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Movement-related potential measures of different modes of movement selection in Parkinson's disease

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Abstract

Movement-related potentials were recorded preceding self-paced voluntary movements in patients with Parkinson's disease and in healthy subjects of the same age group. We compared the Readiness Potential preceding joystick movements in a fixed direction and preceding joystick movements in freely selected directions. In normal subjects the Readiness Potential amplitude was higher preceding freely selected movements than preceding movements in a fixed direction. The Readiness Potential in Parkinson patients failed to be modified by the different modes of movement selection. The modulation of the Readiness Potential by different ways of preparing for movement might be due to the supplementary motor area (SMA) being more strongly engaged by tasks requiring internal control of movements than by tasks that are externally structured. The results suggest that this task-dependent variation of SMA activity is reduced in Parkinson's disease. A failing capacity to adapt SMA activity to different task demands has previously been suggested by evidence from positron emission tomography studies using similar tasks.

Keywords: Parkinson's disease; Movement-related potentials; Readiness potential; Movement preparation; Supplementary motor area; Motor cortex

1. Introduction

In Parkinson's disease (PD), slowness of movement and difficulty initiating movements do not affect all kinds of movements to the same extent. A number of studies have suggested that patients perform movements that are guided by external cues more easily than self-initiated movements (Flowers, 1976; Cools et al., 1984; Robertson and Flowers, 1990; Georgiou et al., 1993). These observations are consistent with theories of the cortical organization of movement that distinguish between externally cued and internally generated movements (Wise, 1984; Goldberg, 1985; Passingham, 1987, 1993). It has been proposed that these different types of movements are supported by different premotor areas, namely, the medial premotor cortex or supplementary motor area (SMA) subserving internally generated movements and the lateral premotor cortex subserving externally cued movements. Since the SMA participates in striato-thalamo-cortical circuitry, a specific im-

pairment of internally generated movements in PD might be mediated by deficient function of the SMA.

Recent evidence from regional cerebral blood flow (rCBF) measurements using positron emission tomography (PET), supports the hypothesis that the SMA has a role in akinesia in PD (Deiber et al., 1991; Jenkins et al., 1992; Playford et al., 1992). Deiber and co-workers investigated cortical activation patterns while subjects performed different tasks involving joystick movements. One task consisted of repetitive movements of the joystick, each time in the same direction. In another task subjects had to perform joystick movements in freely selected directions. The latter task activated premotor areas (including the SMA) more than the former. PD patients were assessed using the same tasks (Playford et al., 1992; Passingham, 1993). Whereas in the repetitive task the SMA was activated relatively normally in patients, the free selection task revealed more clearly an impaired activation of the SMA compared to normals.

We have recently investigated whether the different modes of movement selection that in rCBF studies appear to influence SMA activity, also modulate movement-related potentials recorded from healthy subjects (Praamstra

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et al., 1995a). Using a paradigm very similar to that of Playford et al., we found that freely selected movements yielded a Readiness Potential of higher amplitude than the Readiness Potential preceding repetitive movements in a designated direction. Moreover, significant differences emerged already 800 ms prior to actual movement, showing that seemingly identical movements can be electrophysiologically differentiated according to the way they are prepared. Since rCBF measures have good spatial resolution but cannot provide sufficient insight in the time course of motor preparation, the registration of movement-related potentials complements these measures in a valuable way.

In the present paper, the modulation of the Readiness Potential by different modes of movement selection was used as a tool for the study of movement preparation in PD patients. It was hypothesized that the “selection effect” which differentiates the Readiness Potential preceding movements in freely selected directions from the Readiness Potential preceding movements in a fixed direction, is absent or reduced in PD patients. A study with the same goal and a comparable method appears to be performed simultaneously with ours, and was published recently (Touge et al., 1995). In conjunction with our earlier study (Praamstra et al., 1995a), this now allows a more thorough evaluation of the reported effects, both in healthy subjects of different age groups and in patients with PD.

2. Materials and methods

2.1. Tasks

PD patients and healthy elderly subjects were investigated using two different types of movements:

1. *Movements in a fixed direction*: subjects made repetitive movements by rotating a joystick each time in the same direction.
2. *Movements in freely selected directions*: subjects made joystick movements in any desired direction, without repeating the same direction for more than two successive trials.

