Responses to cued signals in Parkinson’s disease
Distinguishing between disorders of cognition and of activation

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Summary
Impairment of movement execution in Parkinson’s disease could be due to disorders of cognition and/or of activation. These two factors are hard to separate by measuring response times only. Therefore, in this study, response force and event-related EEG potentials were measured continuously during tasks in which subjects had to respond to cued signals. Fifteen patients with Parkinson’s disease and 15 healthy subjects were studied during two tasks: (i) the ‘clock task’, in which the signal’s identity was fully precued but its presentation time was uncertain and (ii) the ‘validity task’ in which the cue did not always predict the response validity. Thus, the clock task required more sustained attention, and the validity task sometimes required fast switching. The patients generally responded slower than control subjects. In the clock task, the response times of both groups changed to the same extent with presentation time, whereas in the validity task the patients were additionally slower than the control group with invalidly cued signals. The patients generally had a weaker response force and a lower rate of force production. In the clock task, both force measures changed with presentation time in the control group only, whereas in the validity task, the two measures increased in both groups to the same extent with invalidly cued signals. The contingent negative variation amplitudes in the patients’ event-related EEG potentials were reduced, reflecting reduced activation of movement preparation, whereas lateralization of the motor cortices (i.e. the lateralized readiness potential) did not differ significantly between groups, reflecting unimpaired response selection. Force and contingent negative variation were generally reduced in the patients showing that their general slowing is at least partially due to impaired activation. Task-specific problems added to the general activation deficit; the lack of modulation of response force by presentation time revealed pronounced deficits of activation in the monotonous clock task. The specific delay of responses with invalidly cued signals, unparalleled by activation measures, might suggest a problem of cognition. The task-specific deficits may reflect a basic dilemma for patients with Parkinson’s disease; cognitive problems may arise in complex tasks but disorders of activation may become pronounced in more simple, monotonous tasks.

Keywords: Parkinson’s disease; response force; event-related potentials; activation

Abbreviations: ANOVA = analysis of variance; CNV = contingent negative variation; EOG = electrooculogram; ERP = event-related EEG potential; LRP = lateralized readiness potential; N180 = negative component at 180 ms; N2 = second negative component; P200 = positive component at 200 ms; P3 = third positive component; S1 = cueing stimulus; S2 = imperative signal

Introduction
A relevant approach to understand the impairments of both motor and cognitive functions in Parkinson’s disease has been the measurement of response times in tasks where patients have to press keys in response to stimuli (for a review, see Jahanshahi et al., 1992). Because the relationships between stimuli and responses can be systematically varied in such experimental settings, substages on the route from stimulus presentation to response execution may be investigated (Frith and Done, 1986; Jahanshahi et al., 1992).

A prominent feature of the response time in Parkinson’s disease is the general delay of responses across all experimental variations, adding to specific delays which were
observed in some tasks only (e.g. Stelmach et al., 1986; Sheridan et al., 1987; Jahanshahi et al., 1992; V. J. Brown et al., 1993; Cooper et al., 1994). This general factor was ascribed by Stelmach et al. (1986) to ‘those ‘input’ and/or ‘output’ processes which are unaffected by advance information’, by Sheridan et al. (1987) both to ‘a basic central problem’ and to ‘a basic slowness of movement’, by Jahanshahi et al. (1992) to ‘slowness of response initiation’, by V. J. Brown et al. (1993) to a ‘motoric impairment’ and by Cooper et al. (1994) to a ‘perceptuomotor factor’, rather than to a ‘cognitive-analytical’ factor which became apparent in more complex tasks only.

This distinction between a specific, cognitive deficit on the one hand and global perceptuomotor slowness on the other hand might map on the distinction between cognition and activation in human information processing. That is to say, movement execution may be impaired in Parkinson’s disease for at least two reasons: with disorders of cognition patients may have difficulties in selecting the correct movement in time; with disorders of activation patients may have difficulties in providing the activation for a selected movement. Both factors may affect response times but they are hard to separate by measuring response times only. Rather, more might be learned about presumed deficits of activation, which might be responsible for much of the ‘global’ slowness, by measuring aspects of activation more explicitly.

**Computational mechanisms and energetical supply of information processing**

Sanders (1983) suggested that stimulus processing occurs in two different though interacting dimensions, the computational and the energy dimension: computational processes include feature extraction, stimulus identification, response selection and motor adjustment. These computational processes are supplied with energy resources, termed arousal, activation and effort (Pribram and McGuinness, 1975). The duration of the computational processes may be measured using effects of experimental variations on response times. In contrast, the energy dimension cannot be measured easily with response times in standard experimental situations. However, it has been suggested in recent years that this dimension may be approached by measuring response force and by measuring the amplitudes of event-related EEG potentials (ERPs), as will be detailed below. Since ‘computational’ and ‘energetical’ are terms with the connotation of computing machines, the terms ‘cognition’ and ‘activation’ will be used instead in the following text.

**Response force as a measure of activation**

In the present context, measurement of response force refers to the standard experimental situation where response times are measured, i.e. subjects are aware that they have to respond as fast and as correct as possible, but they are generally not aware that the force of their response is also being measured. In healthy subjects, this ‘spontaneous’ response force increases with loudness of preceding tones (Jaskowski et al., 1995; Ulrich and Mattes, 1996), under stress (Jaskowski et al., 1994a), under time-pressure (Jaskowski et al., 1994b), and when stimuli are unexpected (Jaskowski and Verleger, 1993). There is no straightforward relationship between response force and response time; larger forces are sometimes associated with fast responses (Jaskowski et al., 1994b), sometimes with slow responses (Jaskowski and Verleger, 1993). Thus, the evidence is compatible with the notion that spontaneous response force varies in healthy subjects according to a dimension of activation, and that this dimension is not entirely reflected in response times. To our knowledge, spontaneous response force has, so far, not been measured in Parkinson’s disease. [In a number of studies on Parkinson’s disease, patients had the explicit task of maintaining or releasing a certain force (e.g. Dettmers et al., 1995; Kunesch et al., 1995) or the size of the EMG burst was measured before self-paced movements (for a review, see Day and Dick, 1990). However, these situations differ from the one discussed here where involuntary response force is measured in the speeded responses to stimuli. In particular, a possible deficit due to malfunction of the basal ganglia might become clearer with involuntary force, not masked by attempts of compensation.]

Thus, if there is indeed a deficit of activation in Parkinson’s disease, then patients’ force should increase less steeply, their maximum force should be smaller, and the impact of experimental factors on these force parameters should be smaller than in healthy subjects. To the extent that these effects would parallel effects on response time, the conclusion would be justified that the response time effects reflect a disturbance of activation.

Furthermore, measuring response force is of interest not only for obtaining information about activation but also for obtaining more detailed information about timing. Measuring response force with a device that transforms force to voltage provides a continuous time course of the developing response, allowing quantification of the temporal dynamics of movements, e.g. by determining the time points when the response starts and when force reaches its maximum. On the basis of such measurements, Stelmach et al. (1989) reported a slow rise of force production in cued choice responses in Parkinson’s disease. One relevant difference from the present study is that the choice was between different levels of force exerted by one hand, i.e. subjects were well aware that force was relevant. Nevertheless, the slower rise appears to be a general phenomenon; e.g. Godaux et al. (1992) reported a lower rate of rise in the EMG in uncued simple responses to visual stimuli. Thus, a lower rate of force production is to be expected for the patients in the present study too.
**ERPs as measures of activation**

ERPs reflect postsynaptic activity arriving at upper layers of cortical pyramidal cells, with enhanced cortical activation generally reflected by ERP negativity, and enhanced inhibition by ERP positivity (Birbaumer et al., 1990). Obviously, these measures have an energetic aspect. This view can be frequently found in ERP research and was made most explicit by Kok and Zeef (1991) and Kok (1997) who suggested that the amplitudes of ERP components reflect energetic aspects of behaviour while the timing of ERP components may be used for measuring computational processes.

