightly more pronounced in patients than in control participants (see Fig. 5). Eimer (1995) has suggested that the first phase of such a biphasic LRP, which he found very clearly in the presence of shared spatial features of stimulus and response, might be related to automatic response activation (see also De Jong et al., 1994).

**Effort and task demands in the movement precueing paradigm**

The amplitude of the P300 was significantly higher for patients than for control subjects. Kramer et al. (1983) and Wickens et al. (1983) have suggested that P300 amplitude may be related to task difficulty. The task used in our experiment probably was more difficult for Parkinson's disease patients than for control subjects, such that the patients had to 'work harder' for the same performance level as control subjects.

The amplitude of the CNV has also been reported to increase with increasing effort and task complexity (McCallum and Papakostopoulos, 1973; McCallum and Pocock, 1983). In our data the CNV was of higher amplitude in control subjects than in Parkinson's disease patients, i.e. at locations near the midline. This difference, however, is most likely due to a reduced contribution from midline structures to the CNV in Parkinson's disease; we return to this finding in the next section. The data further show a significantly higher CNV following informative precues than following neutral precues, which could be attributed to the Parkinson's disease group. This pattern differs from the results reported in several other studies that found a CNV of higher amplitude preceding a more informative stimulus (e.g. Kutas and Donchin, 1980; Van Boxtel et al., 1993; Van Boxtel and Brunia, 1994). In studies that used short (<2 s) S1–S2 intervals, results like ours or equal amplitudes between different cueing conditions have also been reported (e.g. MacKay and Bonnet, 1990). The divergent results are probably related to the fact that response preparation and stimulus anticipation are inherently confounded in the present paradigm. Thus, the observed CNV patterns are always a mixture of effects of the processing of precue and reaction signal. If only the effect of processing the reaction signal is considered, one may expect a lower CNV in the cued condition, as in this condition the anticipated reaction signal conveys less information than in the uncued condition (e.g. Van Boxtel et al., 1993). By contrast, if only the processing of the precue is considered, the opposite prediction can be made. In the cued condition motor preparation can begin after presentation of the precue, whereas this is not possible in the uncued condition. With respect to the present data, i.e.
the higher CNV amplitude for cued than for uncued movements in the Parkinson's disease group, it can be argued that effects related to the processing of the precue prevailed over effects related to the anticipated reaction signal. This is suggested by the distribution of the CNV amplitude difference, which extends to the most lateral electrode sites instead of being confined to locations near the midline, like the group difference in CNV amplitude (see Results; Figs 2B, 3 and 4). In view of this distribution, it seems reasonable to attribute the higher CNV amplitude for cued than for uncued movements to stronger preparatory activity at the lateral convexity (i.e. motor cortex and premotor areas) in the Parkinson's disease group.

Stronger preparatory motor activity might express a difference in effort required for the task, as we suggested for the P300 amplitude difference between the groups. However, it could also indicate a disturbance in the regulation of motor cortical activity. Such a disturbance was recently inferred from a TMS study on the excitability of the motor cortex in Parkinson's disease patients, which indicated decreased activity in corticocortical inhibitory circuits (Ridding et al., 1995). These investigators reasoned that this decrease might be associated with inadequately 'focussed' neural activity in the motor cortex, resulting in a net increase of the neural activity accompanying a movement.

Either of these explanations for stronger preparatory motor activity in the Parkinson's disease group could also underlie the difference in LRP distribution that we found between Parkinson's disease patients and control subjects. Recall that at peak latency and in the early phase of the LRP for cued movements, there were no differences between the distributions, whereas just before the reaction signal, the LRP extended further in frontal direction for patients (see Fig. 6). This might reflect the activation of a larger area of cortex, related to abnormal motor cortical inhibitory mechanisms, as discussed above. Alternatively, the altered distribution of the LRP might be due to activity in areas additional to those normally activated by motor tasks, like earlier reported in patients with recovered motor function after stroke (Chollet et al., 1991; Weiller et al., 1992, 1993) and in patients with motor neuron disease (Kew et al., 1993). It has been suggested that the activation of these areas, i.e. the ventral opercular premotor area and insula, might reflect compensation for lesions of the corticospinal outflow (Kew et al., 1993; Weiller et al., 1993). However, Stephan et al. (1995a) found the same areas activated during imagined movements, and proposed that the recruitment of these areas in patients might reflect a more general phenomenon that occurs with increasing demands, both in physiological and in pathological conditions. Although the reported recruitment of insular and lower premotor areas might be responsible for the changed LRP distribution and the higher CNV amplitude for cued as compared with uncued movements in Parkinson's disease patients, further investigation is needed to confirm this hypothesis. Another candidate structure whose activation might explain the altered distribution is the lateral premotor cortex. The fact that none of the areas considered has shown increased activity in PET studies with Parkinson's disease patients may be related to the fact that only in our task response was speed emphasized.

Jahanshahi et al. (1992) have suggested that instructions play a crucial role in whether or not Parkinson's disease patients preprogramme their responses in an SRT task. According to these investigators, this might explain the inconsistency of the results from studies comparing performance in CRT and SRT tasks, as without explicit instructions, Parkinson's disease patients would be less likely to adopt a preprogramming strategy than control subjects (see also Worringham and Stelmach, 1990). The results discussed in this section point to differences in preparatory cortical activity between Parkinson's disease patients and control subjects, which are probably an expression of the motor pathology of Parkinson's disease. As discussed, they could also mean that the preprogramming of movements is more demanding for Parkinson's disease patients. Thus, the results provide some support for the hypothesis of Jahanshahi et al. (1992). The reason why Parkinson's disease patients are less likely than control subjects to adopt a preprogramming strategy, might be the extra effort required for preprogramming.

