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ORIGINAL COMMUNICATION

**Paul Sauleau**
**Sylvie Raoul**
**François Lallement**
**Isabelle Rivier**
**Sophie Drapier**
**Youenn Lajat**
**Marc Verin**

# Motor and non motor effects during intraoperative subthalamic stimulation for Parkinson's disease

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P. Sauleau · F. Lallement · I. Rivier · S. Drapier · M. Verin
Dept. of Neurology
Medical University of Rennes
Rennes, France

S. Raoul · Y. Lajat
Dept. of Neurosurgery
Medical University of Nantes
Nantes, France

Prof. M. Verin (✉)
Service de Neurologie
Hôpital Pontchaillou, CHU de Rennes
35033 Rennes Cedex, France
Tel.: +33-29/9284-293
Fax: +33-29/9284-132
E-Mail: marc.verin@chu-rennes.fr

**Abstract** Spatial distribution of the clinical effects induced by deep brain stimulation during the intraoperative investigation of the subthalamic nucleus (STN) for Parkinson's disease (PD) was analysed in 17 patients under local anesthesia. The stimulation parameters were 130 hertz, 100 µs, and voltage ranged from 0.05 to 5 volts. Optimal motor response was assessed as the total and lasting disappearance of wrist rigidity on the side opposite to stimulation. Among the adverse effects induced by stimulation, special attention was given to frequently observed autonomic effects (AE). Full motor response was achieved in 49.2 % of the 301 points evaluated, with a mean voltage (MV) of 0.94 volts; paresthesiae occurred in 6.6 % (MV: 2 volts), dystonia in 10.6 % (MV: 3.4 volts), autonomic effects in 19.6 % (MV: 3.1 volts) and oculomotor effects in 31.6 % (MV: 3 volts). The motor target was located in the posterodorsal part of the nucleus and the optimal point for motor response was close to the superior limit of the nucleus. Whereas other adverse effects occurred relatively far from the motor target, AE occurred with statistic significance near this point. Their neural substrates, such as limbic system and their relationship with postoperative behavioral disorders, are discussed.

**Key words** subthalamic nucleus · Parkinson's disease · deep brain stimulation · limbic system

## Introduction

High-frequency subthalamic stimulation is currently the preferred surgical technique to treat motor symptoms in Parkinson's disease (PD) when medical treatment has failed [22]. STN deep brain stimulation improves motor symptoms dramatically in severe PD. Different methods can be used for anatomical location of the STN: direct targeting on T2 MRI or an indirect procedure following ventriculography and stereotactic mapping [6]. Individual variability may result in an incorrect implantation of the lead but careful clinical assessment during intraoperative stimulation with macroelectrodes can avoid misplacement of the electrodes. With this aim in view, we studied intraoperatively 301 contacts to assess the topographic relationship of side-effects with the effective motor zone.

## Patients and methods

### Patients

Seventeen patients (14 men and 3 women) were included in the study. All presented with idiopathic PD with incapacitating motor fluctuations despite optimal medical treatment. PD was akineto-hypertonic and shaking in nine patients and akineto-hypertonic in the other eight. The functional impact of the disease and the lack of possible improvement under medical treatment alone constituted the indication for surgery. The mean duration of the disease was 15 years (range: 8–28) with a mean age at onset of 44 (range: 17–61). Preoperative UPDRS mean motor score during ON phases was 11 and 54 during OFF periods. Mean age at the first operation was 60 years (range:

40–75). For the surgical indication to be retained, each patient had to exhibit sustained dopa-sensitivity characterised by at least 50 % improvement in Parkinsonian symptoms on the UPDRS motor score following the levodopa test.