When applying this distinction to ERP findings in Parkinson’s disease, it is indeed striking to see that the majority of differences found between patients and healthy subjects are differences in amplitudes, both related and unrelated to movement requirements. Smaller amplitudes have been found in Parkinson’s disease for the first component of the Bereitschaftspotential (readiness potential) before self-paced movements (Dick et al., 1989; Vierregge et al., 1994b; Jahanshahi et al., 1995; Cunnington et al., 1995, ‘cues absent’ condition), for the contingent negative variation (CNV) amplitude before cued imperative stimuli (Linden et al., 1990; Wright et al., 1993; Praamstra et al., 1996; Pulvermüller et al., 1996), for the fronto-central P3 (Pulvermüller et al., 1996), for the ‘processing negativity’ i.e. the difference potential between two auditory channels (one to be attended, the other to be ignored) (Stam et al., 1993; Vierregge et al., 1994a; Karayanidis et al., 1995), and for the ‘mismatch negativity’, i.e. the difference potential between deviant and standard tones (both to be ignored) (Pekkonen et al., 1995; but see Vierregge et al., 1994a). In contrast to these differences in amplitudes, few latency differences have been reported. The most consistent latency difference is a slight, often insignificant delay of the P3 component to auditory stimuli (review by Ebmeier, 1992). This pattern of results is in contrast to differences found in other areas of ERP research. For example, the most prominent ERP changes in healthy ageing are delays of latencies, most marked for the P3 in experimental psychology, being a precise measure for the timing of ERP components reflecting response tendencies (e.g. De Jong et al., 1988; Wascher and Wauschkuck, 1996). Thus, this ERP component is sensitive to parameters that reflect activation (peak force: Sommer et al., 1994; rate of force production: Sommer et al., 1994 and van Boxtel et al., 1993, Fig. 3).

In this study, the distinction between ERP measures of cognition and activation will be specifically made for ERP components reflecting response preparation in the interval between a cue and an imperative signal. These components are the CNV and the lateralized readiness potential (LRP) (Fig. 1). The CNV (Walter et al., 1964) is a slow negative shift which develops in the interval between cue and imperative signal. Its later phase, rising until the imperative stimulus, with a topographic maximum at the vertex (similar to the Bereitschaftspotential that precedes self-paced movements), mainly reflects movement preparation (Rohrbaugh et al., 1976) but there may also be contributions of anticipation of the imperative stimulus (Damen and Brunia, 1994; Van Boxtel and Brunia, 1994), of working memory activity (Ruchkin et al., 1994) and of effort invested in the task (Van Boxtel, 1994; Wascher et al., 1996). The CNV reflects rather widespread cortical activation, not restricted to a well-defined area (Elbert et al., 1994). This global increase of cortical activation can be assumed to reflect the activation aspect of movement preparation. On the other hand, there is also a specific aspect of movement preparation. This is the extent to which the motor cortex contralateral to the prepared hand is activated. Being overlapped by the CNV and by components evoked by the imperative stimulus (see Fig. 1), this activity may be made visible by subtracting the EEG activity ipsilateral to the movement (Fig. 1, thin line) from the EEG activity contralateral to the movement (Fig. 1, thick line). The resulting difference potential is called the LRP (Coles, 1989). The LRP has gained considerable impact in experimental psychology, being a precise measure for the timing and extent of response tendencies (e.g. De Jong et al., 1988; Miller and Hackley, 1992; Smid et al., 1996), e.g. even reflecting the covert tendency of preparing the alternative response to the one finally given, in case of interfering information (Gratton et al., 1988; Wascher and Wauschkuck, 1996). Thus, the LRP amplitude, as a measure of response selection, mainly reflects the cognitive aspect of movement preparation. This distinction between the ‘cognitive’ LRP and the ‘activation’ CNV is supported by findings on healthy subjects where the LRP proved insensitive and the CNV proved sensitive to parameters that reflect activation (peak force: Sommer et al., 1994; rate of force production: Sommer et al., 1994 and van Boxtel et al., 1993, Fig. 3).

Thus, if there is indeed a deficit of activation in Parkinson’s disease, then the CNV should be smaller and the impact of experimental factors on the CNV should be smaller than in healthy subjects. To the extent that these effects would
parallel effects on response time, the conclusion would be justified that the response-time effects reflect disorders of activation. If, on the other hand, there is a deficit of the cognitive dimension of behaviour in Parkinson’s disease, then the LRP should be smaller and the impact of experimental factors on the LRP should be smaller than in healthy subjects. To the extent that these effects would parallel effects on response time, the conclusion would be justified that the response-time effects reflect disorders of cognition.

**The tasks**

Two tasks were used in the present study. In both tasks, a cue was followed by an imperative stimulus, which required that one of two keys had to be pressed. To cover a wide range of the patients’ possible problems, the two tasks differed (i) in the validity of the cue stimulus and (ii) in the timing of the imperative stimulus. (i) The imperative signal was perfectly announced by the cue in task 1 (‘fully precued’, in the terms used by Jahanshahi et al., 1992), but not in task 2, where the cue was only 80% valid in one block and had no predictive validity (i.e. 50% validity) in the other block. (ii) The time interval between the cue and the imperative stimulus was fixed at 1 s in task 2, but was variable in task 1 (between 1.2 and 3.6 s), i.e. in this task subjects were informed by the cue how to respond, but did not know in advance when to respond, although 2.4 s was the most probable interval. Therefore, task 1 was more monotonous, requiring vigilance, while task 2 required fast switching in sites at ~180 ms after cue onset (N180), accompanied by ., 1995; and for vibrotactile stimuli, (ii) The time interval between the cue and the imperative signal was perfectly announced by the cue in task 1 (‘fully precued’, in the terms used by Jahanshahi et al., 1992), but not in task 2, where the cue was only 80% valid in one block and had no predictive validity (i.e. 50% validity) in the other block.

Predictions for response times

In the clock task, signals were most frequent at 2.4 s after the cue. From results in young adults (Wascher et al., 1996), we expected that response times would be fastest with the frequent 2.4 s interval. This was also expected to occur in the patients. In addition, the patients were expected to have the same delay as healthy subjects at the other, less frequent cue–signal intervals, and possibly an additional delay at short cue–signal intervals, as was reported by Jahanshahi et al. (1992) in their task with full pre-cuing.

In the validity task, subjects were expected to respond faster to validly than to invalidly cued signals in the 80% validity block whereas this validity advantage should be reduced in the 50% validity block (Gratton et al., 1990). The literature does not allow unambiguous predictions for the patients’ response times, because previous studies on valid/ invalid cueing investigated shifts of spatial attention (Rafal et al. 1984; Yamada et al., 1990; Wright et al., 1993; Bennett et al., 1995; and for vibrotactile stimuli, see Bradshaw et al., 1993) and did not require choice responses (except Bradshaw et al., 1993). If patients with Parkinson’s disease did indeed need more time for translating the information provided by the cue into preparation of their response (Jahanshahi et al., 1992), then their responses might be less affected by the cue than healthy subjects’, because the cue–signal interval of 1 s might be too brief to allow good preparation. Alternatively, because patients with Parkinson’s disease have difficulties in shifting set (e.g. Owen et al., 1993), invalid cueing might induce a larger response delay and more errors in the patients.

**Predictions for response force and ERPs**

In healthy subjects, expected stimuli evoke smaller response force than unexpected ones (Jaskowski and Verleger, 1993), so the healthy subjects’ response force should be smaller in the clock task for the signals appearing at the most probable interval than at other intervals, and should be smaller for validly cued than for invalidly cued stimuli in the validity task. Due to the presumed deficit of activation, these effects should be reduced and response force should be generally smaller in Parkinson’s disease.

From previous studies with young healthy adults in the clock task (Wascher et al., 1996) and in the validity task (Gratton et al., 1990) the following ERP components were expected to be of interest (schematically displayed in Fig. 1).

1) The cue-evoked potential. The visual cue (cuing stimulus) would evoke a negative component at occipital sites at ~180 ms after cue onset (N180), accompanied by a positive component at anterior sites (P200), followed by a centrally focused second negativity at ~300 ms (N2) and a parietally focused positivity at ~400 ms (P3) (cf. for these components e.g. Kenemans et al., 1993; Czigler et al., 1994).

From the few ERP studies that reported visually evoked components in Parkinson’s disease, no reliable alteration of amplitude or latency was expected for the P3 component evoked by the cue (Linden et al., 1990; Tachibana et al., 1992; Wright et al., 1993; Praamstra et al., 1996; Pulvermüller et al., 1996). Evidence on N180 is equivocal; delayed latencies were reported by Wright et al. (1993), but not by Praamstra et al. (1996). Results on P200 were reported by Wright et al. (1993) only, who found a latency delay. Consistently, delayed early posterior P1 latencies were found in Parkinson’s disease (Wright et al., 1993; Praamstra et al., 1996) but this component (preceding the N180) could not be clearly distinguished in the present recordings (cf. Figs 5 and 8). Using Kök’s (1997) scheme introduced above, latency delays would reflect cognitive deficits, while reduced amplitudes would reflect impaired activation.

