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Motor Circuitry Re-organization After Pallidotomy in Parkinson Disease

A Neurophysiological Study of the Bereitschaftspotential, Contingent Negative Variation, and N30

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The aim of the study was to evaluate the reorganization changes in the motor circuitry of the basal ganglia following unilateral posteroventral pallidotomy in Parkinson disease (PD) patients using neurophysiological paradigms. Eight advanced PD patients received a neurophysiological battery 2 months prior and 6 months after unilateral pallidotomy. Examinations were all performed in the practically defined "off" situation. Bereitschaftspotential (BP) and N30 were recorded for each hand alternately. Contingent negative variation (CNV) was obtained using a visual Go/no-Go paradigm. ANOVAs (electrode position; surgery) were applied for BP and CNV results. N30 data were analyzed using Wilcoxon matched-pair tests. A significant increase in amplitude of the late component (NS') of the BP was evidenced with patient performing with the hand contralateral to pallidotomy. No significant amplitude differences were found in CNV after surgery in any lead, or in any of the time windows tested. A trend toward significance was observed corresponding to a postsurgical numerical increase in amplitude of the N30 peak in the hand contralateral to pallidotomy. These results suggest that neurophysiological changes after pallidotomy are mainly in the last stages of movement preparation and execution. **Key Words:** Parkinson disease—Pallidotomy—Bereitschaftspotential—Sensory evoked potentials.

Unilateral posteroventral pallidotomy has a positive effect on motor function in Parkinson disease (PD) (Lang et al., 1997). The main hypothesis of the effects of pallidotomy on the motor circuitry of the basal ganglia is that it releases the thalamus and frontal cortex, and in particular the supplementary motor area (SMA), from excessive pallidal inhibition as a consequence of dopamine depletion in the striatum (Wichmann and DeLong, 1996). This hypothesis has been confirmed in regional blood flow studies that have demonstrated a decrease in SMA activity in PD patients (Rascol et al., 1992), and an increase in activity after pallidal surgery (Grafton et al., 1995; Eidelberg et al., 1996; Limousin et al., 1997).

The SMA is believed to play an important role in the genesis of several neurophysiological examinations, such as the bereitschaftspotential (BP), the contingent negative variation (CNV), and the frontal N30 somatosensory evoked potential (SEP). Studies on these neurophysiological SMA activity markers after

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TABLE 1. *Clinical characteristics of Parkinson disease patients in the current study*

Patient	Sex	Age (years)	Duration of Parkinson disease (years)	Side of pallidotomy	UPDRS III* preoperative†	UPDRS III* postoperative†
1	M	53	18	Right	66	47
2	F	64	18	Right	63	26
3	M	72	17	Right	70	55
4	M	69	18	Left	53	36
5	M	68	12	Right	44	29
6	M	69	18	Left	46	23
7	F	68	23	Left	49	30
8	M	67	18	Right	63	35
Mean ± SD		66.25 5.42	17.75 2.77		56.75 9.29	35.12 10.19

*Pharmacologically "off" situation; †preoperative: 2 months, postoperative: 6 months; SD, Standard deviation; M, male; F, female.

pallidal surgery are still lacking. We investigated how these paradigms reflect the reorganization of functional changes that occur in the motor circuitry after pallidal inactivation.

PATIENTS

This study was performed on 8 consecutive patients who underwent pallidal surgery for PD in our Hospital. There were 5 men and 3 women, with a mean age of 62 ± 8.6 years and disease evolution of 15.6 ± 4.7 years. A right unilateral pallidotomy was performed in 5 patients, and a left pallidotomy was performed in 3 patients (Table 1). Pallidotomy was performed using intraoperative microelectrode recording guidance.