### Surgical procedure

The operation was carried out in two steps: ventriculography under general anesthesia with theoretical computation of the target according to Talairach's method [38] and electrode implantation under local anesthesia 12 hours after suspension of levodopa treatment. A single electrode was introduced by means of a computer-controlled robotised arm (NeuroMate, Integrated Surgical System S. A., Lyon-Bron, France) following a double-oblique trajectory from front to rear and from outside inwards (mean angle of incidence: 57° and 55° respectively). Intraoperative clinical assessment was performed on a DIXI PK08–06AS type electrode (DIXI MEDICAL) featuring six 2-mm long and 0.8-mm thick electric contacts spaced by 0.2 mm insulating material, providing a 13-mm total exploration length. The coordinates of the intended target for the tip of the probe were 4 mm behind and 8 mm below the midcommissural point, 8 mm lateral to the median line. In such a configuration three of the six contacts of the electrode were located in the theoretical subthalamic nucleus, one above and two behind. Intraoperative clinical exploration was performed by unipolar stimulation through a stimulation unit (Screener MEDTRONIC model 3625, Minneapolis MN). Each of the six stimulation contacts of the probe was successively the cathode, the reference was a subcutaneous needle inserted in the shoulder of the patient. The frequency (130 Hertz) and pulse width (100 µs) remained the same throughout the various tests. Voltage was gradually increased from 0.5 to 5 volt in 0.5-volt increments. Finer analysis in 0.1-volt increments was used to narrow-in on the best motor effect. Clinical response quality was assessed by the same neurologist (MV) with the patients' active contribution. Evaluation of the clinical effects was performed on each side as unilateral stimulation was applied; intraoperative data were collected in the same manner by assessing wrist rigidity contralateral to the stimulation side and by recording the occurrence of dyskinesia and adverse events. Continuous cardiovascular monitoring (heart rate and blood pressure) was performed during implantation of the electrodes. Similar analysis was done on bradykinesia; however, it was considered as less informative than rigidity. Indeed, we observed a more variable latency for both the improvement in bradykinesia and the return to baseline after offset of stimulation. Moreover, a greater variability of this symptom in baseline conditions depending on the motivation and fatigue of the patient was observed. In contrast to bradykinesia, improvement in rigidity is considered to be a more reliable effect of stimulation and is predictive of an improvement in other Parkinsonian symptoms [18], even if respective targets for rigidity and bradykinesia could be slightly different. For these reasons, we only present results concerning rigidity. The final course and depth of the electrode were determined by the best effect obtained on rigidity with no side effects and at the lowest voltage. One unsatisfactory result led to modifying electrode depth or performing a new course. Each electrode displacement was monitored by radiography. Once the optimal result was achieved, the neurosurgeon removed the trial electrode and replaced it with the permanent model 3389 MEDTRONIC electrode (Minneapolis MN).

### Data collection and representation method

The focus of each stimulation contact was located in relation to the middle of the bicommissural line (AC-PC) by superimposing the electrode positioning picture with that of the corresponding ventriculography. Distances were measured on a graded transparent sheet of paper, and then readjusted using a computerized spreadsheet. All contact foci of the 17 patients were represented on a single diagram. Contacts' coordinates were expressed as millimeters along three axes originating from the middle of the bicommissural line; the first axis was the bicommissural line oriented rearwards, the second axis was the perpendicular to AC-PC from top to bottom, and the third axis was the perpendicular line to the midsagittal plane oriented from right to left.

## Results

The study involved 33 subthalamic nuclei for side effects and 32 nuclei for effectiveness on rigidity. One patient's left side and another's right side were excluded. Only those contacts whose intraoperative clinical effects were unambiguous were taken into consideration. On average, two trajectories were performed for complete evaluation of the subthalamic area on each side. The results we provide concern the effects of monopolar unilateral stimulation. In total, 301 contacts were studied. The volume represented by those 301 points clearly exceeded the nucleus boundaries and was used to analyse the effects of stimulation both on the STN and on adjacent structures.

### Antiparkinsonian motor effect

Of the 301 contacts analysed, 148 reflected optimal motor effect, including total and durable disappearance of rigidity on the side opposite to that of stimulation. The mean voltage of those contacts was 0.94 (±0.8) volts (range 0.05–3.5 volts). The average dot coordinates of those 148 points (so-called motor point) were 1.4 (±1.8) mm; 1.8 (±3.1) mm; 11.8 (±1.4) mm.