In both conditions the movements were performed in a self-paced way at a rate of approximately once every 5–10 s. There were four experimental blocks of 6-min duration each, in both conditions. In condition 2 these four blocks were identical. In condition 1 the four blocks differed with respect to the direction subjects were assigned to move the joystick. That is, in one block subjects made movements to the left, in the next block to the right, in the third block forward, and in the last block backward. Thus, the comparison between the two different modes of movement selection is not confounded by intrinsic differences between movements in different directions. Subjects were alternately presented with a block in which they made freely selected movements and a block in which they made

movements in a designated direction. The order of testing the eight blocks was rotated.

2.2. Subjects

Thirteen patients with a clinical diagnosis of idiopathic PD were studied (10 men, 3 women; age range 50 to 73 years; mean 61.4 ± 7.7). They fulfilled the criteria of the UK Parkinson's Disease Society Brain Bank (Hughes et al., 1992) for the diagnosis of PD and all were L-dopa responsive. All were treated with L-dopa (plus decarboxylase inhibitor), and some also with deprenyl and/or a dopamine receptor agonist. The mean disease duration was 8 ± 3 years (range 4 to 14 years). All but two patients were studied at least 10 h after their last dose. The remaining two patients had their last dose 4 h earlier. Motor disability was evaluated by means of the motor subscale of the United Parkinson's Disease Rating Scale (UPDRS) (Lang and Fahn, 1989), and ranged between 15 and 50 (mean 31 ± 10) at the time of the investigation. Three patients were rated grade II, nine grade III, and one patient grade IV on the Hoehn and Yahr scale (Hoehn and Yahr, 1967).

Thirteen healthy control subjects (5 men, 8 women; age range 47 to 71 years; mean 59.8 ± 7.0) were also studied. None of them had a neurological disease. Control subjects as well as patients were right handed. They gave informed consent for the study, which was approved by the local ethics committee.

2.3. Data acquisition

The EEG was recorded with Ag/AgCl electrodes placed at the midline sites Fz, Cz, Pz, and at 26 lateral sites, F3 and F4, F1 and F2, FC5 and FC6, FC3 and FC4, FC1 and FC2, C5 and C6, 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 linked mastoids. Vertical and horizontal EOG were recorded bipolarly from above/below the right eye and from the outer canthi of each eye. Electrode impedance was kept below 5 kOhm. Electrical activity was amplified using a bandpass of 0.016 to 35 Hz and digitized at a rate of 200 samples per second. Trials contaminated by artefacts were removed prior to averaging. Electromyographic activity (EMG) was recorded bipolarly with Ag/AgCl electrodes attached 8 cm apart to the dorsolateral surface of the right forearm. EMG was bandpass filtered from 10 to 70 Hz and rectified prior to averaging. Electrical activity was averaged for an analysis period of 2750 ms starting 2250 ms prior to movement-onset. The baseline was calculated from the first 250 ms.

Movements were made by rotating a 12-cm joystick mounted perpendicularly on the right arm of the chair. The joystick was constrained to move only left-right and forwards-backwards. The extent of movements, measured from the tip of the joystick, was approximately 2.5 cm

(12°). All movements could be performed by flexion/extension and pronation/supination movements of the wrist and forearm with the elbow resting on the chair's arm. Movements in each of the four possible directions caused the closure of a switch, which delivered a trigger pulse used for averaging. Averaging with reference to switch closure was preferred to averaging timelocked to EMG onset, given the fact that in condition 2 averages were constructed across movements involving different muscles.

2.4. Data analyses

Subject averages were constructed for each of the two experimental conditions, i.e., for the movement-related activity preceding movements in a fixed direction and for the activity preceding freely selected movements, respectively. For each of these subject averages, mean amplitudes were computed in selected time intervals, separately for each electrode site. The selected time windows include the latencies associated by some investigators with separate sub-components of the Readiness Potential (e.g., Dick et al., 1989). The time windows were selected on the basis of an inspection of the grand average waveforms, which revealed an effect on Readiness Potential amplitude in the last 500 ms before movement-onset. Thus, statistical analysis was performed on successive time windows in this interval, i.e., –500 to –400 ms, –400 to –300 ms, –300 to –200, –200 to –100, –100 to 0 ms. The early phase of the Readiness Potential was quantified by the mean amplitude in the time frame from –1000 to –500 ms preceding movement-onset. The analysis windows are numbered from 1 to 6 according to their positions on the time axis. In the Results section the F -values per window are listed. Of the corresponding p -values only the highest (most conservative) value is given.