Inclusion criteria included a history compatible with idiopathic PD (London Brain Data Bank; Hugues et al., 1992), and a Hoehn and Yahr score of 3.0 or higher while on medication. Patients were excluded if there were dementia criteria on neuropsychological evaluation, severe atrophy on CT scan, presence of any other surgical contraindication, or severe systemic disease. The study was approved by the Hospital Ethical Committee, and informed consent was obtained from each patient before enrollment in the evaluation protocol.

Clinical assessment was performed before (2 months) and after (6 months) surgery using the motor section (part III) of the Unified Parkinson Disease Rating Scale (UPDRS) (Fahn et al., 1987). Pallidotomy was clearly effective for every patient (Table 1); hence, a significant improvement in clinical state was found after surgery (mean UPDRS scores in "off" situation: before surgery, 56.7 and after surgery, 35.1; $P < 0.001$).

NEUROPHYSIOLOGICAL STUDIES

The neurophysiological battery consisted of BP, CNV, and frontal SEP (N30) obtained twice: 2 months preoperatively and 6 months after surgery. These examinations were performed in a quiet laboratory room and in the same order (BP, CNV, and N30). In all recording sessions, patients were in a "practically defined off" situation; that is, 12 h without antiparkinsonian drug treatment. All recording methods and paradigms were performed in accordance with the guidelines of the International Federation of Clinical Neurophysiology (Deuschl and Eisen, 1999).

The BP and CNV electrophysiological recordings were obtained with an analog amplifier (Grass 8-pluss-EEG) and further processed using analog/digital converter Neuroscan 3.0 (Herdnon, USA). The CNV paradigm was administered through Neurostim software (Herdnon, USA). The SEP electrophysiological recordings were obtained with Nicolet Compact Four (Madison, WI, USA).

All studies were recorded via Ag/AgCl surface electrodes placed in the Fz, F3, F4, Cz, C3, C4, Pz, P3, and P4 positions of the 10/20 International System. To study changes in neurophysiological parameters independent of the side of the pallidotomy, the electrodes were named Fc, Cc, and Pc to define the electrodes positioned on the scalp over the hemisphere contralateral to the pallidotomy and Fi, Ci and Pi to define the ipsilateral leads. All electrodes were referred to both ear lobes. The electrodes were filled with conductive gel. The skin resistance was kept under 5 KΩ and was controlled repeatedly during each recording session.

For BP and CNV recording, an electro-oculogram (EOG) was also recorded from an electrode placed 1.5

cm lateral and 1.5 cm superior to the right outer canthus, referenced to the right earlobe. Bandpass filters applied for both EEG and EOG were 0.03 to 70 Hz.

Recording Methods

Bereitschaftspotential

For BP recording the conventional method was used (Shibasaki et al., 1980). Brisk voluntary unilateral extensions of the middle finger at the metacarpophalangeal joint were repeated at a self-placed rate of every 4 to 5 seconds. The surface EMG was recorded from the extensor muscle of the middle finger. The EEG segments from 2 seconds before to 1 second after the trigger movement were digitized and stored at a sampling rate of 400 Hz. The stored EEG segments (70 to 100 trials) were averaged time-locked to the precise onset of the rectified EMG, which was determined through off-line inspection of each trial. During this procedure, any trials noted with apparently significant artifacts were excluded. The baseline was determined as the average of the initial 100-msec epoch of the analysis window for each channel.

BP amplitude was measured as previously described (Kulisevsky et al., 1995; Dick et al., 1989; Tamas and Shibasaki, 1985): in brief, the amplitude of the BP 650 msec before EMG onset that represents the size of the early component of the BP and the late component of the BP (negative slope) which was calculated by subtracting the maximal BP negativity peak from the BP negativity peak at 650 msec before EMG onset. The early and late components of the averaged BP were identified by visual inspection. BP was recorded for each hand alternately in two separate sessions.

BP changes after pallidotomy from all scalp electrode positions were studied by an analysis of variance (ANOVA) for repeated measures with a first within factor "surgery" with two levels (before and after surgery) and a second within factor "electrode position" with nine levels. Greenhause Gaisser correction for multiple levels in the factor was applied. Any $P < 0.05$ was considered significant.

