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## Involvement of electrophysiological localization of the subthalamic nucleus in deep brain stimulation for Parkinson's disease

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**SUMMARY:** Involvement of electrophysiological localization of the subthalamic nucleus in deep brain stimulation for Parkinson's disease.

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*We studied the involvement of the electrophysiological localization of the subthalamic nucleus (NST) using a multi-unit recording technique by means of semi-microelectrode in a set of thirty Parkinson's patients who benefited from a bilateral stimulation of the NST and who were operated on under local or general anesthesia. The multi-unit recording technique by means of semi-microelectrodes appeared efficient, capable of improving the localization of the NST and leading to improvement in clinical results. We believe that the use of our technique will allow for time savings while providing good results, and that the choice of the angle of the trajectory will allow for improved localization of the NST and thus improved clinical results.*

**RIASSUNTO:** Ruolo della localizzazione elettrofisiologica del nucleo subtalamico in pazienti affetti da malattia di Parkinson sottoposti a stimolazione cerebrale profonda.

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*Abbiamo analizzato il ruolo della localizzazione elettrofisiologica del nucleo subtalamico (NST), utilizzando un sistema di registrazione multi-unitaria con semielettrodi in un gruppo di trenta pazienti affetti da malattia di Parkinson sottoposti a stimolazione cerebrale profonda del NST sotto anestesia sia locale che generale, valutando i risultati ottenuti e confrontandoli con i dati presenti in letteratura.*

**KEY WORDS:** Subtalamo - Stimolazione cerebrale profonda - Malattia di Parkinson.  
Subthalamus - Deep brain stimulation - Parkinson's disease.

### Introduction

Parkinson's disease is notably difficult to deal with in the advanced stages, with the apparition of dyskinesias, unforeseeable blockages and motor fluctuations. The discovery of L-DOPA had pushed functional surgery into the background during the 1970s. But the 1990s saw a resurgence of functional stereotactic neurosurgery after Benabids et al. described their experience of stimulating the thalamus (nucleus VIM) in the treatment of tremor, and Latinens et al. described their experience with pallidotomy (1). Later, Benazzouzes et al. showed, on two monkeys rendered Parkinsonian by means of administration of MPTP, that high-frequency stimulation of the subthalamic nucleus (STN), which is hyperactive in Parkinsonian monkeys, could reduce rigidity and bradykinesia (2). This

opened up new horizons for functional neurosurgery, while considering the STN as a possible target in the treatment of the Parkinson's disease (3). Since then, many Parkinson's patients have benefited from deep cerebral stimulation of the subthalamic nucleus.

The surgical technique consists of a radiological localization phase and a phase of electrophysiological recording. This recording has the goal of optimizing localization of the target while highlighting neuronal hyperactivity in this nucleus. The utility of this localization in terms of efficiency of stimulation remains to be demonstrated. Also, the goal of this study was to evaluate the role of electrophysiologic localization in the clinical results of Parkinson's patients treated with bilateral chronic stimulation of the NST and to try to define some factors predictive of the success of this therapeutic strategy. The particularity of this survey is that the electrophysiologic location did not consist of a unicellular recording of the neuronal activity pattern by means of microelectrode, but rather of a multicellular recording quantified using a semi-microelectrode.

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## Materials and method

### *Patients*

Our survey was of about 30 Parkinson's patients (15 women and 15 men) in an advanced stage of disease (average evolution length: 12.6 years), complicated by disabling motor fluctuations and dyskinesias caused by pharmacological treatment, and not having surpassed the age of 75 (average age at the time of the operation: 60.1 years; minimum 47 years, maximum 72 years).

### *Pre-operative situation*

One of the major criteria for setting surgical indications was the existence during a pre-operative L-DOPA test of an improvement of the Unified Parkinson's Disease Rating Scale version 3.0 (UPDRS III), score of more than 40% in the on-medicine state in relation to the off-medicine state. Patients were not required to present mood or higher function disturbances, the cognitive state being evaluated by means of neuron-psychological tests, in particular the Mattis Dementia Rating Scale. Cerebral RMN was normal, showing no signs of significant cortical atrophy.