Four-way repeated measures analyses of variance (ANOVA) were carried out for each analysis window, with CONDITION (fixed vs. free), HEMISPHERE (left vs. right), and ELECTRODE as within-subjects variables, and GROUP (PD patients vs. normal subjects) as between-subjects variable. Additional three-way ANOVAs, including only the three within-subjects variables, were applied to patients and normal subjects separately. The levels of the variable ELECTRODE were reduced from 13 to 3 by grouping the electrodes in rows. Thus, over the left hemisphere the following electrodes were grouped together: F1, FC1, C1, CP1, (the most medial electrode row); F3, FC3, C3, CP3, (the middle row); F5, FC5, C5, CP5, (the most lateral row). The same grouping was applied to the right hemisphere electrodes. The grouping served to keep interactions involving the variable ELECTRODE interpretable, and to focus the analysis on the dimension of the scalp distribution that might best reveal differential contributions from the SMA and MI. Interactions with the variable ELECTRODE were checked by a second analysis on normalized data, as suggested by McCarthy and Wood

(1985). This second analysis reduced all initially significant interactions to values that were no longer significant. Geisser–Greenhouse conservative F -tests were used.

The number of movements was analyzed by analyses of variance with CONDITION as within-subjects variable and GROUP as between-subjects variable.

Finally, to gain some insight into the subjects' behaviour in the free selection tasks, we analyzed to which extent choices of movement direction were random. We calculated a "randomness score" based on a comparison of the observed frequencies of different response pairs (digrams) with the expected number of all possible digrammic sequences if a subject made a completely random choice (Evans, 1978). A comparable method was applied by Playford et al. (1992). The randomness is expressed in an "information statistic" that varies between 0 and 1, with higher values indicating poorer randomization. This index was transformed into z -scores in order to correct for the different number of movements subjects performed. The z -scores were subjected to an analysis of variance with BLOCK (four levels) as within-subjects variable and GROUP as between-subjects variable.

3. Results

Task performance. The number of movements made in fixed blocks was 172 ± 17 (mean \pm S.D.) for normal subjects and 201 ± 18 for patients. Movements in freely selected directions numbered 182 ± 21 for normal subjects and 221 ± 36 for patients. Analyses yielded significant main effects of GROUP ($F(1,24) = 16.36$, $p < 0.001$) and of CONDITION ($F(1,24) = 13.93$, $p < 0.01$). The interaction GROUP by CONDITION was not significant.

The randomness score calculated for the normal subjects was 0.54 ± 0.047 , and for patients 0.59 ± 0.067 . The z -transformed values (2.22 ± 1.82 vs. 3.83 ± 2.94) suggested that patients chose movement directions in a less random fashion than normal subjects. Statistical comparison performed on the z -scores showed the difference to be not significant, however.

Readiness Potential morphology and distribution. In each of the analysis windows 1 to 6 there was a significant asymmetry with higher Readiness Potential amplitudes contralateral than ipsilateral of the moving limb (main effect of HEMISPHERE: $F(1,24) = 11.10, 10.60, 16.72, 22.95, 40.76, 52.31$; $p < 0.01$). In the same epochs a significant main effect of ELECTRODE ($F(2,48) = 53.00, 46.79, 41.25, 41.34, 44.05, 56.65$; $p < 0.001$), is related to an amplitude gradient from midline to lateral electrode sites.

There were no significant group differences in Readiness Potential morphology and distribution. Whereas comparison of Fig. 1a,b shows that the Readiness Potential of patients has a flatter initial phase and a somewhat steeper rise in the last 500 ms preceding movement-onset, the