Contingent Negative Variation

The CNV component was developed in warned reaction time paradigms (using a TV screen), when a warning stimulus (S1) is followed by the response or imperative stimulus (S2) after a brief period of time (called foreperiod). Two seconds after the warning signal (S1: yellow star of 25 mm diameter; 500 msec duration), either a green square of 60 mm diameter (S2h) or a red square of 35 mm diameter (S2m) (1 sec duration) were delivered as a target signal in a random order but at almost equal frequency on average. The patient was instructed to press a button as soon as a green square appeared (Go signal) but not to move the finger when the red square appeared (No-Go signal). 120 trials were performed in each condition (50% each of Go and No-Go). Response was expected within 1500 msec after the onset of the imperative stimuli.

Previous to the analysis of CNV component, all waveforms were lowpass filtered (8 Hz, −24 dB). The EEG segments from 2 seconds before to 1 second after the trigger movement were digitized and stored at a sampling rate of 400 Hz. Noted trials with apparently significant artifacts and erroneous responses of the subjects were rejected in off-line analysis. The stored EEG segments were averaged time-locked to S1 for each task condition separately. The baseline was determined by averaging the 500-msec epoch just before the time of S1 presentation for each channel to measure the amplitude of CNV at a certain time. The mean amplitude of four time windows of 500 msec was used to evaluate the CNV component (−2.000 to −1.500 msec; −1.500 to −1.000 msec; −1.000 to −500 msec; and −500 to 0 msec). Go and No-Go trials were averaged together since the CNV should be equivalent for all trials before the imperative stimulus, as subjects are not aware whether the trial was Go or No-Go until the imperative stimulus was given. The CNV was recorded for the hand contralateral to the pallidotomy side.

Changes after pallidotomy of CNV from all scalp electrode positions were studied by an analysis of variance for repeated measures (ANOVA) with a within factor "surgery" with two levels (before and after surgery) and a second within factor "electrode position" with nine levels. Greenhause Gaisser correction for multiple levels in the factor was applied. The four CNV time windows were separately considered. Any $P < 0.05$ was considered significant.

Frontal Somatosensory Evoked Potential N30

Median nerve somatosensory evoked potentials were recorded from both arms in all subjects. The median nerve was stimulated at the wrist (cathode proximal) with square-wave pulses (5 to 10 mA) producing a painless thumb twitch. The stimuli consisted of 0.2-msec square wave pulses delivered at a rate of 1.1 Hz. Stimulus intensity was adjusted to the motor threshold for the thenar muscles. Cerebral responses were recorded for 64 msec (bandpass 30 to 2,000 Hz) from frontal (Fc/Fi) and

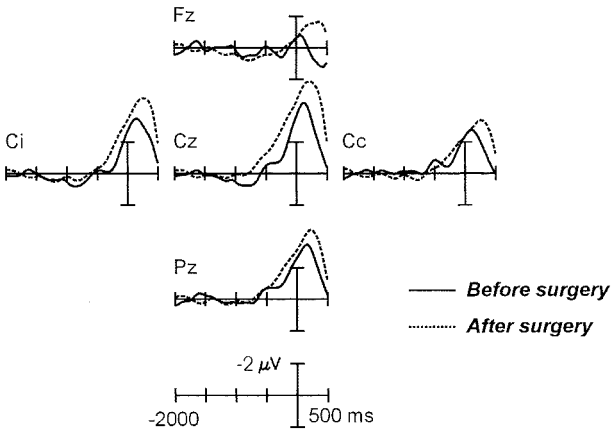

FIG. 1. Movement-related cortical potentials before and after surgery. Mean data from all patients performing an index finger extension movement with the contralesional hand. Note that the early Bereitschaftspotential (BP) is almost absent before and after surgery (characteristic finding of PD patients in "off" situation).

parietal (Cc/Ci) electrodes contralateral to the side of stimulation referred to both ear lobes. We averaged 1,000 responses, and at least two trials were performed on each limb to ensure reproducibility.