2) The CNV. As mentioned above, reductions of CNV are observed in Parkinson’s disease (Linden et al., 1990; Wright et al., 1993; Praamstra et al., 1996; Pulvermüller et al., 1996) and thus can be expected in the present tasks, possibly reflecting the patients’ disorder of activation.

3) The LRP. The LRP was expected to develop during the cue–signal interval of the clock task, because response
Selection was possible after the cue, and to reach its maximum during the actual response. Similarly, in the validity task the LRP was expected to occur in the cue–signal interval of the 80% validity block, and to be absent in the cue–signal interval of the 50% validity block (Gratton et al., 1990). Gross deviations of the patients’ LRPs from those of the healthy subjects were not expected. [This expectation was confirmed by the first report on the LRP in Parkinson’s disease, by Praamstra et al. (1996), published while this paper was being revised; they found normal LRPs in Parkinson’s disease, except for a more frontocentral topographical distribution.] However, the detailed time course of the LRP in the validity task might provide clues with regard to the patients’ possible problem in processing the cue or in switching to the alternative response; if cue processing were impaired, the patients’ LRP should be less marked in the cue–signal interval. If switching to the alternative response were impaired, the final LRP after the imperative signal should continue to reflect preparation of the cued response, even after invalidly cued stimuli.

To summarize, the present study used the measurement of response force, of cue-evoked ERP components, of the CNV and of the LRP, in addition to response times, in two cued choice-response tasks, in order to describe, on a fine-grained level, the deficits of movement preparation in Parkinson’s disease. Possible deviations of the patients in these measures should be evaluated within the framework of a distinction between cognition and activation. The main question was to what extent the measures of activation (response force, rate of force production, CNV amplitude) would be affected. To the extent that these effects would parallel effects on response time, the conclusion would be justified that the response-time effects reflect disorders of activation.

Experiment 1: the clock task

Methods

Subjects

Fifteen patients suffering from idiopathic Parkinson’s disease according to the UK Parkinson’s Disease Society Brain Bank criteria (Gibb and Lees, 1988) and 15 healthy control subjects, matched in age, sex and education with the patients, were recruited for the two experiments. Details of the two groups are listed in Table 1. Patients were aged 46–72 years, with a disease duration between 2 and 9 years. Patients with unpredictable motor fluctuations, depression or dementia were not included in the study. The control group, matched for age, sex and years of education to the patients (Table 1), did not suffer from any neurological or psychiatric disorder. All subjects had normal or corrected-to-normal vision. The experiment usually took place during the morning hours when the patients were at their best clinical state. Immediately after the first recording session, the Unified Parkinson’s Disease Rating Scale (UPDRS; Fahn et al., 1987), the Hoehn–Yahr score (Hoehn and Yahr, 1967) and the Schwab–England activity score of daily living (Schwab and England, 1969) were recorded for the patients by the same clinical examiner. The study was approved by the Ethics committee of the Medical University of Lübeck, and all patients and control subjects gave their informed consent to participate in the study.

Stimuli and procedure

The task is illustrated in Fig. 2. A white ring (outer diameter 10 cm, ~5° of visual angle) was displayed around the centre of the screen, representing the face of a clock, on which a clearly visible red pointer moved continuously, needing 4.8 s for one revolution.

Whenever the red pointer was at the 6 o’clock position, which we shall refer to as ‘6h’, a blue H or F (visual angle 0.5°) was presented in the centre of the clock-face. This letter was the cueing stimulus (S1), indicating which response would have to be made to the imperative signal (S2). ‘H’ indicated a left-hand response, ‘F’ a right-hand response. S2 was a change of colour of the clock-face from white to yellow, which could occur at ‘9h’ (3.7 % of trials), ‘10.30h’ (7.4 %), ‘12h’ (66.7 %), ‘1.30h’ (7.4 %), or ‘3h’ (3.7 %), i.e. 1.2, 1.8, 2.4, 3.0 or 3.6 s after the cue. No S2 stimulus appeared in 11.1 % of the trials. These ‘catch trials’ were introduced in order to focus the subjects’ attention all the time to the clock and to reduce triggering of responses by anticipation. Subjects were informed about the distribution of S2 stimuli. The S1 stimulus remained on the screen until a response was given or until the pointer reached 4h.

Subjects were seated in a comfortable armchair in which an isometric force-sensitive key was mounted at the end of each armrest. Subjects positioned their arms along the armrests and were asked to respond as quickly as possible to S2, according to S1, by depressing the relevant key with the thumb, avoiding premature responses. The armchair was situated in a sound-proof, electrically shielded chamber. Stimuli were presented on a Multisync monitor with an observation distance of ~1.3 m. The presentation of the task was controlled by a Commodore Amiga 2000 computer. Four hundred and six trials were presented in a continuous sequence, with a short break after 203 trials. If a wrong key was pressed five times, the session was interrupted and the information ‘H-left; F-right’ was presented anew for 10 s on the screen. If premature responses accumulated, subjects were verbally reinstructed as well.

Recording and data processing

The EEG was recorded from Fz, Cz, Pz, Oz, C3’ and C4’ (1 cm in front of C3 and C4) using Ag/AgCl electrodes (Picker–Schwarzer) with electrodes affixed at the mastoids (linked via a 5 kΩ resistor) as reference. The electro-oculogram (EOG) was recorded bipolarly both vertically from above and below the left eye (vertical EOG) and horizontally from the outer canthi of both eyes (horizontal...
Table 1  Individual data of the Parkinson’s disease patients and summary data of both groups

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>School (years)</th>
<th>Age (years)</th>
<th>Diagnosis/ side</th>
<th>Medication</th>
<th>DOPA (mg/day)</th>
<th>UPDRS III</th>
<th>Hoehn/ Yahr</th>
<th>Schwab/ England</th>
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<td>15</td>
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<td>3</td>
<td>M</td>
<td>8</td>
<td>65</td>
<td>8/R</td>
<td>L-Dopa + Benserazide</td>
<td>350</td>
<td>15</td>
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<td>2/B</td>
<td>L-Dopa + Benserazide</td>
<td>150</td>
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Patient group summary (8 F and 7 M; side: 8 R, 4 L and 3 B)

Mean 9.4  60.2  5.1
±SD  ±1.4  ±9.8  ±2.7

Control group summary (8 F and 7 M)

Mean 9.9  61.7
±SD  ±1.9  ±8.1

School: years of school education. Diagnosis: years since diagnosis. Side: more affected side (R = right, L = left, B = both).

EOG). The EEG and EOG were amplified with a Nihon-Kohden 4421 amplifier with a 5-s time constant (0.03–35 Hz band-pass).

Response force was recorded continuously from the isometric force-sensitive keys. Exceeding a criterion of 1.5 N was counted as a response, and it was fed back to the subject by a short pip. This criterion is well in the range used with the usual all-or-none response keys.

The recording of each trial was triggered by a signal from the Commodore Amiga 2000 at ‘6h’. Data (EEG, EOG and response force) were sampled at 100 Hz, from 100 ms before S1 to 4600 ms after S1, i.e. from 100 ms before ‘6h’ until ‘5h’ of the next revolution, were analogue-to-digital converted and stored on an 80486 microcomputer.

Off line, the EEG data were screened for artefacts with our own software; thus, trials with zero lines, out-of-scale values, slow drifts >60 µV, fast shifts >100 µV/500 ms and saccades were excluded from further analyses. Trials with incorrect, premature or too slow key-press responses (see below for criteria) were also excluded from further analysis. Trials with blinks or with small eye movements were not excluded, but these artefacts were removed from the data. To this end, the transmission of the vertical EOG was estimated by regression in areas of maximal vertical EOG...
channels weighted by their transmission coefficients. Averaged differences were low-pass filtered at 8 Hz.

Data analysis
Performance. Trials with incorrect, premature (until 50 ms after the actual S2) and too slow (>1.5 s after S2) keypress responses were counted as errors and excluded from further analysis.

Since response force was recorded continuously, several parameters of the response could be defined within the time course of the subjects’ force output (see Fig. 3). These were: the start of the movement; response time; force peak latency; force peak amplitude; subthreshold duration; and rate of force production. The moment when the force was 0.5 N larger than a 100-ms pre-S1 baseline was defined as start of the overt response (‘response start’). The moment when 1.5 N was exceeded was defined as the response time. Latency and amplitude of the maximal force exerted on the keys between 50 ms and 1500 ms after S2 were designated as force peak latency and force peak amplitude. The time between start and response time was designated as subthreshold duration. The rate of force production was defined as the force peak amplitude divided by the movement duration, with movement duration determined as the time between response time and force peak latency. (Movement duration was not separately analysed as a measure of timing, because it is confounded by differences in force peak amplitude, i.e. the larger the force peak is, the longer is movement duration.) All these parameters were defined in each single correct response and were then averaged across trials, separately for each of the five presentation times (‘9h’ to ‘3h’) and for each subject. In addition, as a measure of the intra-individual variability of response times, the SD of the single-trial response times was calculated, separately for each of the five presentation times and for each subject.