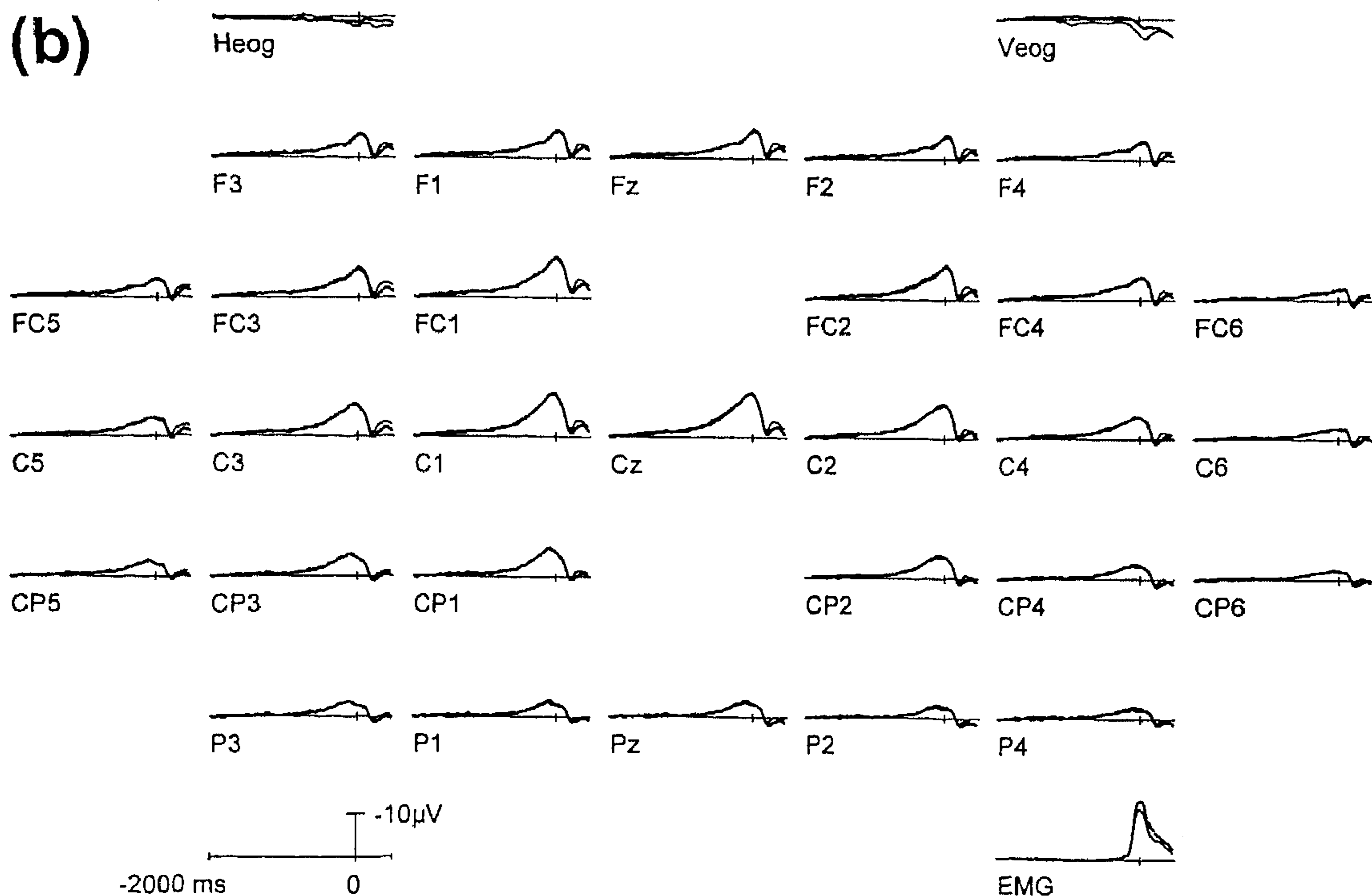