The following SEP parameters were considered:

1) peak latency of parietal N20 and frontal N30 waves;

2) peak-to-peak amplitude of the parietal wave N20 (P14–N20) and the frontal wave N30 (P20–N30).

Furthermore, the parietal/frontal index (PFI) was obtained by dividing the N20 by the N30 amplitude. The PFI is useful to attenuate the high intersubject variability of SEP's absolute amplitudes (Rossini et al., 1995).

The mean ± standard deviation of each considered SEP parameter was measured. Statistical analysis was performed by means of nonparametric Wilcoxon matched pairs test to compare the electrophysiological data obtained both preoperatively and postoperatively. Any $P < 0.05$ was considered significant.

Pearson correlation analysis was used to assess the linear relationship between the percentage of amplitude changes of early BP, late BP, CNV (four time windows), PFI, and percentage reduction of parkinsonian motor clinical scale (UPDRS part III).

RESULTS

Bereitschaftspotential

Hand contralateral to the pallidotomy

When studying the early component of the BP, analysis of variance showed a significant effect of the electrode position factor [$F(2.1,15.2) = 4.159$, $P = 0.03$], and no significant effect of surgery factor [$F(1.0,7.0) = 0.361$, $P > 0.5$] or the interaction between surgery and electrode position [$F(2.8,20.1) = 0.522$, $P > 0.5$].

The analysis of variance of the late BP component showed a significant effect of surgery factor [$F(1.0,7.0) = 6.265$, $P = 0.04$], and no significant effect of electrode position [$F(1.9,13.4) = 1.84$, $P = 0.088$] or the interaction between the two factors [$F(1.6,11.8) = 1.224$, $P > 0.5$]. We found a significant increase in amplitude in the channels: Ci: $P = 0.033$; Cz: $P = 0.023$; and Cc: $P = 0.049$. (Fig. 1).

Hand ipsilateral to the pallidotomy

The analysis of variance of the early component of the BP showed a significant effect of electrode position [$F(2.5,17.8) = 4.887$, $P = 0.01$], but no significant effect of surgery factor [$F(1.0,7.0) = 1.225$, $P > 0.3$] or the interaction between both factors [$F(3.0,21.6) = 1.024$, $P > 0.3$].

The analysis of variance of the late component of the BP showed no significant effect of surgery factor [$F(1.0,7.0) = 0.820$, $P > 0.3$], electrode position [$F(2.2,15.6) = 1.793$, $P = 0.197$] or the interaction between both factors [$F(2.8,20.2) = 0.176$, $P > 0.5$].

No significant correlation was found between either early or late BP percentage of amplitude changes and percentage of amplitude changes of CNV (four time windows), PFI and percentage reduction of UPDRS part III score.

Contingent negative variation

Average waveforms of the CNV across the different electrode positions are shown in Fig. 2. For the time window −500 to 0 msec, analysis of variance revealed no effects for surgery factor [$F(1.0,7.0) = 0.42$, $P > 0.5$], for topography (electrode position) [$F(2.1,18.4) = 1.28$, $P > 0.3$], and for the interaction between electrode and surgery [$F(2.8,19.1) = 0.74$, $P > 0.5$]. Similar results were found when studying the other time windows.

No differences were found between the paradigm performance before and after surgery. The mean reaction time was the same in both phases (506 ± 146 msec before and 537 ± 150 msec after surgery), and the accuracy (hits and misses) was almost identical in both conditions.

No significant correlation was found between the percentage of amplitude change of CNV (four time windows) and the percentage of amplitude change of early BP, late BP, PFI, and percentage reduction of UPDRS part III score.