Effects of the factors Time (‘9h’, ‘10.30h’, ‘12h’, ‘1.30h’ and ‘3h’) and Group (patients, control subjects) on each of these response parameters as well as on the percentage of error trials were tested by analysis of variance (ANOVA) with repeated measures. For patients, all response parameters were additionally inspected, to see whether there was any difference in performance between the more affected and the less affected side, as assessed by the summed UPDRS-III item values.

ERP parameters. Analyses of the ERPs were restricted to the central condition (‘12h’) because this was the condition with largest number of trials, yielding the most reliable ERP averages. N180, P2, N2, P3 and CNV were determined in the average of each subject’s accepted trials. The LRP is defined as the average difference (contralateral minus ipsilateral) relative to the responding hand. Therefore, for the LRP, trials had to be averaged separately for right-hand and left-hand responses, the difference C3’–C4’ was formed for right-hand responses, C4’–C3’ for left-hand responses, and both differences were averaged (Coles, 1989). These averaged differences were low-pass filtered at 8 Hz.

N180 was defined as the most negative peak at Oz between 120 ms and 280 ms. Group differences of latency and amplitude were analysed by t tests. P200 was measured as the most positive peak between 150 ms and 250 ms at Fz, Cz and Pz. N2 was measured as the most negative peak between 200 ms and 450 ms at Fz, Cz and Pz. P3 was measured as the most positive peak between 300 ms and 700 ms at Fz, Cz, Pz and Oz. Effects of the factors Topography (Fz, Cz and Pz; plus Oz in case of P3) and Group on amplitudes and latencies of N2, P2 and P3 were tested by ANOVAs with repeated measures for the factor Topography. The CNV was measured as the mean amplitude 200 ms prior to S2 at all electrode sites. Separate ANOVAs with repeated measures for the factor Topography were calculated for the sagittal topography (Fz, Cz and Pz) and for the lateral topography (C3’, Cz and C4’). Since for both topographies an interaction of Group×Topography was found, these analyses were repeated separately for both groups.

The LRP was measured in steps of 500 ms from 10 to 2000 ms after the onset of S1, during the last 200 ms prior to S2, and in the 200 ms around the maximum of asymmetry at the time of the overt response. These mean amplitudes were tested for group differences by t tests.

Components evoked by the imperative stimulus were not investigated since they do not reflect response preparation. Furthermore, these components overlapped with the reset of the slow negativity and therefore could not be identified reliably.

Interactions including the factor Topography were recalculated using the vector-sum normalization proposed by
McCarthy and Wood (1985), whenever the shape of the scalp distribution was similar but the extension differed between groups. All effects with degrees of freedom $>1$ in the numerator were corrected using the Greenhouse–Geisser Epsilon ($\varepsilon$). The exact probability was recalculated with the STAT-SAK software package (Dallal, 1986).

Results
One patient had to be excluded from all analyses because of too many premature responses. One control subject was excluded because of too many movement artefacts in the EEG. Additionally, for the LRP analyses three subjects of each group were excluded because of excessive horizontal eye movements. Therefore LRP analyses included 11 patients and 11 control subjects, whereas all other analyses included 14 patients and 14 control subjects.

Response parameters
In patients, none of the response parameters differed systematically between the more affected and the less affected side. Therefore this distinction was omitted in further analyses.

The results of the ANOVAs on all response parameters are listed in Table 2, means and SDs in Table 3. The time course of force production in the central (‘12h’) condition is plotted in Fig. 6 (below), upper panel.

First, results of response times will be reported, as would be obtained with conventional all-or-none keys, when their thresholds were set to 1.5 N. Secondly, additional timing parameters are reported which were obtained from the time-course of force. Thirdly, effects on response force are reported.

Response times (see Fig. 4). These were smallest for the central (‘12h’) condition in both groups. The patients responded significantly later than the control group. This delay was uniform for all five S1–S2 intervals (i.e. there was no Group $\times$ Time interaction, see Table 2).

Additionally, patients’ intra-individual variability of response times was significantly larger than that of the control group (Tables 2 and 3). Further analysis of this variability, by ‘vincentizing’ each subject’s single response times in deciles (not detailed here, for brevity) showed that the patients came close to the control group with their faster responses but were disproportionally delayed for their slower responses.

The percentage of error trials did not differ significantly between time points. The patients tended to make more errors than the control group (e.g. at ‘12h’ 11.0% versus 8.5%) but this difference was not significant [$F(1,26) = 2.09$, $P = 0.16$]. The rather large percentage of error trials may reflect the fact that the task demanded constant vigilance for pressing the keys at the correct time.

Other timing parameters (see Tables 2 and 3). The later the imperative stimulus appeared, the earlier subjects started their response in relation to the onset of the imperative stimulus (effects of Time on start and on subthreshold thresholds were set to 1.5 N. Secondly, additional timing duration in Table 2). Negative start values (Table 3) indicate that subjects started their subthreshold response even before presentation of the imperative stimulus. Like response times, force peak latencies were fastest for the central (‘12h’) condition in both groups.
Table 2  Response analyses in the clock task: ANOVA results

<table>
<thead>
<tr>
<th></th>
<th>Group Time</th>
<th>Group × Time</th>
<th>(\epsilon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response time</td>
<td>11.88**</td>
<td>46.43***</td>
<td>1.13 0.36</td>
</tr>
<tr>
<td>Response variability</td>
<td>11.75**</td>
<td>17.48***</td>
<td>0.40 0.66</td>
</tr>
<tr>
<td>Response start</td>
<td>4.90</td>
<td>72.06***</td>
<td>0.53 0.46</td>
</tr>
<tr>
<td>Force peak latency</td>
<td>15.31***</td>
<td>43.92***</td>
<td>0.51 0.36</td>
</tr>
<tr>
<td>Subthreshold duration</td>
<td>1.92</td>
<td>58.49***</td>
<td>0.71 0.43</td>
</tr>
<tr>
<td>Force peak amplitude</td>
<td>12.80**</td>
<td>3.09*</td>
<td>4.49** 0.66</td>
</tr>
<tr>
<td>Rate of force production</td>
<td>25.74***</td>
<td>6.53***</td>
<td>3.39 0.66</td>
</tr>
</tbody>
</table>

Entries are F-values and their probabilities for falsely rejecting the null hypothesis. Degrees of freedom were 1,26 for effects of Group and 4,104 for effects of Time and of Group × Time. Probabilities for the latter two effects were determined after the conservative Greenhouse–Geisser correction. The correction coefficients (\(\epsilon\)) are listed on the outer right. Response variability is the intra-individual SD of response times across trials. For definition of all other response parameters, see Fig. 3. *P < 0.05; **P < 0.01; ***P < 0.001.