Movement-related potentials and externally cued versus internally generated movements

A much debated issue in research on movement preparation in Parkinson's disease is the role of the SMA in self-initiated (internally generated) movements. As mentioned in the Introduction, certain features of the RP preceding self-paced voluntary movements have been interpreted as evidence for a reduced SMA contribution to this potential in Parkinson's disease (Dick et al., 1987, 1989; Simpson and Khuraibet, 1987; Feve et al., 1992). Recently, the SMA contribution to the RP and its reduction in Parkinson's disease have been further delineated by movement-related potential studies drawing upon PET results in related tasks (Praamstra et al., 1995, 1996a, b; Touge et al., 1995). Preferential involvement of the SMA in internally generated movements has been contrasted with stronger engagement of the lateral premotor cortex in externally cued movements (e.g. Goldberg, 1985; Passingham, 1987). However, according to a recent study in which externally triggered and self-initiated movements were directly compared using PET and movement-related potentials, the functional distinction between medial (SMA) and lateral premotor areas should not be overstated (Jahanshahi et al., 1995; see also Passingham, 1993). Similarly, Cunnington et al. (1995) suggested that in normal subjects, the SMA is involved in internally generated (sequential) movements, but also in externally cued movements if temporally predictable cues allow for a predictive mode of movement control. From their movement-related potential recordings in Parkinson's disease patients,
on the other hand, these authors inferred that for movements in the absence of external cues, Parkinson’s disease patients invoke ‘defective internal control mechanisms (operating via the SMA)’, whereas these mechanisms may be bypassed when external cues are provided (Cunnington et al., 1995, p. 948).

The present study has some bearing on the issue of a division of labour between lateral and medial premotor areas, and on the relevance of this division for the understanding of movement preparation in Parkinson’s disease. Disregarding the differences between tasks and labels used for the premovement potentials, we found, like Cunnington and co-workers, a reduced amplitude of the premovement potentials recorded at the midline. Given the extended electrode array used in our recordings, the distribution of the CNV amplitude difference between patients and controls could be evaluated, and was shown to have a gradient from medial to lateral (see Figs 3 and 4). This distribution supports earlier hypotheses about a reduction of the CNV amplitude in Parkinson’s disease patients. Amabile et al. (1986) and Wright et al. (1993) found such a reduction, which they attributed to an impaired activation of the SMA. This view is supported by an effect of L-dopa on the CNV amplitude (Amabile et al., 1986) and on the restitution of SMA activity indicated by regional cerebral blood flow measured with PET after dopaminergic medication (Jenkins et al., 1992; Rascol et al., 1994). Further evidence for an SMA contribution to the CNV comes from magnetoencephalographic studies (Ioannides et al., 1994) and a combined magnetoencephalographic and PET study (Stephan et al., 1995b).

It should be noted that neither in our study, nor in any other known to us, has the reduction of the CNV come close to the reduction reported by Cunnington et al. (1995). In fact, some investigators have reported a normal CNV amplitude in Parkinson’s disease (Bötzel et al., 1995; Jahanshahi et al., 1995). Thus, the conclusion of Cunnington et al. (1995) that in externally cued movements the SMA is bypassed in Parkinson’s disease may be too strong. The reduced CNV amplitude in our patient data was accompanied by robust lateralized premovement activity and an enhancement of the CNV preceding cued relative to uncued movements. These findings represent a sure sign of active preparation for movement and are probably due to activity of the motor cortex and premotor areas at the lateral convexity. However, this activity certainly propagates to the midline recording site where Cunnington et al. (1995) measured premovement potentials. An alternative interpretation of their data is, therefore, that in the presence of external cues, patients did not adopt a preprogramming strategy. As a result, there was no preparatory cortical activity as such.

To summarize, we think that evidence from pre-movement potentials recorded before self-initiated and externally cued movements suggests that medial premotor structures are involved in both kinds of movements. In addition, the contribution of the SMA to premovement potentials in Parkinson’s disease may be reduced for both kinds of movements. Clearly, this evaluation does not support the notion that the role of the SMA is confined to internally generated movements. Rather, as suggested by Jahanshahi et al. (1995), it may be more appropriate to conceive of SMA and lateral premotor cortex as elements in a ‘volitional action system’, which are activated depending on the demands in a particular task. Possibly, within such a system, our finding of an altered distribution of the LRP and the concomitant CNV changes in Parkinson’s disease indicate a compensatory shift of activity from the SMA to lateral (pre)motor structures. The present data provide a stronger argument for such a shift than the movement-related potential data that have previously been suggested to support compensatory changes (Dick et al., 1989). As to the structures involved, the argument remains hypothetical, however, since the neural sources of movement-related potentials recorded at the scalp can be estimated, but not be determined in a definitive way.

**Conclusions**

The main conclusions of the present study are based on the simultaneous consideration of electrophysiological measures and RT data. The RT data confirm earlier studies indicating that Parkinson’s disease patients can use advance information to plan movements. The electrophysiological findings add, first, that this is accomplished in the same way as by control subjects, as suggested by the timely development of an LRP when patients are informed about the response side. Secondly, the higher P300 amplitude in Parkinson’s disease patients indicates that task performance of patients and controls required more effort from the former than from the latter group. Thirdly, the frontal extension of the LRP distribution, the reduced CNV amplitude, and the stronger modulation of the CNV as a function of the information provided by the precue point to considerable differences between patients and controls in the cortical activity preceding movement. These differences may be, in part, an expression of the disease (deficient SMA function; insufficiently ‘focussed’ cortical activity), but could also reflect compensatory changes.

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