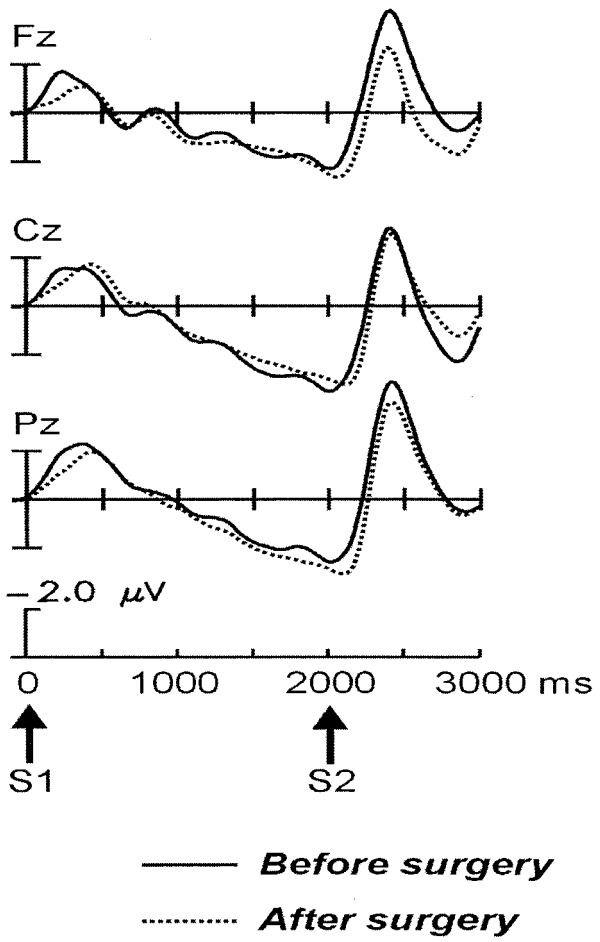

FIG. 2. Mean CNV traces for Parkinson disease subjects before and after pallidotomy. Potentials are shown from the warning stimulus (S1) until 1.000 msec after the imperative stimulus (S2) (total duration 3.0 s).

Frontal somatosensory evoked potential (N30)

The results are presented in Tables 2 and 3. The N30 and N20 waves were clearly identifiable in all the recordings.

Hand contralateral to the pallidotomy

When this potential was obtained after stimulation of the hand contralateral to the pallidotomy, the comparison of the peak latency of the potential N30 before surgery and after surgery revealed no significant differences. The amplitude of this wave increased after surgery (2.27 ± 1.00 μV vs. 3.56 ± 1.52 μV) with a tendency toward significance at the Wilcoxon test ($P = 0.091$). No significant changes were detected in N20 wave latency or amplitude. The selective effect of pallidotomy on N30 wave was strengthened by the PFI reduction from 1.31 ± 0.60 to 1.04 ± 0.55 showing a tendency toward significance ($P = 0.063$) (Fig. 3).

Hand ipsilateral to the pallidotomy

When SEPs were obtained after stimulation of the hand ipsilateral to the pallidotomy, comparison of the latency and amplitude of N30 potential before surgery and after surgery showed no significant differences. Neither was the comparison of amplitudes of this wave significant: before surgery and after surgery. Amplitude and latency of the N20 wave also revealed no significant differences before and after surgery. PFI also showed no significant changes after surgery.