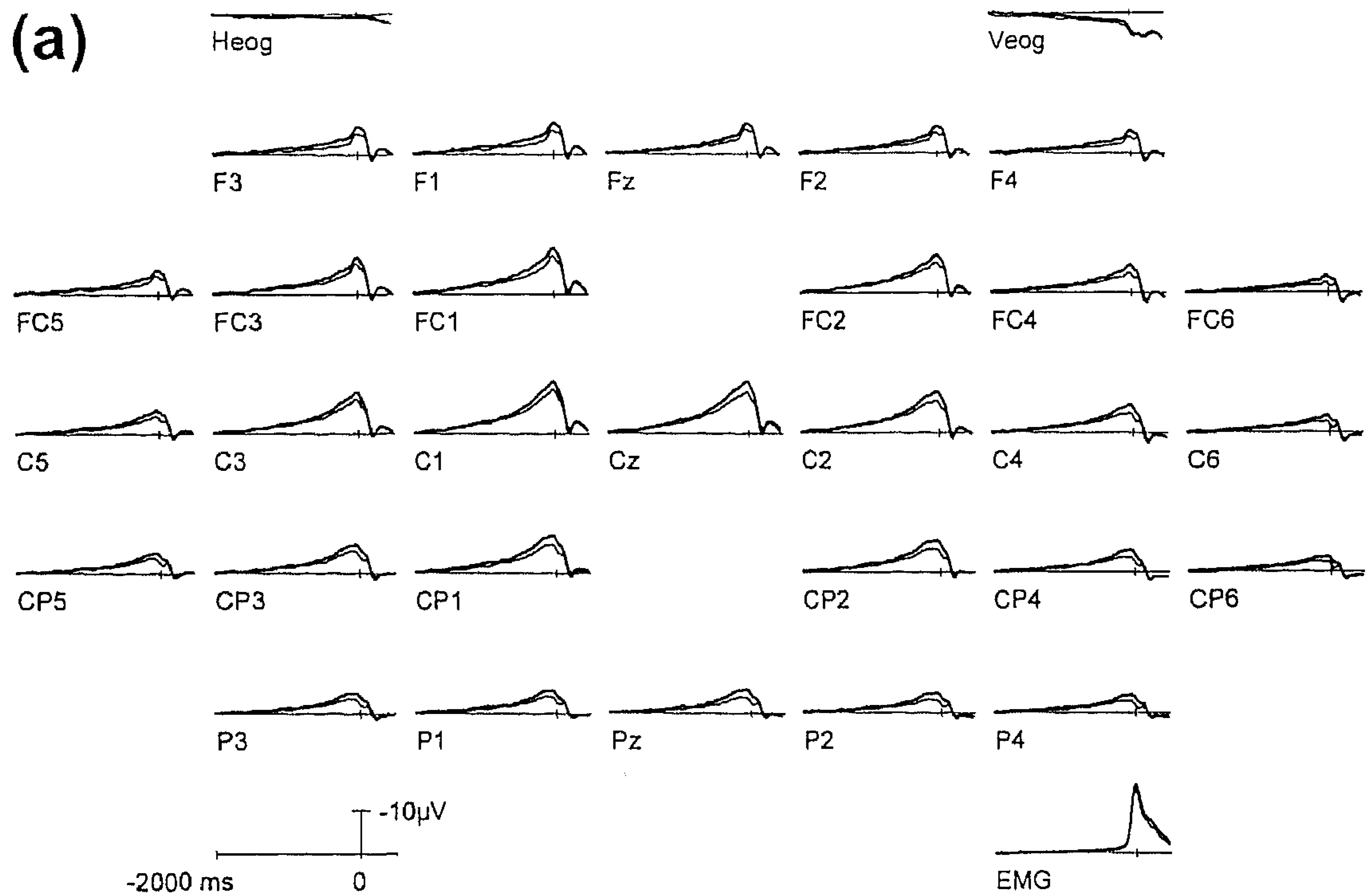