### *Surgical procedure*

The patients abstained from taking anti-Parkinson's medications from the evening prior to surgery. Twenty (20) patients benefited from bilateral stimulation of the NST achieved in a single session, and 10 others in two sessions. The choice of the type of anesthesia was discretionary; no particular parameters guided this choice.

First, a Leksell's stereotactic system was put in place. Then, a 15 mm-diameter hole was drilled 2 cm in front of the coronal suture. Through this craniotomy, an electrode-needle could be lowered into the deep cerebral structures by means of a micropositioner in order to assure electrophysiological localization.

### *Surgical localization: 1. Radiology*

The location of the NST was first determined by magnetic resonance exam (MRI) with 1 to 2.5 mm scans. The data from the MRI were then integrated into the neurosurgical navigation system. An initial localization of the subthalamic nucleus was thus permitted by the observation of the axial MRI sections in T2 weighted images.

A ventriculography was done with the goal of allowing a second localization of the NST, more indirect than the MRI, according to standardized anatomical coordinates. The NST is considered to be located 10.5 to 12 mm outside of the bi-commissural line (ÇA-CP) (x coordinate), 11 mm before the posterior corner (CP), that is to say 0 to 3 mm behind the middle of this ÇA-CP line (y coordinate) and 4 to 5 mm below it (z coordinate) (4). The vertical approach angle (on the sagittal plane) and the horizontal approach angle (on the anterior-posterior plane) were measured on the radiological series obtained during surgery. The stereotactic coordinates of the target were calculated using Schaltenbrand's atlas (5).

### *Surgical localization: 2. Electrophysiology*

The multi-unit electrophysiological recording of the activity of the NST was done by means of a semi-microelectrode, and the implantation of the electrode was bound to the detection of the characteristic neuronal hyperactivity of the STN. Recordings began at a depth 10 mm below the theoretical target and were all done in millimeters.

During the trajectory, the only neuronal structures that could be recorded were, in order, the thalamus (reticular nucleus), the NST (separated from the previous structure by the zona incerta) and the locus niger. The traversal of a neuronal group corresponded to a straightforward increase of the amplitude of the signal.

The recorded signal was analyzed in 10 one-second samples by means of the Phasis II device signal analysis program.

The background noise level being 0.7 mV, neuronal hyperactivity

was defined as the recording of a signal of more than 1.4 mV in amplitude. Obtaining this value of amplitude on at least four consecutive millimeters represented for us the major criteria of a good electrophysiological signal of the NST in its main axis. In the case of an unsatisfactory trajectory, a second trajectory was achieved, anterior, posterior, lateral or medial to the first, according to available radiological images.

### *Surgical localization: 3. Clinical*

Among the patients operated on under local anesthesia, the effect that the stimulation of the target produced on the symptoms of the illness was evaluated by means of clinical tests.

The evaluation took into account the rigidity of upper and lower limbs, simple but timed manual tasks, modifications of tremor and the appearance of intervening undesirable effects.

After location of the good trajectory, the definitive stimulation electrode was put in place and bound by subcutaneous cables to a programmable Rell II Medtronic (USA) battery, generally placed below the clavicle. This procedure was applied bilaterally, in one or two operative phases, as we indicate below.

### *Post-operative clinical assessment*

Patients' clinical state was evaluated one year after the surgery using the UPDRS III. The assessment took place at 9 o'clock in the morning after a 12-hour interruption of the anti-Parkinson's medicines in the following order: off-medication/off-stimulation, off-medication/on-stimulation, one medication/off-stimulation and finally one medication/off-stimulation. Finally, pharmacological treatment in terms of L-DOPA dose was indicated.