TABLE 2. *Amplitude, peak latency, and amplitude ratio (PFI) of parietal and frontal component of short-latency SEPs in Parkinson disease patients recorded when stimulating the medial nerve ipsilateral to the pallidotomy side*

	Preoperative evaluation					Postoperative evaluation				
Patient	N20 Ampl (μV)	Lat (ms)	N30 Ampl (μV)	Lat (ms)	PFI	N20 Ampl (μV)	Lat (ms)	N30 Ampl (μV)	Lat (ms)	PFI
1	1.8	18.4	1.7	26.0	1.0	2.5	19.6	1.4	30.8	1.7
2	1.5	20.4	4.1	25.2	0.3	2.5	19.6	4.2	27.6	0.5
3	2.9	21.0	2.0	29.2	1.4	2.8	21.6	2.3	29.6	1.1
4	4.5	22.4	1.5	30.0	2.8	2.4	21.6	0.9	29.6	2.7
5	2.7	22.8	3.9	27.2	0.7	3.1	21.1	4.0	28.4	0.7
6	2.5	21.1	2.8	27.7	1.1	2.7	20.7	2.9	28.4	1.2
7	3.0	20.4	4.8	28.0	0.6	3.5	20.4	5.6	28.0	0.6
8	1.5	22.0	1.3	29.6	1.1	2.5	22.0	2.5	26.4	0.9
Mean ± SD	2.6	21.0	2.8	27.9	1.1	2.7	20.8	3.0	28.6	1.2
	1.0		1.4	1.8	0.8	0.4		1.6	1.4	0.7

SEP, somatosensory evoked potential; PFI, parietal/frontal index.

TABLE 3. *Amplitude, peak latency, and amplitude ratio (PFI) of parietal and frontal component of short-latency SEPs in Parkinson disease patients recorded when stimulating the medial nerve contralateral to the pallidotomy side*

	Preoperative evaluation					Postoperative evaluation				
Patient	N20 Ampl (μV)	Lat (ms)	N30 Ampl (μV)	Lat (ms)	PFI	N20 Ampl (μV)	Lat (ms)	N30 Ampl (μV)	Lat (ms)	PFI
1	2.19	18.00	1.3	29.2	1.6	2.3	18.8	3.2	26.0	0.7
2	2.25	18.80	2.0	26.4	1.0	5.3	19.1	6.9	25.6	0.7
3	2.44	20.80	2.8	28.4	0.8	1.4	22.0	3.0	29.2	0.4
4	5.24	24.00	2.6	30.0	1.9	5.3	22.8	2.8	27.6	1.9
5	2.25	19.60	1.8	29.2	1.1	2.7	23.6	2.4	29.6	1.1
6	2.55	20.70	2.2	28.5	1.2	3.6	21.2	3.6	27.1	1.1
7	1.58	22.80	4.0	27.2	0.3	2.0	20.4	3.3	27.2	0.6
8	2.25	21.20	1.0	30.0	2.0	5.3	22.0	3.2	26.4	1.7
Mean ± SD	2.60	20.74	2.2	28.8	1.3	3.5	21.2	3.5	27.3	1.0
	1.19		1.0	1.6	0.6	1.7		1.5	1.5	0.5

SEP, somatosensory evoked potentials; PFI, parietal/frontal index.

No significant correlation was found between PFI and percentage of amplitude changes of early BP, late BP, CNV, and percentage reduction of UPDRS part III score.

DISCUSSION

This study shows that electrophysiological methods are valuable to detect functional changes of the motor circuitry after unilateral pallidotomy. We found a selective significant increase in amplitude of the late component of BP and a numerical increase with a tendency toward significance of the frontal component of SEPs. The CNV, however, revealed no changes after the surgical procedure.

Some methodological limitations of the present results should be considered. The small sample size, although similar to previous studies in this field, precludes a definitive answer regarding the validity of each one of the explored paradigms to study the SMA changes. However, valuable exploratory data were obtained on the utility of the BP and the N30 paradigm. On the other hand, we cannot definitively exclude a possible neurophysiological repercussion of the cranial bone incision (15 mm diameter) performed during the surgical act. The bone incision is located in the frontal bone 20 mm from the midline, very close to F3/F4 10/20 international system leads. However, the small size of the hole—which otherwise is covered with a plastic resistant tap, the differential effect of the surgery on the amplitude of different leads in the three paradigms, and the absence of asymmetry on the conventional EEG after surgery lead us to suppose that the effect of this skull defect on the present study is minimal.