Fig. 1. (a) Grand averages of the normal subjects' Readiness Potentials preceding right-hand movements in fixed direction (thin line) and in freely selected directions (thick line). The layout of traces reflects the arrangement of electrodes on the subjects' heads. EMG recorded from the right forearm is displayed in the lower right corner. (b) Grand average of the patients' Readiness Potentials preceding right-hand movements in a designated direction (thin line) and freely selected directions (thick line).

amplitude difference in the -1000 to -500 ms time frame failed to reach significance ($F(1,24) = 3.37$, $p = 0.079$). Differences in the later time frames were very small.

Readiness Potential task effects. The modulation of Readiness Potential amplitude in normal subjects (see Fig. 1a) corresponded to a significant effect of CONDITION in the analysis windows extending from -300 to 0 ms ($F(1,12)$ for windows 4, 5, and 6 = 5.29, 5.16, 6.18; $p < 0.05$). The averaged Readiness Potentials of PD patients showed no such amplitude modulation (see Fig. 1b). Statistical analysis confirmed the absence of an effect for CONDITION in PD patients (F -values in the analysis windows 4 to 6 ranging from 0.03 to 0.29). In spite of the presence of a significant task effect in normal subjects and its absence in patients, the four-way ANOVA across both groups yielded a GROUP by CONDITION interaction that only approached significance ($F(1,24)$ for windows 4, 5, and 6 = 3.02, 3.37, 2.85; with $p = 0.079$ in window 5 being the value nearest to significance). As the amplitude values for both movement conditions in patients were in the range of the amplitudes for fixed movements of normal subjects, the interaction trend seems due to a difference between patients and normal subjects in the free selection condition.

4. Discussion

A considerable number of studies have been devoted to the investigation of movement preparation in PD using the Readiness Potential (Deecke et al., 1977; Deecke, 1985; Barrett et al., 1986; Simpson and A.J. Khurabet, 1987; Dick et al., 1987, 1989; Tarkka et al., 1990; Fève et al., 1992). Dopaminergic pharmacological effects on the Readiness Potential are now well established and abnormalities of the Readiness Potential seem to be correlated with disease progression (Dick et al., 1987; Fève et al., 1992). However, the Readiness Potential has not consistently been found to be abnormal in PD (Barrett et al., 1986). This might be explained by differences in the severity of disease and in the medication state of the patients examined in the various studies. Another explanation for these inconsistent findings, however, might be that most studies used simple repetitive finger movements to elicit the Readiness Potential. This undemanding task might not be the most suitable one to bring out the suspected abnormalities in the cortical organization of movement in PD. This conjecture is confirmed by a recent study that investigated the Readiness Potential preceding voluntary dorsiflexion movements of the foot and preceding the initiation of gait in PD (Vidailhet et al., 1993). In normal subjects the Readiness Potential preceding a standing stepping movement was larger than before foot movement while sitting. In PD patients, however, no such increase of preparatory activity was observed.

The study by Vidailhet and co-workers supports the hypothesis that specific impairments of complex and sequential movements in PD are related to deficient preparation of movement, possibly due to compromised basal ganglia output to the SMA (Vidailhet et al., 1993). Instead of comparing movements of different complexity, our study focussed on another aspect of movement preparation by comparing different ways of selecting the same movement. Even though identical movements are executed, different patterns of movement-related electrical activity are predicted when movements can be prepared by different processes subserved by different neural substrates. Importantly, a recent review on the specific functions of motor areas, suggested that the distinction between different modes of movement selection might represent an important principle governing the division of labor between the different motor areas (Wise et al., 1991).

Since our study was focussed on different ways of selecting a movement, we wanted movement execution not to be very different between normal subjects and patients. As the Readiness Potential is recorded with self-paced movements, task performance could not be monitored using reaction times. However, the EMG traces (as represented in Fig. 1), suggest that both groups made equally fast and brisk movements. In addition, patients made even more movements than normal subjects, suggesting that they were not greatly impaired in the execution of these movements. As they also did not differ significantly in the randomness of movement directions, differences in movement-related potentials are more likely a result of differences in movement preparation than due to differences in performance. One might suggest that the faster rate of movement in patients has also influenced the Readiness Potentials. However, as the analysis of the number of movements showed no Group by Condition interaction, the different rates of movement do not importantly affect the comparison of Readiness Potentials between the fixed and free selection conditions.

With respect to the morphology and distribution of the Readiness Potential, we found no overall differences between patients and normal subjects, apart from a tendency to a flatter onset and steeper late phase of the potentials recorded in patients. The normal appearance of the Readiness Potential seems consistent with a recent report of normal SMA activation in PD patients undergoing long-term levodopa treatment (Rascol et al., 1994). However, neither a normal configuration of the Readiness Potential, nor normal levels of blood flow in the SMA, as found by these investigators, are sufficient proof of normal function. As our further results suggest, it is not the level of activation per se, but rather the modulation of this level with different task demands that differentiates PD patients from normal subjects.