### *Parameters analyzed and statistics*

Various parameters were analyzed, in every case with the population separated into two groups:

- clinical results of the comparison of the UPDRS scores between the off-medication/off-stimulation and off-medication/ on-stimulation conditions: good in the case of reduction of the score superior or equal to 55%; bad in the case of reduction inferior to 55%;
- quality of the electrophysiological localization: good in the case at least four values of more than 1.4 mV bilaterally were obtained; bad in the contrary case;
- type of anesthesia, local or general;
- the value of the "vertical" angle of the trajectory on the coronal plane: less than 15°; superior or equal to 15° (average of the right and left values);
- the value of the "horizontal" angle on the sagittal plane: less than 50°; superior or equal to 50° (average of the right and left values);
- the improvement of UPDRS scores in one-medicine condition during the preoperative L-DOPA test: good in the case of reduction of the score superior or equal to 60%; bad in the case of reduction less than 60%.

The values of the different parameters for each of the pairs of subgroups were compared by means of a non-parametric Mann-Whitney matched test for the numeric values and by means of a Fisher test for the qualitative values (type of anesthesia). Finally, in order to retrospectively study the influence of the type of anesthesia used and the value of the angle of trajectory, matched subgroup analysis was done for both of these factors.

## Results

With regard to anesthesia, 13 patients were operated on under local anesthesia and 17 patients under general anesthesia. No undesirable effects were observed in our

patient set during the operation or during the short- or long-term post-op periods. One year after surgery, the average improvement ( $\pm$  gap-type) of the UPDRS score in the on-stimulation/off-medicine state was  $54.5\% \pm 15.2$  (from 34.0 to 81.8%) in relation to the off-stimulation/off-medicine state. The reduction of the consumption of L-DOPA was  $58.9\% \pm 26.0$ . The 15 best results corresponded to an improvement of nearly 64% in UPDRS score with a reduction of the doses of L-DOPA of about 70%. All patients presented a supplementary gain in the one medication/on-stimulation condition.

The average number of trajectories was 2.0 on the right and 1.7 on the left. The length of recording time for each trajectory was approximately 20 minutes. In 29 cases (48.3% of the cases) the first trajectory was immediately satisfactory. The maximum number of trajectories was 5 in one case and 4 in two other cases. The average angles were  $15.2^\circ \pm 5.9$  for the "vertical" angle of the trajectory on the coronal plane, and  $49.6^\circ \pm 8.8$  for the "horizontal" angle of the trajectory on the sagittal plane. The number of good electrophysiological localizations, established by more than 4 points of the 1.4 mV superior amplitude trajectory; bilaterally, was assured for 18 patients (60% of the cases).

#### *Parameters associated with clinical improvement*

In comparing the patients according to the percentage of improvement in the UPDRS score between the off-medication/off-stimulation and off-medication/on-stimulation conditions, the only meaningful predictive criteria was quality of the electrophysiological localization.

#### *Parameters associated with electrophysiological localization*

In comparing the patients according to the quality of the electrophysiological localization as established by the recording of at least 4 points of amplitude superior to 1.4 MV bilaterally, the only significantly different criteria was the magnitude of post-operative clinical improvement shown in the UPDRS score in the on-stimulation state.

#### *Parameters associated with the type of anesthesia*

In comparing the patients according to the type of anesthesia (local or general), the only significant criteria were the value of the "horizontal" angle of the trajectory on the sagittal plane and the quality of electrophysiological localization

#### *Parameters associated with the angle of the trajectory*

In comparing the patients according to the value of the "vertical" angle on the coronal plane, the only significant criteria were the value of the "horizontal" angle of the trajectory on the sagittal plane and the quality of the electrophysiological localization

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gnificant criteria were the type of anesthesia and the quality of the electrophysiological localization.

#### *Parameters associated with the results of the preoperative L-DOPA test*

In comparing the patients according to improvement in the UPDRS score in the one-medicine condition during the preoperative L-DOPA test, the only significant criterion was the value of the "horizontal" angle of the trajectory on the sagittal plane, which did not appear applicable with regard to the analysis.