Finally, all neurophysiological paradigms were recorded from the same scalp locations using the same electrode placement. As a result, the late BP probably would not be analyzed at the most appropriate site. Some authors have reported that a better location for BP recording is approximately 1 cm anterior to C3 and C4 (Damen and Brunia, 1987) (precluded in this study because of the presence of the bone incision), others used C3' and C4' positions (Kutas and Donchin, 1980), and others used C1/C2 (Pramsta et al., 1995) or C1'/C2' (Shibasaki et al., 1980) locations.

One of the main findings of our study is that after pallidal surgery, the significant increase of the amplitude of BP occurred only in the second part of the potential (negative slope). Although a previous study of BP modifications after bilateral deep brain pallidal (5 patients) and subthalamic (6 patients) stimulation revealed no significant changes either in early or late BP components (Brown et al., 1999), our results completely agree with the findings of Limousin et al. (1999), who analyzed BP changes after pallidotomy in a series of 10 PD patients. These findings are somewhat unexpected given that functional surgery of basal ganglia in PD has been shown to increase the impaired activation of the SMA, which is thought to play a major role in the preparation for movement and in the generation of the early component of the BP (Grafton et al., 1995; Eidelberg et al., 1996; Limousin et al., 1997). Thus, in the study by Limousin et al. and in our own, improvement in movement execution was not preceded by changes in the early processes of movement preparation. One possibility is that, as that the late component of BP is generated more from the primary motor area than from the SMA, the BP changes obtained after surgery reveal an increased activity of predominantly primary motor area rather than SMA. In

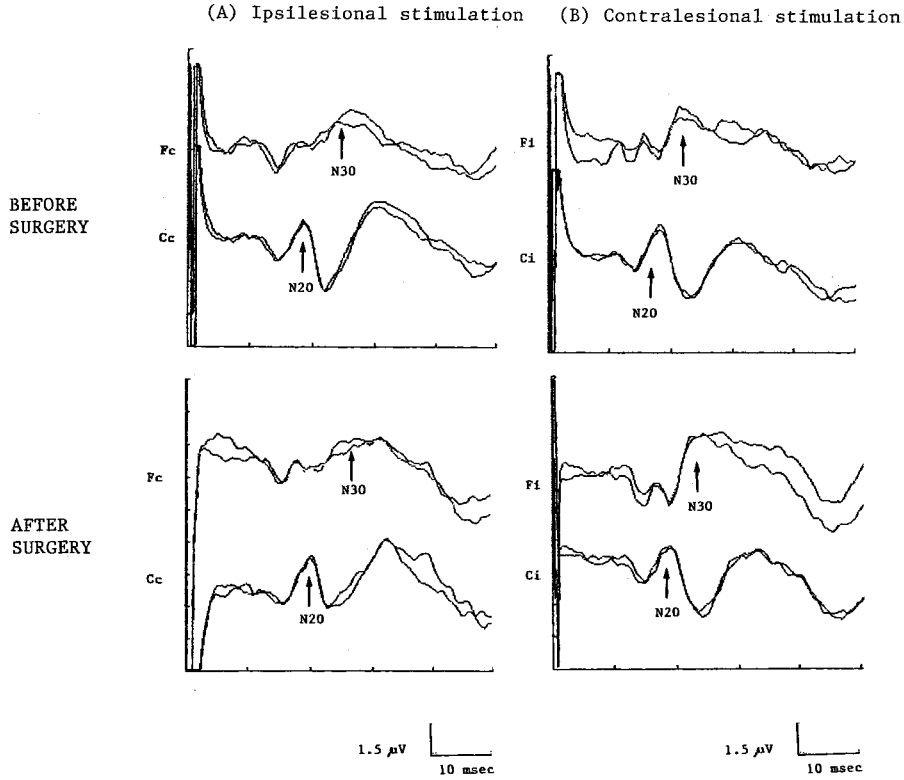

FIG. 3. The figure shows the frontal (N30) and parietal (N20) components of somatosensory evoked potential (SEPs) to median nerve stimulation in a representative advanced PD patient. The SEPs were recorded preoperatively (upper frame) and postoperatively (lower frame). It is noteworthy that the frontal N30 amplitude is selectively enhanced after pallidotomy only when the potential was obtained after stimulation of the hand contralateral to the pallidotomy (B). Each trace is the result of the superimposition of two consecutive trials.