Those 148 points were classified as four increasing voltage classes from 0.05 to 3.5 volts. Fig. 1 shows the average dot of each class. The voltages necessary to achieve the same motor effect were higher in the lower part of the diagram and decreased as the AC-PC line was being approached. This diagram revealed a voltage gradient that tended toward an average dot which corresponded to the best motor effect achieved with the lowest voltages. The coordinates of that 33-contact point were: 0.6 (±1.9) mm; 0.1 (±2.9) mm; 12.3 (±1.4) mm; the mean voltage associated to that point was 0.18 volt (Fig. 2). In seven patients, we observed dyskinesias occurring mainly in the legs. The mean point for dyskinesias was superimposed on the mean point for improvement in rigidity.

### Adverse effects

Only those adverse effects which were directly linked to stimulation were considered, i. e., occurring at a given stimulation threshold and disappearing when stimulation was suspended; reproducibility on the same contact

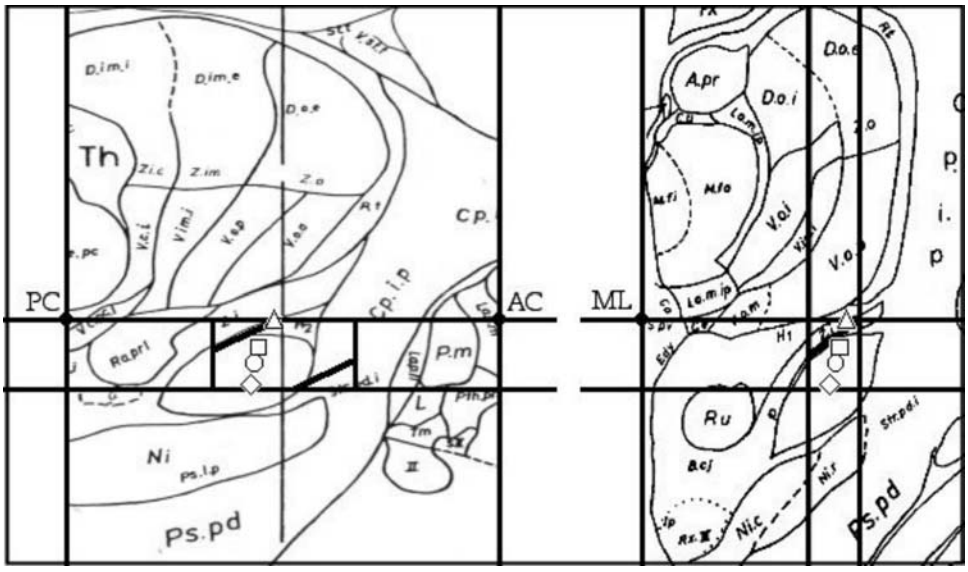


**Fig. 1** Sagittal and frontal location of the average dots required to produce a full and sustainable antiparkinsonian effect on rigidity, distributed into four voltage classes: Δ = 0.05 to 0.4 volt (33 contacts); □ = 0.5 to 0.6 volt (51 contacts); ○ = 1 to 2 volts (52 contacts) and ◇ = 2.5 to 3.5 volts (12 contacts). *AC* anterior white commissure; *PC* posterior white commissure; *ML* median line. In order to facilitate anatomical considerations, Talairach's theoretical limits of the STN and Schaltenbrand's plates (12 mm from the median line and 3 mm behind the middle of the bicommissural line) were superimposed