The modulation of the Readiness Potential by different modes of movement selection was clearly present in the control subjects, as illustrated in Fig. 1a. This "selection

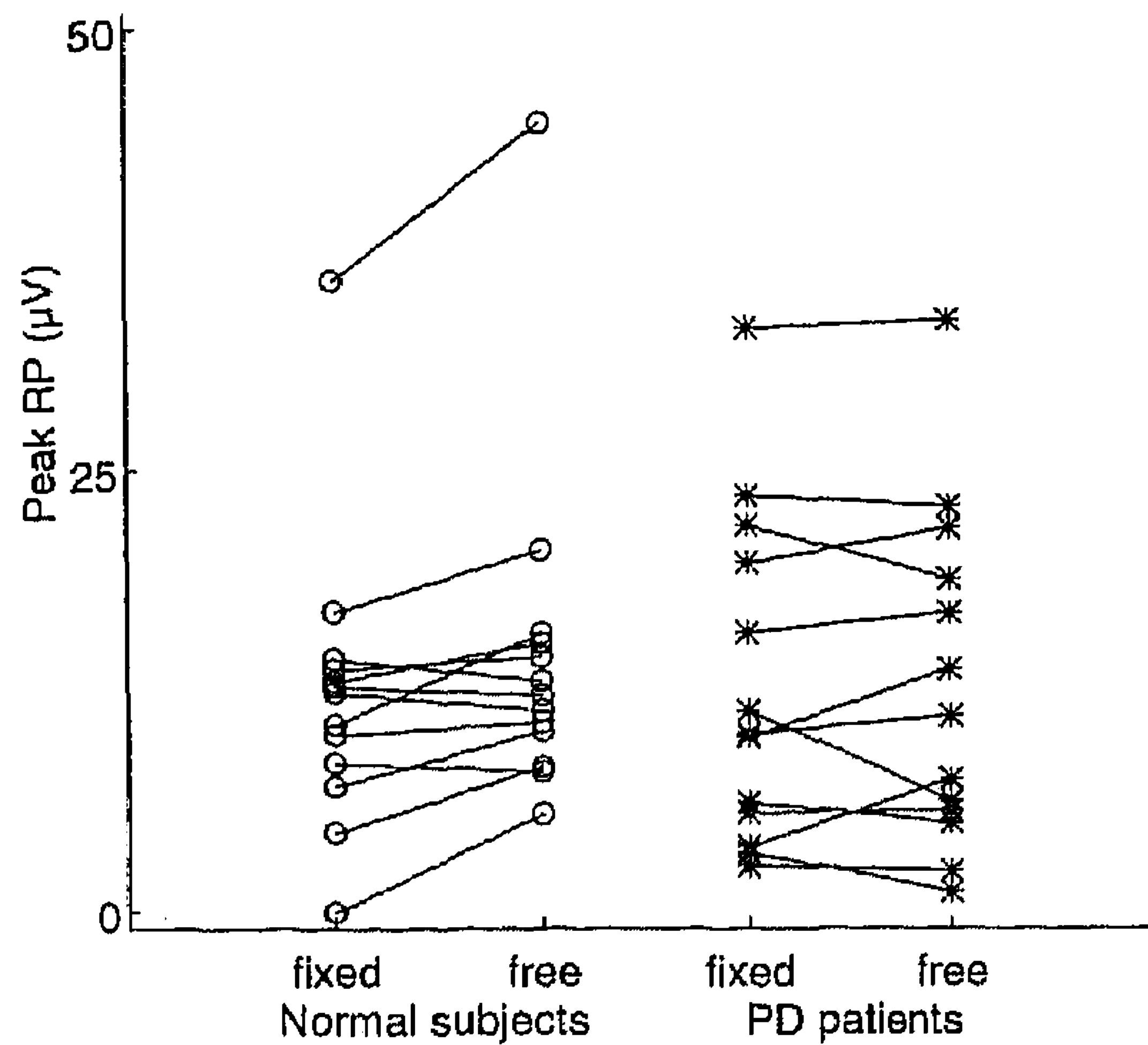


Fig. 2. Summary of the Readiness Potential amplitudes in the latency window from -100 to 0 ms for each of the normal subjects and patients. 'Fixed' and 'free' indicate the tasks with fixed and freely selected movement directions, respectively. The represented values are measured from electrode Cz.

effect'' on the Readiness Potential was absent in PD patients, as shown in Fig. 1b. However, the complete dissociation between patients and normal subjects, suggested by the averaged Readiness Potentials, is not supported when we look into the individual data, represented in Fig. 2. Here it is shown that the "selection effect" on the Readiness Potential is somewhat variable even in normal subjects. This accounts for the Group by Condition interaction being only marginally significant. In this respect, the effect is weaker than was found by Touge et al. (1995). In an absolute sense, the effect measured in the present study, is also weaker than what we have previously observed in younger subjects (Praamstra et al., 1995b). Whereas in the present report the Readiness Potentials for fixed and for freely selected movements diverged significantly from -300 to 0 ms, they already differed at -800 ms in our previous study. Since there were no major methodological differences, the different results suggest a considerable age influence on the "selection effect".