Table 3  Response analyses in the clock task

<table>
<thead>
<tr>
<th></th>
<th>‘9h’</th>
<th>‘10.30h’</th>
<th>‘12h’</th>
<th>‘1.30h’</th>
<th>‘3h’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response time (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>668 ± 217</td>
<td>534 ± 125</td>
<td>422 ± 72</td>
<td>463 ± 90</td>
<td>523 ± 80</td>
</tr>
<tr>
<td>Control group</td>
<td>524 ± 109</td>
<td>423 ± 67</td>
<td>337 ± 68</td>
<td>366 ± 55</td>
<td>385 ± 65</td>
</tr>
<tr>
<td>Response variability (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>171 ± 62</td>
<td>140 ± 64</td>
<td>133 ± 62</td>
<td>107 ± 43</td>
<td>110 ± 31</td>
</tr>
<tr>
<td>Control group</td>
<td>140 ± 70</td>
<td>94 ± 31</td>
<td>78 ± 27</td>
<td>64 ± 21</td>
<td>63 ± 22</td>
</tr>
<tr>
<td>Response start (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>404 ± 230</td>
<td>147 ± 248</td>
<td>31 ± 244</td>
<td>232 ± 284</td>
<td>495 ± 561</td>
</tr>
<tr>
<td>Control group</td>
<td>186 ± 261</td>
<td>131 ± 349</td>
<td>344 ± 415</td>
<td>553 ± 531</td>
<td>890 ± 747</td>
</tr>
<tr>
<td>Force peak latency (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>795 ± 223</td>
<td>670 ± 129</td>
<td>552 ± 92</td>
<td>598 ± 105</td>
<td>643 ± 82</td>
</tr>
<tr>
<td>Control group</td>
<td>634 ± 119</td>
<td>525 ± 87</td>
<td>432 ± 87</td>
<td>462 ± 75</td>
<td>479 ± 76</td>
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<tr>
<td>Subthreshold duration (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>264 ± 138</td>
<td>387 ± 237</td>
<td>453 ± 274</td>
<td>694 ± 310</td>
<td>1018 ± 568</td>
</tr>
<tr>
<td>Control group</td>
<td>338 ± 250</td>
<td>555 ± 352</td>
<td>682 ± 416</td>
<td>919 ± 518</td>
<td>1275 ± 734</td>
</tr>
<tr>
<td>Force peak amplitude (N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>4.8 ± 1.6</td>
<td>4.9 ± 1.8</td>
<td>4.7 ± 1.6</td>
<td>5.0 ± 1.9</td>
<td>4.6 ± 1.6</td>
</tr>
<tr>
<td>Control group</td>
<td>7.2 ± 1.8</td>
<td>6.8 ± 1.6</td>
<td>6.2 ± 1.3</td>
<td>6.7 ± 1.6</td>
<td>7.7 ± 2.0</td>
</tr>
<tr>
<td>Rate of force production (cN/ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>3.9 ± 1.0</td>
<td>3.8 ± 1.1</td>
<td>3.7 ± 1.0</td>
<td>3.9 ± 1.4</td>
<td>4.0 ± 1.3</td>
</tr>
<tr>
<td>Control group</td>
<td>7.1 ± 2.4</td>
<td>7.1 ± 2.4</td>
<td>6.9 ± 2.1</td>
<td>7.5 ± 2.6</td>
<td>8.6 ± 3.3</td>
</tr>
</tbody>
</table>

Means ± SDs for the five positions of imperative stimuli, separately for patients and control group. Response variability is the intra-individual SD of response times across trials. For definition of all other response parameters, see Fig. 3.

Like response times, response start and force peak latency were significantly delayed in the patients, i.e. they started their keypress later, reached the criterion later and reached their force peak later. Subthreshold duration, i.e. the time between start and criterion, was not prolonged in the patients.

Response force. The control subjects’ peak force varied significantly as a function of time, with least force exerted for ‘12h’ responses. In contrast, the patients’ peak force always remained the same (see Tables 2 and 3 and Fig. 4). Across all five time points, patients had smaller rate of force production than the control group (see Tables 2 and 3 and Figs 4 and 6).

Also the rate of force production varied significantly as a function of time in the control group, with more rapid force changes occurring for responses after ‘12h’. In contrast, the patients’ rate of force production always remained the same (see Tables 2 and 3 and Fig. 4). Across all five time points, patients had smaller rate of force production than the control group (see Tables 2 and 3 and Figs 4 and 6).

To summarize, global differences between groups were found for all response parameters, both for timing and for force. In addition, specific differences in the effect of presentation time were found on peak force and on rate of force production, i.e. on the activation parameters only, not on the timing parameters.

Event-related potentials
The grand means of the ‘12h’ trials are displayed in Fig. 5. On the average, 191 trials were included in the average of each subject, with a minimum number of 60 trials. [More
Fig. 4 Clock task. Response times, force peak amplitude and rate of force production for the five time points in the two groups. While response times were just prolonged in patients, force peak amplitude and rate of force production showed hardly any variation over time in patients. In contrast, in healthy control subjects force peak amplitude showed a pattern similar to response times, and rate of force production increased after '12h'.

Fig. 5 Clock task. ERPs from 100 ms before the cue (S1) to 1500 ms after the imperative stimulus (S2), for imperative stimuli at '12h' only. Negativity is plotted upwards. Only components prior to the imperative stimulus were analysed. The most significant alteration of the patients' ERP was a reduction of the CNV at Cz.

trials tended to be included in the control group than in the patients, 208 versus 173, $F(1,26) = 3.48, P < 0.08$. The presentation of the cue stimulus evoked an occipital N180/ anterior P200, a centrally focused N2 and a parietally focused P3 (see Fig. 5). These components were followed by the CNV, which rose until the imperative signal. Only effects involving the Group factor are considered in the following description, omitting main effects of Topography.

The P200 latency was delayed in the patients [$F(1,26) = 4.96, P < 0.05$], in particular at Pz [Group × Topography: $F(2,52) = 4.65, \varepsilon = 0.67, P < 0.05$]. The N2 amplitude was largest at Fz in the patients, and at Cz in the control group [Group × Topography: $F(2,52) = 4.32, \varepsilon = 0.78, P < 0.05$]. Inspection of Fig. 5 suggests that the patients' P200 delay might be a consequence of their lack of a distinct centroparietal N2; in the control group, the N2 limits their
The loss of response dynamics in Parkinson’s disease is clearly visible in the upper traces. For the LRP, increases in activation of the central scalp site contralateral to the movement relative to Experiment 2 was conducted in a separate session for the same subjects, taking place within 1 week of S1 either before or after it (balanced within each group). The LRP did not differ significantly between the two groups.

Experiment 2: the validity task

Methods

Subjects

Experiment 2 was conducted in a separate session for the same subjects, taking place within 1 week of Experiment 1, either before or after it (balanced within each group).

Stimuli and procedure

In contrast to Experiment 1 the interval between the cue (S1) and the imperative stimulus (S2) was held constant at 1 s, and the validity of the cued information was no longer 100%. In two separate blocks, the S1 information was valid for 80% of the trials (80/20 condition) or for 50% of the trials (50/50 condition). In the latter case, S1 had no objective informational value.

At the beginning of each trial the blue letters F or H (visual angle 1.5°) were presented for 200 ms in the middle of the screen. One second after the onset of the blue letter a second, yellow letter, identical in size and font to the first letter was presented for 200 ms which was either the same letter as the blue one (= valid trials) or the other one (= invalid trials). Subjects were instructed to respond as fast as possible to a yellow H with the left hand and to a yellow F with the right hand. Subjects were informed about the probability of valid trials and were encouraged to take this probability into account for their response preparation during the S1–S2 interval. The S1 of the next trial was presented 3 s after the onset of the S2.

Each condition consisted of 200 trials, with a short break after 100 trials. The order of conditions was balanced across subjects within each group. The experimental environment was the same as in Experiment 1.

Recording and data processing

These methods were identical to Experiment 1.
Data analysis

Performance. The parameters measured were the same as in Experiment 1. Each of the performance parameters was tested with a two (valid versus invalid) by two (80/20 versus 50/50) by two (patients versus control subjects) ANOVA with repeated measures.

EEG parameters. N180, P200, N2, P3 and CNV were defined as in Experiment 1 and were tested with a two (80/20 versus 50/50) by two (patients versus control group) ANOVA with repeated measures. The distinction between valid and invalid trials was not made, except for the LRP measured after S2, since information about the validity of a trial was not available before S2. As in Experiment 1, LRPs were measured between S1 and S2, and after S2 around the maximum of the response.

For the interval between S1 and S2, the LRP was defined as contralateral minus ipsilateral relative to the cued side. The LRP time windows differed from Experiment 1, due to the shorter S1–S2 interval and due to more noise in these data. The baseline was defined as the 300-ms epoch from 100 ms before S1 to 200 ms after S1. This was necessary due to fluctuations in the patients’ data that occurred briefly after S1 and would have raised their LRPs in a negative direction if the baseline had been defined only before S1. The baseline actually used gives a more conservative estimate of the size of the LRP; see Fig. 9.) LRPs were measured as mean amplitudes (referred to baseline) in eight consecutive 100-ms windows, from 200–300 ms after S1 to 900–1000 ms after S1. These amplitudes were tested against zero (i.e. whether there was a significant LRP at all) by t tests, separately for the two conditions and separately in the two groups. Further, these amplitudes were compared between conditions and groups using the two by two ANOVA, like the other ERP components.

The LRPs after S2, around the maximum of the response, were defined separately for valid and invalid trials as contralateral minus ipsilateral to the actual correct response, not to the cued side. Mean amplitudes were measured in a time window 300–500 ms after S2 (cf. Fig. 9, right-hand side), were referred to the mean amplitude of the 100 ms before S2 as their baseline, and were analysed with a two (validly versus invalidly cued) by two (80/20 versus 50/50) by two (patients versus control group) ANOVA with repeated measures.