fact, the amplitude change of the late component of BP might be due to the improvement of finger movement after surgery (smaller twitch of the fiducial point with respect to the presurgical movement). It should be noted, however, that the late component of the BP is the most reproducible measure in studies that attempt to quantify BP changes before and after an intervention in the same group of subjects (Evidente et al., 1999). Furthermore, as reported in a previous study (Limousin et al., 1999), we only found changes in the amplitude of the BP when movement was performed with the index finger contralateral to the pallidotomy, thus agreeing with contralateral improvement in motor symptoms after unilateral pallidal surgery (Lang et al., 1997).

Differences between BP and CNV are well known, the latter being less specific of SMA activity, principally in the early stages of motor preparation (Ikeda et al., 1994). It is currently accepted that late CNV is not identical to BP because the CNV paradigm with no motor task in response to the second signal can still elicit a negative potential before the second signal (Ruchkin et al., 1986). Moreover, it has been reported that CNV reflects frontal cortex function during early stages of response preparation in a similar manner as the early component of the BP (Hamano et al., 1997). In the present study, the absence of CNV changes amplitude after pallidal surgery in PD agree with the hypothesis that pallidal surgery improves mainly the movement execution, as measured by the late component of the BP, but not the motor preparation as measured by the early component of the BP or the CNV potential. However, a previous study of CNV potential after bilateral subthalamic surgery in a series of 10 PD patients revealed an increase in its amplitude (Gerschlager et al., 1999). One possible explanation for the discrepancy with our results is the small number of subjects included in both studies and that bilateral subthalamic stimulation would increase the activity of SMA further than unilateral pallidotomy. This disagreement, certainly, warrants further investigation.

On the other hand, both the genesis and implication of SMA on the N30 potential remain controversial (Rossini et al., 1989; Huttunen and Teräväinen, 1993). Only one previous work analyzes changes on N30 potential after functional surgery on PD (Pierantozzi et al., 1999). This

work was performed on 6 PD patients (4 after bilateral pallidal stimulation and 2 after subthalamic stimulation) comparing SEP parameters when generators of deep brain stimulation were "off" or "on" (although patients were studied some minutes after turning "off" the generators to avoid interferences). They found a significant increase in N30 amplitude after both pallidal and subthalamic DBS stimulation. Accordingly, in our study we found a numerical increase with a tendency toward significance in N30 amplitude when the basal ganglia "motor" circuitry receiving the pallidotomy was stimulated. Again, one possible explanation for the more consistent changes found in these DBS-implanted patients could be that bilateral surgical procedures lead to a more intense increase of the activity of SMA or related areas. Another explanation would be the different N30 recording scalp positions. In fact, in the work of Pierantozzi et al., they used central instead of lateral positions to record the N30 amplitude.

The small number of subjects studied might explain the absence of significant correlation between postsurgical changes in BP and N30 and reduction of clinical scores. More studies are needed to establish the relationship between PD clinical scores and neurophysiological measures.

In conclusion, our exploratory study reveals that neurophysiological changes associated with pallidotomy were observed mainly in the last stages of movement preparation and execution (presumably by acting on the motor loop and improving function in the primary motor cortex, premotor cortex and SMA proper). Early preparatory processes involved in early BP and CNV, characteristic of projection targets of the frontal associative basal ganglia loops, were unaffected. (Wichmann, 1996)

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