Possibly due to its reduced magnitude in comparison to our previous study, the "selection effect" also lost its topographical specificity (see below), as there was, in contrast to the results of Praamstra et al. (1995a), no significant Condition by Electrode interaction. Nevertheless, the effect's topography seems to be more reliably represented in our recordings than in the data reported by Touge et al. (1995), given the larger number of subjects and the larger number of recording electrodes. Notably, in the latter study there is a discrepancy between the illustrated waveforms, which show a stronger "selection effect" at anterior compared to posterior electrodes, and the statistical evaluation, which reports the effect to be weakest at the frontal electrode F4.

The interpretation of the results is facilitated by the

recent PET studies that we already referred to (Deiber et al., 1991; Jenkins et al., 1992; Playford et al., 1992). As these studies used very similar tasks as we employed, it is likely that the structures herein identified as related to the free selection of movements and found deficient in PD, are also the sources of the "selection effect" in our investigation. Among these structures were the dorsolateral prefrontal cortex, the SMA, and the anterior cingulate cortex. The dorsolateral prefrontal cortex is not likely to contribute very strongly to the modulation of the Readiness Potential. As shown in Fig. 1a, this modulation is equally pronounced at parietal and frontal electrode sites, which argues against a predominantly frontal generator. The SMA, however, is one of the purported generators of the Readiness Potential (Deecke, 1987; Ikeda et al., 1992), and it seems plausible that it contributes to the "selection effect". This is supported by the fact that the effect is strongest at electrode sites near the midline (Praamstra et al., 1995a). It could be argued, however, that the SMA contribution to the Readiness Potential occurs earlier before movement-onset than where we found the Readiness Potential modulation. According to an influential model of the Readiness Potential, SMA activity precedes activity in the primary motor cortex, the latter being responsible for the late part of the Readiness Potential (Deecke, 1987). However, it was recently shown by intracranial recordings that the SMA is active during the entire time course of the Readiness Potential (Ikeda et al., 1992). Thus, the time at which the Readiness Potentials for fixed and freely selected movements diverge, is not incompatible with the divergence (i.e., the "selection effect") being related to the SMA. In support of this claim, a dipole source analysis applied to the Readiness Potential, yielded a source located in the midline as the generator of the "selection effect" (Praamstra et al., 1995b, Praamstra et al., in press).

It has to be noted that neither intracranial recordings of the Readiness Potential (e.g., Ikeda et al., 1992) nor analyses based on scalp-recorded data, have taken into account a subdivision of the SMA that has recently been suggested on the basis of animal studies (Luppino et al., 1991). The proposed division into pre-SMA and SMA-proper appears to be consistent with PET studies showing a posterior focus in the SMA associated with execution of movement and an anterior focus related to the selection of movement (for a discussion see Jahanshahi et al., 1995). Jahanshahi and co-workers found underactivation of this anterior focus, and of anterior cingulate and dorsolateral prefrontal cortex, in PD patients performing self-initiated movements. Importantly, Readiness Potentials recorded in the same patients under conditions comparable to the PET measurements, were also reduced in patients. These data support contributions to the Readiness Potential arising from multiple structures located in the midline, while implicating the pre-SMA and anterior cingulate cortex rather than SMA as being responsible for abnormalities of the Readiness Potential in PD. Thus, most likely, the

modulation of the Readiness Potential by different modes of movement selection, is also due to these structures.

In conclusion, the present results extend our previous description of a modulation of the Readiness Potential by different modes of movement selection (Praamstra et al., 1995a). This effect is not only present in young subjects, but also in healthy elderly people. It is now shown, corroborating Touge et al. (1995), that the effect is absent in PD patients even though they had no difficulty in performing the tasks. Its absence in PD patients converges with the results from PET studies using related tasks, and adds to the existing evidence for a deficit in the internal generation of movements.

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