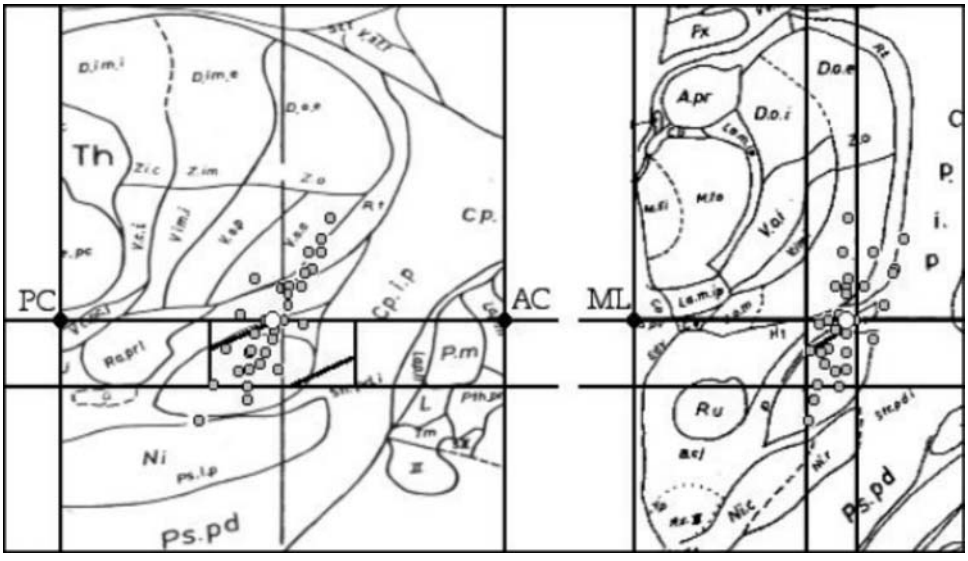


**Fig. 2** Sagittal and frontal location of the 33 contacts corresponding to a full and sustainable antiparkinsonian effect on rigidity for voltages < 0.4 volt, and the mean corresponding point (○). This figures shows the individual variation and the dorsal extension of the area leading to improvement in rigidity. *AC* anterior white commissure; *PC* posterior white commissure; *ML* median line. Same comments as for Fig. 1

and with the same stimulation threshold; increasing intensity of the signs as stimulation voltage was increased. Four types of adverse effects were identified on 174 contacts. These were, in decreasing order of frequency, oculomotor disorders (95 contacts), autonomic disorders (59 contacts), dystonic disorders (32 contacts) and sensory disorders (20 contacts).

Oculomotor effects were noted during the exploration of 25 nuclei (32 % of contacts). They were monocular effects with tonic deviation of one eye on the stimulation side. The mean voltage for those effects was 3.04 (±1.2) volts. The coordinates of the corresponding average dot were 2.5 (±1.5) mm, 4.0 (±3.0) mm, 10.7 (±1.5) mm and that average dot was inward and downward in relation to the motor point (Fig. 3).

Motor adverse effects strictly opposite to the stimulation side were recorded during the exploration of 11 nuclei (11 % of the contacts): facial hemispasm, either isolated or associated with hand dystonia on the same side, isolated foot extension dystonia. Hemispasm intensity increased proportionally to the voltage applied: under low voltage, eyelid closing was only partial and became complete and associated with facial contraction under higher voltage. The mean voltage under which those effects were induced was 3.41 (±1.0) volts. The coordinates of the corresponding average dots were 2.6 (±1.4) mm, 5.1 (±3.2) mm, 11.7 (±1.2) mm and the average dot was low and outside of the motor point (Fig. 3).

Sensory effects opposite the stimulation side were noted during the exploration of 7 nuclei (7 % of the con-