#### *Respective influence of anesthesia and angle of trajectory on electrophysiological localization and clinical results*

As the type of anesthesia and the value of the angle of the trajectory appeared to be factors that influenced electrophysiological localization, and since this last factor was the only explanatory factor of the quality of the post-operative clinical result, we wished to compare the respective influences of these different factors, while forming matched groups, either based on the type of anesthesia or on the angle of the trajectory.

With regard to the type of anesthesia used, it appears that the value of the vertical angle influences the quality of electrophysiological localization ( $P = 0.001$ ), but not the clinical result ( $P = 0.507$ ). The value of the horizontal angle does not influence the electrophysiology ( $P = 0.293$ ), nor the clinical result ( $P = 0.535$ ).

With regard to the angle of the trajectory, it appears that local anesthesia has the tendency to improve the quality of electrophysiological localization ( $P = 0.067$  and  $0.018$  matching the vertical and horizontal angles, respectively), but without influencing the clinical result ( $P = 0.931$  and  $0.729$ ).

## **Discussion**

The results of this study show that electrophysiological localization is important for the localization of the NST and is the determinant factor for the clinical efficiency of this therapeutic strategy, a result which is in agreement with the findings in other studies on this topic (7), but which also shows that recording with semi-microelectrodes is an adopted technique that can lead to results comparable to those obtained with other techniques. Recording by semi-microelectrodes is a simple and fast method, and its efficiency has already been proven in the localization of the VIM (8). This technique, unlike single-unit recording, has the disadvantage of being unable to recognize the nature of the cells recorded, and the neuronal discharge "pattern" cannot be characterized. However, it appears sufficiently precise to achieve the objective of localizing the NST.

The clinical results presented here are comparable to

those in the literature and show an improvement of post-operative UPDRS scores in the on-stimulation/ off-medicine condition of 59.3% among patients who were well-marked electrophysiologically, with a 68% reduction in utilization of L-DOPA or its equivalents. (9).

Some studies have shown that the target identified on the IRM is not always the one that gives the best response (10), hence the interest in using electrophysiological localization for a better localization of the target, especially since the use of electrophysiological techniques allows for the analysis of the clinical effects of the stimulation of the target during the operation, when said operation is performed under local anesthesia (11).

Thus, electrophysiology corrected about 50% of the initial trajectories, determined by radiological criterion. Neurophysiological techniques are the only ones that allow target localization to be ensured.

The multi-unit electrophysiological technique that we used is fast, compared to the techniques of unit recording, and is also quantified. The characteristics of the signal we chose were obtained from a method of quantification of the electromyographic signal, in the interest of making it available on all EMG machines.

The criteria of selection of the Parkinson's patients stimulation of the NST, like sensitivity to L-DOPA, does not seem to be a factor that impacts electrophysiological localization or the clinical result, which converges with data in the literature (12).

In our patient set, type of anesthesia was not a factor of influence on the clinical results, but allowed for im-

proved electrophysiological localization. Thus, local anesthesia improved neurophysiologic localization but was not sufficient to improve the clinical results. However, some authors prefer to operate in local anesthesia because it permits microelectrode analysis of unit neuronal activity during passive or active movements in order to refine the localization of the NST (11).

The most applicable criteria in the improvement of electrophysiological localization appear to be the angulations of the trajectory on the coronal plane. This is of course in relation with the spatial orientation of the NST. Prior to surgery, it was necessary to determine this spatial orientation of the NST according to imagery data in order to adapt the angulations of the trajectory to each patient, and to permit "traversal" of the NST at its largest axis.

## Conclusions

The electrophysiological localization of the NST is of a crucial importance for good localization of the target. The technique of recording using semi-microelectrodes is an efficient and adaptable one which achieved good clinical results. Our survey shows that one of the most important predictive factors for electrophysiological localization is the vertical angle of the trajectory on the coronal plane. A  $>15^\circ$  angle improves electrophysiological localization and will in all probability allow for improvement in clinical results.

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