Results

One control subject was excluded because of failure to follow the instructions. Three subjects (one control subject and two patients) were excluded because they had not enough artefact-free trials with correct responses in all conditions. Therefore all analyses were done for 13 patients and 13 control subjects.

Response parameters

The results of the ANOVAs on all response parameters are listed in Table 4, and means and SDs are listed in Table 5. Response times, force peak amplitude and rate of force production are plotted in Fig. 7.

Response times. Response times were smaller in valid than in invalid trials, and this effect was larger in the 80/20 condition than in the 50/50 condition (see Table 5 and Table 4, Condition × Validity, and Fig. 7). The patients responded generally later than the control group. In addition, validity had a larger effect on their response times than it did in the control group (effects of Group and of Group × Validity in Table 4; see also Table 5 and Fig. 7).

As in Experiment 1, the patients’ intra-individual variability of response times was larger than that in the control group (Tables 4 and 5).

Errors. Errors were made in 3.6% of the valid trials and 8.2% of invalid trials [Validity: F(1,24) = 16.37, P < 0.001]. The errors did not differ significantly for valid trials between the 50/50 and the 80/20 condition but did differ for invalid trials [5.7% versus 10.7%; Condition × Validity: F(1,24) = 5.30, P < 0.05]. The patients did not make significantly more errors than the control group.

Other timing parameters. Like response times, both response start and force peak latency were earlier in valid than in invalid trials, with larger effects in the 80/20 than in the 50/50 condition (Tables 4 and 5). The time between start and criterion (subthreshold duration) was not significantly affected by condition and validity.

While force peak latency was affected by the same Group effects as response time, the response start was not delayed in the patients (Tables 4 and 5). Since their response times were delayed (cf. above), their subthreshold duration (i.e. response time minus response start) was significantly larger than in the control group, by >100 ms. Further, subthreshold duration tended to be shortened in the control group with invalidly cued stimuli, in particular in the 80% valid condition [F = 4.04, P < 0.06; cf. Tables 4 and 5]. Possibly with these 20% invalidly cued stimuli, the control group attempted to compensate for their lack of preparation by faster increase of subthreshold force. In contrast, the subthreshold duration did not change between validly and invalidly cued stimuli in the patients.

Response force. Response force was larger in invalid trials, in particular in the 80/20 condition (Tables 4 and 5 and Fig. 7). These effects were the same in the patients, and also the apparently clear overall difference in force between groups (Fig. 7) was not significant (Tables 4 and 5).

Rate of force production was reduced for invalid trials in the 50/50 condition and enhanced for invalid trials in the 80/20 condition (Condition × Validity in Table 4; see also
Table 4 Response analyses in the validity task (ANOVA results)

<table>
<thead>
<tr>
<th></th>
<th>G</th>
<th>C</th>
<th>G × C</th>
<th>V</th>
<th>G × V</th>
<th>C × V</th>
<th>G × C × V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response time</td>
<td>8.81**</td>
<td>0.17</td>
<td>0.19</td>
<td>56.17***</td>
<td>8.21**</td>
<td>21.80***</td>
<td>1.77</td>
</tr>
<tr>
<td>Response variability</td>
<td>8.28**</td>
<td>1.50</td>
<td>0.25</td>
<td>55.55</td>
<td>0.02</td>
<td>0.45</td>
<td>0.97</td>
</tr>
<tr>
<td>Response start</td>
<td>0.18</td>
<td>0.16</td>
<td>0.13</td>
<td>33.40***</td>
<td>3.10</td>
<td>11.00**</td>
<td>0.34</td>
</tr>
<tr>
<td>Force peak latency</td>
<td>13.86***</td>
<td>1.30</td>
<td>0.92</td>
<td>63.60***</td>
<td>8.39**</td>
<td>17.89***</td>
<td>1.71</td>
</tr>
<tr>
<td>Subthreshold duration</td>
<td>19.31***</td>
<td>1.39</td>
<td>1.33</td>
<td>3.50</td>
<td>0.02</td>
<td>0.40</td>
<td>4.04</td>
</tr>
<tr>
<td>Force peak amplitude</td>
<td>2.13</td>
<td>1.84</td>
<td>0.34</td>
<td>20.32***</td>
<td>0.36</td>
<td>5.53*</td>
<td>0.02</td>
</tr>
<tr>
<td>Rate of force production</td>
<td>11.87**</td>
<td>0.42</td>
<td>0.43</td>
<td>0.27</td>
<td>0.04</td>
<td>7.93**</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Entries are $F$-values and their probabilities for falsely rejecting the null hypothesis. Degrees of freedom were 1,24 for all effects. 

G = Group; C = Condition (50/50 versus 80/20); V = Validity. Response variability is the intra-individual SD of response times across trials. For definition of all other response parameters, see Fig. 3. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 5 Response analyses in the validity task

<table>
<thead>
<tr>
<th></th>
<th>50:50 Valid</th>
<th>50:50 Invalid</th>
<th>80:20 Valid</th>
<th>80:20 Invalid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response time (ms)</td>
<td>511 ± 96</td>
<td>569 ± 125</td>
<td>471 ± 94</td>
<td>589 ± 109</td>
</tr>
<tr>
<td>Control group</td>
<td>428 ± 70</td>
<td>451 ± 60</td>
<td>412 ± 85</td>
<td>468 ± 72</td>
</tr>
<tr>
<td>Response variability</td>
<td>142 ± 54</td>
<td>155 ± 54</td>
<td>155 ± 59</td>
<td>152 ± 73</td>
</tr>
<tr>
<td>Control group</td>
<td>95 ± 25</td>
<td>97 ± 25</td>
<td>106 ± 30</td>
<td>111 ± 58</td>
</tr>
<tr>
<td>Response start (ms)</td>
<td>290 ± 142</td>
<td>368 ± 139</td>
<td>281 ± 134</td>
<td>403 ± 137</td>
</tr>
<tr>
<td>Control group</td>
<td>341 ± 91</td>
<td>363 ± 77</td>
<td>310 ± 121</td>
<td>395 ± 66</td>
</tr>
<tr>
<td>Force peak latency</td>
<td>683 ± 143</td>
<td>751 ± 156</td>
<td>632 ± 131</td>
<td>760 ± 158</td>
</tr>
<tr>
<td>Control group</td>
<td>530 ± 79</td>
<td>560 ± 75</td>
<td>513 ± 74</td>
<td>574 ± 76</td>
</tr>
<tr>
<td>Subthreshold duration</td>
<td>221 ± 121</td>
<td>201 ± 83</td>
<td>190 ± 80</td>
<td>186 ± 79</td>
</tr>
<tr>
<td>Control group</td>
<td>87 ± 43</td>
<td>88 ± 52</td>
<td>101 ± 57</td>
<td>73 ± 33</td>
</tr>
<tr>
<td>Force peak amplitude</td>
<td>6.2 ± 3.4</td>
<td>6.3 ± 3.5</td>
<td>5.6 ± 2.7</td>
<td>6.2 ± 3.2</td>
</tr>
<tr>
<td>Control group</td>
<td>10.3 ± 10.1</td>
<td>10.6 ± 10.2</td>
<td>9.3 ± 8.8</td>
<td>9.9 ± 8.4</td>
</tr>
<tr>
<td>Rate of force production (cN/ms)</td>
<td>4.1 ± 2.0</td>
<td>4.0 ± 1.8</td>
<td>3.9 ± 1.6</td>
<td>4.1 ± 1.9</td>
</tr>
<tr>
<td>Control group</td>
<td>8.8 ± 5.2</td>
<td>8.6 ± 4.9</td>
<td>8.1 ± 4.0</td>
<td>8.4 ± 3.6</td>
</tr>
</tbody>
</table>

Means and SDs for the validly and invalidly cued stimuli in the two conditions of the validity task, separately for patients and control group. Response variability is the intra-individual SD of response times across trials. For definition of all other response parameters, see Fig. 3.

Table 5 and Fig. 7). While these effects did not differ significantly in the patients, the rate of force production was reduced overall in the patients (Tables 4 and 5 and Fig. 7).

Thus, global differences between groups were found for most parameters of the response, both for timing and for force parameters. In addition, specific group differences in the effect of validity were found on response time (and peak latency), but not on peak force or on rate of force production, i.e. on the timing parameters only, not on the activation parameters.

**Event-related potentials**

Since there was neither an effect of condition nor an effect of validity for the ERPs before S2, the average activity of all trials is plotted in Fig. 8. On average, 324 trials were included in the average for each subject, with a minimum number of 192 trials. [Number of included trials did not differ significantly between control group and patients, 325 versus 323, $F(1,24) = 0.01$, n.s.]