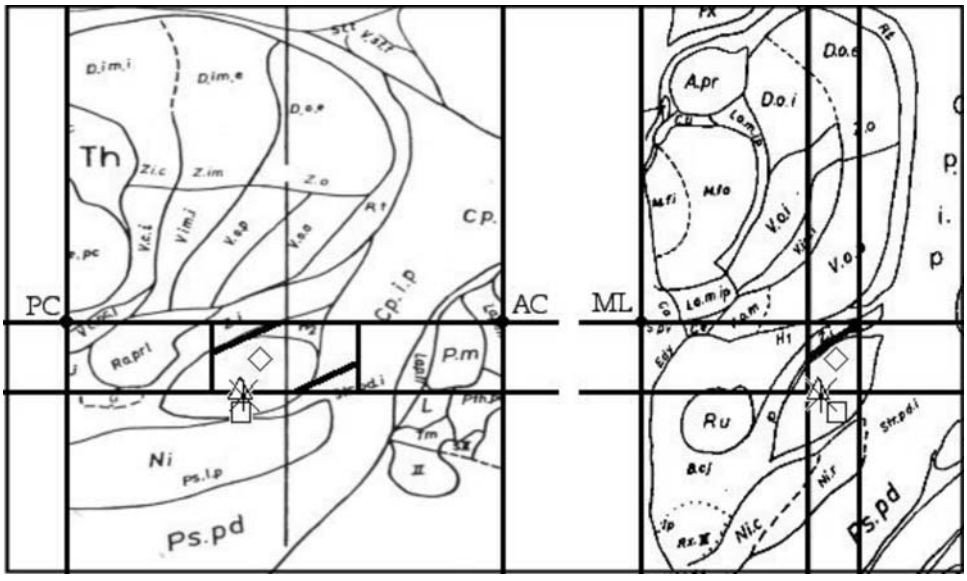


**Fig. 3** Sagittal and frontal location of the average dots corresponding to the four types of adverse effects: oculomotor (*), autonomic (◇), dystonic (□) and sensory (Δ). *AC* anterior white commissure; *PC* posterior white commissure; *ML* median line. Same comments as for Fig. 1

tacts): paresthesiae, essentially in the hand or foot, rarely facial or involving the entire body half. Paresthesiae were sometimes transient and only occurred when the stimulation threshold was raised. The mean voltage of those contacts was 2.04 (±1.1) volts. The coordinates of the corresponding average dot were 2.8 (±2.4) mm, 3.7 (±2.7) mm, 10.6 (±1.5) mm and that average dot was low and inside the motor point (Fig. 3).

Autonomic effects were recorded during the exploration of 22 subthalamic nuclei (20 % of the contacts) and were present in 15 patients. Two types of autonomic effects were noted.

First, the group of effects subjectively felt by patients included feelings of general malaise with variable severity:

- confusion and indefinite malaise, a feeling of chest congestion or abdominal discomfort, a feeling of imminent fainting.
- a feeling of anguish or anxiety, or stress.
- a feeling of cold or warmth, either diffuse or restricted to the face.

The second group included the effects objectively identified by the medical team:

- unilateral mydriasis, more often bilateral and asymmetrical, more marked on the stimulation side (Fig. 4). Mydriasis was the first vegetative effect to occur and occurred reliably on stimulation onset and offset.
- excessive sweating, either diffuse or restricted to one half of the body, of the face or nostrils, neck base, the back or the thorax front (Fig. 4).
- flushing, either diffuse or hemifacial.
- tachycardia (on average the heart rate increased of 25 bpm, without obvious sign of arrhythmia) and blood pressure variations with hypertension (on average both systolic and diastolic pressures increased by 20 mmHg). Tachycardia followed stimulation onset within a few seconds but hypertension was delayed by about one minute. Return to baseline was also delayed after the offset of stimulation by within a few minutes.

These objective effects were associated with first group symptoms. Dizziness, over sweating and pupil abnormalities were the most frequent clinical association. Such vegetative effects were clearly a direct effect of unilateral stimulation. Some patients had the usual autonomic symptoms commonly seen in Parkinson's disease but none complained of a past history of syncope or marked vegetative symptoms. Presurgical mood assessment did not reveal any particular stress predisposition. In baseline conditions, the cardiovascular parameters were stable, the patients reported no specific feeling of anxiety or dizziness (in the acceptable limits of the stress induced by such surgery), pupils were symmetric and no special sweating was obvious. Vegetative effects were only induced on specific contacts, occurred on onset and disappeared on offset of stimulation.