The P200 latency was delayed in the patients [$F(1,24) = 8.68, P < 0.01$] without topographic differentiation. No differences between patients and control group were found for P200 amplitude or for latencies and amplitudes of N180, N2 and P3. As in the clock task, Fig. 8 suggests that the P200 delay might be related to the somewhat less distinct ensuing N2, but this argument cannot be made with certainty.

The amplitude of the CNV was reduced in the patients, both in the sagittal axis [$F(1,24) = 24.89, P < 0.001$] and in the horizontal axis [$F(1,24) = 21.20, P < 0.001$]. No interaction of Group × Topography was found after vector-sum normalization, either for the sagittal axis [$F(3,72) = 0.64, n.s.$]
Fig. 7 Validity task. Response times, force peak amplitude and rate of force production for all conditions in healthy control subjects and Parkinson’s disease patients. The effect of validity is enlarged in the patients. Force peak amplitude and rate of force production are reduced for patients.

Fig. 8 Validity task. ERPs from 100 ms before the cue (S1) to 900 ms after the imperative stimulus (S2). Negativity is plotted upwards. Only components prior to the imperative stimulus were analysed. In contrast to the first experiment, the CNV was reduced at all recording sites.

or for the horizontal axis \([F(3,72) = 0.30, \text{n.s.}]\). Thus, in contrast to Experiment 1, the reduction of the patients’ CNV was not restricted to Cz. Rather, a global reduction of negativity was found over the entire cortex.

LRPs between S1 and S2 are plotted on the left side of Fig. 9. On the average, 169 trials were included in each subject’s average in the 50% condition, and 166 trials in the 80% condition, with a minimum number of 106 and 104 trials, respectively [number of included trials did not differ significantly between control group and patients, \(F(1,24) = 0.00, \text{n.s. for both conditions}\)]. The LRP s differed significantly from baseline in several 100-ms windows in the control group as well as in the patients, both in the 80% condition and in the 50% condition, indicating that response selection indeed occurred according to the cue. The significant windows are marked in Fig. 9. While there were more significant windows in the 80% than in the 50% condition, suggesting that motor preparation was more marked when the cue had a higher validity, the Condition effect did not reach significance in any 100 ms window, i.e. in no 100-ms window was the LRP reliably larger in the 80% than in the 50% condition. Further, Fig. 9 suggests that LRP s were larger from 300–500 ms in the control group (in the 80% condition) and from 600–800 ms in the patients (in the 50% and 80%
Cognition and activation in Parkinson’s disease could be attributed to problems either of cognition or of activation. The rationale behind this approach was as follows. Peak value of response force, rate of force production, as well as the amplitude of the CNV are indicators of activation. Therefore, effects on response time that are paralleled by effects on those measures are probably mediated by activation and, in contrast, effects on response time unparalleled by effects on those measures are probably due to differences in cognitive processes. An additional clue to cognitive differences in the domain of response selection would be given by effects on the LRP. Thus, answers were sought to the following questions. (i) What effects are found in force amplitude, rate of force production and CNV amplitude, and are these effects in parallel to the effects on response times? (ii) What effects are found for the LRP, and are these effects in parallel to the effects on response times? (iii) Is additional insight provided by the additional measures of response timing? The results to be discussed in the following sections are schematically displayed in Table 6.

The patients’ response times were generally delayed in both tasks, and further specifically delayed with invalidly cued stimuli in the validity task. Also, in both tasks, the patients’ response times varied more across trials than those of the control group (replicating findings of V. J. Brown et al., 1993). The patients came close to the control group with their fastest responses, but were overly delayed with their slower responses.

Effects of Parkinson’s disease on activation measures

Peak amplitude of response force
The patients’ response forces were generally smaller in the clock task compared with those of the control group. The reduction was not significant in the validity task, presumably due to the large inter-individual differences in the control group (Table 5). In addition, the patients’ forces did not vary with presentation time in the clock task, in contrast to the control group.

Rate of force production
The patients’ rate of force production was generally smaller than that of control subjects (in agreement with earlier findings, e.g. Stelmach et al., 1989; Godaux et al., 1992). In addition, the patients’ rate of force production did not vary with presentation time in the clock task, in contrast to the control group.

CNV amplitude
The main finding was the reduction of the CNV in the patients compared with that of control subjects. It occurred in both tasks but was more widely distributed topographically.

Discussion
We investigated response times of patients with Parkinson’s disease in two tasks in which responses had to be made to precued imperative signals. By measuring the time course of response force and of ERPs the delays of patients’ responses conditions, but there was no effect of Group in any of the 100-ms windows, except for a tendency from 700–800 ms for larger LRPs in the patients [F(1,24) = 3.94, P < 0.06].

After S2, distinct LRPs were observed around the time of responding (right side of Fig. 9). On average, 86 and 83 trials were included in the each subject’s validly and invalidly cued average of the 50% condition, and 135 and 31 trials in the 80% condition, with minimum numbers of 53, 52, 80 and 18 trials, respectively [number of included trials did not differ significantly between the control group and patients in any of the four conditions, F(1,24) ≈ 0.06, n.s.].

These LRPs were larger after invalidly than after validly cued S2s [F(1,24) = 12.56, P < 0.01], because their amplitudes were referred to the pre-S2 level, which was in the same direction as the post-S2 LRP with validly cued stimuli but in the opposite direction with invalidly cued stimuli. There were no effects of Condition or of Group on the amplitude of the post-S2 LRP. In particular, although Fig. 9 suggests that LRPs were larger in the control group than in the patients, the effect of Group was not significant [F(1,24) = 1.92, P = 0.18].

To summarize, the most prominent difference of the ERPs between the two groups was the smaller CNV amplitude in the patients.
Effects of experimental factors on CNV and LRP were not tested in the clock task, because only the ‘12h’ condition was analysed. Effects of validity were not testable on CNV in the validity task, because validity was not revealed before the signal, i.e. after the time point where CNV was measured. CNV = contingent negative variation; LRP = lateralized readiness potential.

in the validity task than in the clock task. CNV reductions were also found in most previous studies (Linden et al., 1990; Wright et al., 1993; Praamstra et al., 1996; Pulvermüller et al., 1996; but no reduction in Oishi et al., 1995), though with different topographical extent (central, frontal and parietal: Wright et al., 1993; central and parietal, but not frontal: Pulvermüller et al., 1996; only central: Praamstra et al., 1996). Previous studies also reported that the amount of CNV reduction depended on the task; larger differences between patients and control subjects were found by Praamstra et al. (1996) after uninformative cues (four-choice response after S2) than after informative cues (limiting the response alternatives to two), and by Linden et al. (1990) after fully informative cues (one response alternative) than after uninformative cues (two response alternatives). This variability of CNV reduction with topography and task, both between and within studies, is hard to subsume under a general rule. It might be related to the fact that the CNV is a varying mixture of activation of response preparation, stimulus expectation and effort (van Boxtel, 1994; cf. the Introduction), so each of these processes might be differentially affected in Parkinson’s disease, depending on the task and on the patients’ status. The differences in details notwithstanding, the CNV reduction appears to be a general phenomenon in Parkinson’s disease and can be globally interpreted as reflecting the patients’ reduced activation.

**Comparison of activation and response time**

Taken together, all three indicators of activation were generally reduced in the patients, both in the clock task and in the validity task (although there is a lack of significance for the effect on peak force in the latter task). According to the rationale of our approach, this means that the patients’ general increase in response times was, at least partially, due to this general reduction of activation. Yet, besides this parallel there were also task-specific dissociations between the indicators of activation and response times. (i) In the clock task, effects of presentation time differed between groups for the indicators of activation but not for response times. Evidently, in this task some activation factor is relevant which is not reflected by response times. (ii) In the validity task, effects of invalid cueing differed between groups for response times, but not for the indicators of activation. Evidently, in this task some factor is relevant which is not related to activation. According to the rationale of our approach, this suggests some cognitive impairment of responding. This assumption would be in accordance to the prediction derived from Owen et al. (1993), which assumed that the patients would have difficulties with invalidly cued stimuli due to an impairment in shifting from the originally intended response to the alternative response.