Stimulation induced autonomic signs on both STN with no symmetry in 7 patients. There was no lateralization in the other 8 patients: autonomic effects occurred in four patients during left STN stimulation and during right STN stimulation in the other four. The occurrence of autonomic signs was voltage-dependent and the intensity of the same autonomic sign increased with voltage. The whole range of autonomic signs was obtained with a stimulation threshold equal to or higher than 1.5 volt and the mean voltage required for autonomic effects to occur was 3.14 (±1.1) volts. The coordi-

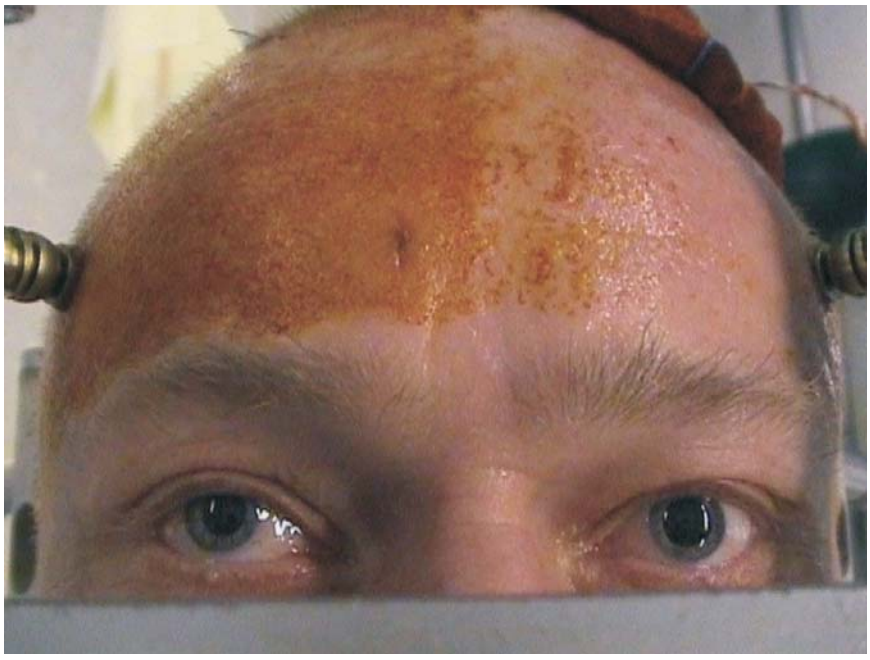

**Fig. 4** Hemihydrosis and left-predominant asymmetrical mydriasis during intraoperative stimulation of the left subthalamic region

nates of the corresponding average dot were 1.4 (±1.6) mm, 2.1 (±2.3) mm, 11.6 (±1.2) mm and were superimposable with the average motor point (Fig. 3).

## Discussion

The MEDTRONIC model 3389 permanent electrode features four 1.5-mm-long contacts, 1.27 mm in diameter and separated by 0.5 mm intervals. The area of the DIXI electrode is 5.03 $mm^2$, that of the MEDTRONIC is 5.98 $mm^2$. The difference in area between these two electrodes being only 16 %, intraoperative stimulation with the DIXI electrode was considered as representative of the chronic stimulation achieved with the permanent electrode. This method therefore permits the closest assessment of the effects to be expected under chronic stimulation.

That the location of the STN in this study is done on atlases and not MRI or electrophysiological recordings could be considered as limitations. Recent data based on MRI confirm the high variability of the STN in different patients and point out the lack of precision of the atlases [23]. In our study however, the Talairach's mapping of the STN was only used for the surgical targeting and the definite position of the electrodes was based only on the clinical effects of stimulation. The data we provide are presented according to less variable structures meaning the bicommissural line and the median line on the frontal plan. From this point of view, the results are independent of any atlas and can be superposed on any representation of the subthalamic area. In order to facilitate anatomical considerations, Talairach's theoretical limits of the STN and Schaltenbrand's plates (12 mm from the median line and 3 mm behind the middle of the bicommissural line) were superimposed on the figures.