**Effects of Parkinson’s disease on cognitive measures**

**The LRP amplitude**

The LRP amplitude, indicating the degree of differential activation of the contralateral motor cortex, did not differ significantly between groups. In particular, the patients’ LRPs were as large as those of the control group, not only in the clock task but also in all conditions in the validity task. This result is in agreement with the only other published evidence on the LRP in Parkinson’s disease, that of Praamstra et al. (1996). Our results and those of Praamstra et al. (1996) on the LRP add new evidence to the view expressed by several authors that response selection is not compromised in Parkinson’s disease (Stelmach et al., 1986; R. G. Brown et al., 1993; V. J. Brown et al., 1993), at least not in two-choice tasks (R. G. Brown et al., 1993; Cooper et al., 1994). In particular, the LRPs did not provide support for the notion that an S1–S2 interval of 1 s might be too short for the patients to select their response according to the cue. Nor did the LRPs provide support for the assumed cognitive problem in shifting from a prepared response; LRPs did not
continue to develop to prepare the cued response instead of the actually required response in case of invalidly cued responses (i.e. the patients’ LRPd did not decrease below baseline after the S2 in Fig. 9). Such a rigidity of preparation reflected by LRPd would have fitted the notion of difficulties in cancelling a selected response. This was not the case; the LRPd after S2 in all conditions in both groups reflected preparation of the required response only.

**Additional ERP measures**

In the visual potentials evoked by the cue, the P200 peak was delayed in the patients. This difference was consistent in both tasks and replicates the result reported by Wright et al. (1993). Authors of other previous ERP studies on Parkinson’s disease with visual stimuli did not report results on this component (Linden et al., 1990; Tachibana et al., 1992; Praamstra et al., 1996; Pulvermüller et al., 1996). Neither in the present data nor those of Wright et al. (1993) were these latency delays accompanied by delays of ensuing components, contrary to the delay of P200 latency in healthy elderly compared with young adults (e.g. see Kenemans et al., 1995). This observation lends plausibility to the suggestion made in the Results section. It appears (particularly in the clock task) as if the patients’ delayed P200 latency is a consequence of their lack of a distinct centroparietal N2. In the control group, the N2 limits their preceding P200 to form a sharp peak, whereas this is not the case in the patients (cf. also Fig. 2 of Wright et al., 1993). Therefore, the meaning of the P200 delay remains ambiguous in terms of the distinction between cognitive and activation impairment; if it was a true latency delay it might reflect a cognitive deficit, whereas if it is due to the less distinct centroparietal N2 it would reflect an deficit of activation.

Returning to the meaning of the LRP results, our approach has to deal with the problem that the patients’ delay of responses to invalidly cued stimuli is neither in parallel to an effect on the indicators of activation (response force, CNV), nor to an effect on LRP amplitudes which were meant to indicate the cognitive process of response selection. A possible solution to this problem will be discussed after the next paragraph.

**Effects on other measures of response timing**

Considering the behaviour under the 0.5 N criterion (‘response start’) instead of the 1.5 N criterion (‘response time’) is here of particular interest, because response start yielded a pattern of results in the validity task different from response time (whereas in the clock task response start was affected by presentation time and group similarly to response time): neither was response start generally later in the patients than in the control group in this task (Unlike response time), nor was the extra delay induced by invalidly cued stimuli on the patients’ response start large enough to differ significantly between patients and control group (Unlike the effect on response time). Note that this difference between response start and response time was not due to enlarged variability of the response-start measure; while variance between subjects was indeed somewhat larger for response start than for response time, there was not even a tendency for the mean values of response start to be later in the patients (Table 5). Consequently, the difference between response time and response start (‘subthreshold duration’) was significantly larger in the patients; this would not have been the case if the response-start results were simply more variable than the response-time results.

This finding of task differences in the delay of the patients’ response start is similar to the report of Sheridan et al. (1987) on ‘pre-motor response time’ (the time from stimulus onset to EMG activity onset). Pre-motor response time was delayed in Parkinson’s disease in a ‘simple-response’ task in which the response was already defined by S1, as in the present clock task, but was normal in a ‘choice-response’ task in which the response was not defined before S2, as in the present validity task. In contrast to pre-motor response time, the patients’ overt movements were delayed in both tasks of Sheridan et al. (1987), i.e. the relationship between pre-motor response time and response time was the same as the present relationship between response start and response time.

Which factors may be responsible for the different behaviour of response start (0.5 N criterion) and response time (1.5 N criterion) in the validity task? (i) Validly cued stimuli. The patients’ response start was not delayed, but the time to exceeding the response-time criterion was. We suggest that this is due to the deficit of activation; in the case of the response being already selected, activation is lacking for completing the movement needed for responding. (ii) Invalidly cued stimuli. With these stimuli, the patients’ response time was additionally delayed. This may be due to the summation of two factors whose single effects were not, or only marginally, statistically significant. First, the patients’ response start was already slightly delayed. This might reflect the cognitive impairment of switching. As noted, this delay was, however, not significant by itself, nor was this impairment manifested by the patients’ overly preparing the cued invalid response, as would be visible in the LRP. The second effect was an acceleration of ‘subthreshold duration’ in the control group, at least in the 80% condition; this time between response start and response time was reduced in the control group with invalidly cued stimuli (cf. Table 5). Obviously, the control subjects compensated for their lack of preparation to the non-cued stimulus with faster increases of their force. The patients did not do this; such a difference might be interpreted as an additional deficit of activation. Also, this effect fell short of significance ($P < 0.06$). However, the sum of these two non-significant effects yielded the significant additional delay of the patients’ response time. Thus, according to this interpretation, the delay seen with invalidly cued stimuli consisted of a cognitive portion and an activation portion.
Conclusions

The general delay of the patients’ response times was accompanied in both tasks by reductions of response force, of rate of force production and of CNV amplitude before S2. The patients’ specific delay with invalidly cued stimuli was likewise related to activation differences; with these stimuli, the control group reduced the ‘subthreshold duration’ from response start to the overt response, probably in order to compensate for the lack of preparation. The patients did not do so. In the clock task, presentation time affected the control subjects’ forces; peak and rate of force production varied with the probabilities of the presentation times. This was not the case in the patients.

In summary, these data provide evidence for the notion that activation differs considerably between patients with Parkinson’s disease and healthy subjects, and further that the differences in response times are related to these differences in activation. Patients with Parkinson’s disease have the known deficit in initiating behaviour without external cues (e.g. Cunnington et al., 1995). The present data suggest that this deficit also plays an important role in response-time tasks. Although designed to measure cognitive problems above all, these tasks present the patients with the problem of getting enough activation to respond.

In the clock task, differences occurred in indicators of activation beyond the differences in response times. This might be due to the structure of this task; the imperative signal was a simple ‘Go’ signal, and the outer ring turned yellow, in the same way for left and right responses. All information necessary for response selection had already been provided by the cue and then had to be upheld for some time (1.2–3.6 s) until this ‘Go’ signal. In contrast, in the validity task, the imperative signal was informative, differing for right and left responses, and was not redundant; it either confirmed or contradicted the cue. Thus, in the clock task the imperative signal did not provide new specific activation for the response.

Thus, these measurements suggest that patients with Parkinson’s disease face a dilemma in cued response tasks. On the one hand, task requirements should not be too complex, because then some cognitive problem may become evident, as possibly in the present data with invalidly cued stimuli. On the other hand, tasks must not be too monotonous; they have to provide sufficient external stimulation in order to activate responses. Speculatively, this dilemma might have contributed to the conflict between the various studies on response times in Parkinson’s disease, where sometimes particular disadvantages were found in the more complex choice-response tasks, sometimes in the more monotonous simple-response tasks. More generally, the results here suggest that both the cognitive factor and the activation factor are relevant to the impairment of responses in Parkinson’s disease.

A possible mechanism for the impairments of both motor and cognitive functions may be a disturbance of gate control at the thalamic level. The degenerative changes of the dopaminergic system originating in the substantia nigra (Marsden, 1982, 1994) and the reduction of dopaminergic supply of putamen and caudate nucleus lead to changed output to cortical areas via thalamic nuclei (Alexander et al., 1986; Cote and Crutcher, 1991). The role of the thalamus as a relay station has recently been emphasized. Extending the model of Skinner and Yingling (1977) who had proposed that thalamic nuclei serve as gates for sensory afferences on their way to the cortex, Brunia (1993) proposed that thalamic nuclei also serve as gates for motor afferences, with these gates being influenced by the reticular nucleus, the frontal cortex, the cerebellum and the basal ganglia. Applying this model to the disorders of activation and cognition in Parkinson’s disease, one may assume that the reduced input from the basal ganglia might impair the opening of thalamic gates, both for new and unfamiliar sensory afferences and for planned motor afferences. The impairment of afferences might contribute to the cognitive problem, while the impairment of efferences might be considered as a problem of providing activation for an intended movement.

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