### Antiparkinsonian motor effect

In this series, the average motor zone appeared in the posterior and dorsal part of the nucleus, according to both Talairach's theoretical diagram and Schaltenbrand's mapping [35, 38]. These results are consistent with previous studies conducted in monkeys [26, 40] and in man [3, 29] which located the sensorimotor region of the nucleus in its dorsal part. Low voltages corresponded to a reduced stimulation volume, the average dot obtained with voltages below 0.4 volt represented the optimal stimulating zone, skirting the AC-PC line. As defined by both Talairach's theoretical diagram and Schaltenbrand's mapping, the STN upper border is below the bicommissural line with 12- to 13-mm laterality [35, 38]. At that level, the STN is separated from Vop nucleus by the H2 bundle (along 1 mm) and by the zona incerta (along 1.5 mm) [14]. Indeed, it can be hypothesized that the optimal stimulation point is localized in the very top part of the nucleus or even beyond the STN limits, inside the zona incerta and the fields of Forel. This suggestion is a reminder of Andy's [4], Spiegel's [37], and Mundinger's [24] lesions of the posterior subthalamic region including the fields of Forel and the zona incerta. Our study confirms several recent publications based on MRI and electrophysiological data showing that sub-

thalamic stimulation is also effective in the area between the upper subthalamic nucleus and the white matter dorsal to the STN and suggesting that the therapeutic target of subthalamic stimulation includes the pallidothalamic bundle, the pallidosubthalamic tract, and/or the zona incerta, in addition to the STN itself [7, 15, 39].

## Adverse effects

Adverse effects were particularly frequent during the stimulation of the subthalamic region, as observed in 174 (57.8 %) of the 301 contacts studied. They were also found in 77 (52 %) of the 148 contacts that corresponded to full and sustained motor effect, which reflected the close topographic relationship that exists between the motor zone and that of adverse effects. Also, motor or sensory adverse effects were more frequently observed in contacts where the motor effect was partial or transient whereas ocular and autonomic effects were more frequently noted in contacts where the motor effect was full and durable (27 and 24 %, respectively): the brain structures responsible for oculomotor and autonomic effects were close to the motor target and closer to it than the structures responsible for dystonic effects and paresthesiae. Paresthesiae are consistent with current diffusion to the medial lemniscus, dystonic effects with current diffusion to the internal capsule. The oculomotor effects might be explained by stimulation of fibers going to or coming from the oculomotor nucleus (III cranial nerve nucleus). Vegetative effects also have to be considered as adverse effects during electrodes implantation even if patients do not complain of such events in the long term [16]. As their anatomo-physiological substratum still remains poorly understood, precise examination of these symptoms and their clinical consequences could be of crucial importance (see below).

The frequency of adverse effects noted in this series and their proximity to the motor zone of the STN are consistent with the absolute necessity to perform rigorous, intraoperative clinical exploration in a conscious patient. Indeed, patient cooperation is needed to identify all the adverse effects that could be overlooked by clinicians, such as diplopia without any substantial strabismus or subjective autonomic effects.

## Autonomic effects

### Localization of autonomic effects

The average dot of autonomic effects was localized in the postero-dorsal region of the STN, according to both Talairach's theoretical diagram and Schaltenbrand's mapping [35, 38], considered as the sensorimotor region of the nucleus; it was superimposed with the average dot corresponding to antiparkinsonian effectiveness under any voltage, was localized within and more caudally than the average stimulation point that corresponded to the lowest voltages inducing an optimal antiparkinsonian effect (Fig. 1). Two mechanisms of action could be evoked.

In first analysis, it could be argued that the stimulation volume corresponding to the autonomic effects observed under 3.14 volts mean voltage was sufficient to involve autonomic structures neighboring the STN and connected with the hypothalamus meaning the median forebrain bundle lying medially to the STN and the zona incerta and the Forel's Fields above the nucleus. Autonomic effects have been described during electric stimulation or lesion experiments in animals [1, 10], subthalamic surgery for extrapyramidal pathology in man [8, 25, 34, 35, 37] or during stimulation of a more medial area between the postero-lateral hypothalamus and the STN [33]. The localization and type of those effects, essentially tachycardia and mydriasis homolateral to the stimulation, are consistent with those observed in our series.

However, in this study, the laterality of the average dot of the contacts responsible for autonomic effects in relation to the median line and standard deviation ($11.6 \pm 1.2$ mm) clearly argue in favor of autonomic localization within the STN itself.

The STN can be divided into a main, sensorimotor and dorsolateral territory, an associative, ventromedial smaller territory and a yet more restricted limbic territory situated at the end of its medial extremity [26]. Indeed, another source of autonomic effects could be localized in the limbic compartment of the STN itself as neurons in the medial tip of the nucleus share common characteristics in morphology and connections with the adjacent lateral hypothalamic area [13]. It is also well known that vegetative effects occur during limbic system activation and have common pathways [1, 12, 16, 33]. Common models of basal ganglia functioning suggest that the cortico-basal loops, including the STN and the substantia nigra, involve limbic and associative functions in addition to motor ones [2]. The existence of such a circuitry in man remains still under debate, although several facts argue in favor of a role of the basal ganglia in controlling emotions and behavior. The diffusion of current during stimulation of the sensorimotor region of the nucleus may therefore simultaneously involve the motor and non-motor, limbic and associative areas of the STN. Publications on behavioral disorders associating mood and emotional disorders by stimulation or STN lesions are consistent with that view. Positron emission tomography (PET) scanning studies provide evidence that the STN modulates non-motor circuitry and influences the anterior cingulate cortex (a component of the limbic loop implicated in motor control, cognitive and emotional behaviors) [21, 36]. Stimu-

lation of the limbic part of the STN has been considered as responsible for behavioral disorders and mood changes [5, 11, 17, 28, 32]. On the other hand, PET scanning studies also showed evidence for the involvement of the anterior cingulate in central cardiovascular control (heart rate and blood pressure) in response to mental stressor tasks [9]. These studies underline the strong connections between emotional, cognitive and autonomic systems through the limbic system and suggest a possible activation of the autonomic system by stimulation of the STN.

### Clinical significance and consequences of autonomic effects

The existence of autonomic effects induced by subthalamic stimulation raises the question of their physiological significance and clinical consequences during chronic stimulation. The issue of the cognitive effects of chronic subthalamic stimulation is currently subject to conflicting findings although there is ground for thinking that the surgical procedure carries no major clinical consequences [5, 17, 27, 28, 32]. However, little is known about the effects of deep brain stimulation on mood and behavior. A few reports indicate that STN stimulation might induce mood changes or emotional disorders. In the immediate postoperative follow-up, most indicate improvement in depression [5, 32], disinhibition [32], hypomania or mania [19, 20, 30], euphoria and hilarity [19] when, in the long term, apathy is a frequent symptom [20, 32]. The fact that most teams have observed immediate postoperative behavioral disorders raises the issue of the direct influence of subthalamic stimulation on the limbic system. The occurrence of autonomic effects in the operating theater and immediately after surgery could be the only marker of limbic dysfunction and reflect a higher risk of post-operative behavioral or psychiatric disorders. With the prospect of a better screening of patients at risk, the autonomic effects of stimulation must be closely monitored, keeping in mind the anatomo-physiological correlations between limbic and autonomic structures.

At a time when the effectiveness of STN high-frequency stimulation for the treatment of PD appears to have been clearly acknowledged, optimizing the management of patients eligible for that type of surgery necessarily includes a better understanding of the effects of electric stimulation on non-motor physiological systems involving personality, behavior and cognitive functions. That reflection is all the more valid as new indications for the technique are being increasingly considered for the treatment of some psychiatric pathology such as compulsive obsessive disorders, where the behavioral and affective component is prominent.

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