

Targeting the basal ganglia for deep brain stimulation in Parkinson's disease

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Article abstract—The revitalization of surgery for Parkinson's disease (PD) has fueled discussion about the best methodology to define the target. Placement of electrodes for deep brain stimulation (DBS) requires the usual stereotactic technique but the argument is mainly centered on whether or not microrecording neuronal activity is necessary. We compared the accuracy of calculating the coordinates X (medio-lateral) and Y (rostral-caudal) considered by the classic stereotactic method, i.e., definition of the AC-PC intercommissural line by MRI and a digitized version of the Schaltenbrand's atlas, with final electrode placement according with microrecording and microstimulation in 21 patients. For both the globus pallidum internum (GPi) ($n = 21$) and the subthalamic nucleus (STN) ($n = 36$) there was, respectively, a 43% and 45% mismatching of more than 3 mm between the theoretic coordinates and the final site of electrode location. This applies to both the X and Y planes. Accuracy was not improved in patients ($n = 11$) in whom the bilateral procedure was undertaken in a single day. We conclude that proper electrode positioning of the STN and GPi requires fine electrophysiologic assessment. **Key words:** Stereotactic techniques—Microrecording—Stimulation—Targeting—Basal ganglia surgery.

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There is presently a vigorous debate about the most convenient method for locating the target for both ablative surgery and deep brain stimulation (DBS) in the treatment of Parkinson's disease (PD). The classic approach has consisted of defining the coordinates by imaging methods such as ventriculography and, more recently, by CT and MRI of the brain. Functional neurosurgeons also use macrostimulation with the lesioning probe as a means of physiologic assessment. The reintroduction of surgery for PD rests on the concept of reducing the increased neuronal activity in the sensorimotor region of the globus pallidum internum (GPi) and subthalamic nucleus (STN).¹ This is mainly achieved by applying the microrecording-guided technique,² an approach that is not universally accepted as an essential requirement for routine surgical procedures in PD.^{3,4}

This adverse opinion is especially raised when DBS is to be applied. The technique of DBS offers the possibility of assessing the correct placement of the electrode by intraoperative monitoring of the clinical changes in parkinsonian signs, a feature that *a priori* should reduce the need for detailed functional assessment. The relative ease in obtaining adequate control of tremor without microrecording when electrodes are implanted in the ventralis intermedius nucleus (Vim) of the thalamus has probably contributed to strengthening this point of view. However, surgery of the thalamus is quickly disappearing

as a choice for PD, and therefore this type of experience adds little to the argument.

The essential point is whether or not definition of the target is mainly anatomic (imaging) or requires physiologic (microrecording and microstimulation) support. Regarding the latter, some experienced teams, including some of the authors (BN and JG), believe that macrostimulation without microrecording is enough to place the electrodes. This is a rapidly changing theme. Recent experience with targets such as the STN and GPi in patients without tremor is forcing many teams to acquire more sophisticated techniques. We review our experience in approaching the STN and GPi to apply DBS for the treatment of PD.

General principles of targeting and DBS. The overall procedure is divided into various steps: (a) image acquisition and coordinate calculation; (b) mapping the region to be operated on; and (c) electrode implantation.

(a) The Leksell model G stereotactic frame is commonly used, but several other models are used around the world. Once the frame has been placed on the skull under local anesthesia, a CT brain scan or an MRI is performed to locate the coordinates of the anterior and posterior commissures (AC and PC). These coordinates and the length of the intercommissural (AC-PC) line are fed into a computer program of the digitalized sagittal stereotactic map from the

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Shaltembrand-Bailey atlas, which generates a sagittal map of the region to be targeted. In a few centers, contrast-positive ventriculography is carried out a few days before surgery to assess the AC-PC line and coordinates.

(b) Physiological corroboration of the target is necessary to ensure proper placement of the electrode. This can be achieved by two different approaches. (i) Macroelectrode stimulation: With this technique, an electrode with a tip of 1 to 1.5 mm generates a large electrical pulse on the order of 0.5 to 1.5 mAmps or 1 to 10 Volts. Macrostimulation is quick and relatively easy to implement. It allows the establishment of the boundaries of the targeted nucleus with respect to adjacent structures (i.e., internal capsule, sensory radiation, optic tract) that should not be included within the electromagnetic field produced by the implanted electrode. Macrostimulation does not enable recognition of the somatotopic organization or the anatomic limits of the nuclei; (ii) Microrecording and microstimulation (10–100 μ Amps, 0.2–0.7-ms pulse, 200–300 Hz); this is performed with an electrode (platinum–iridium or tungsten) whose tip is about 10–20 μ m and which has an impedance of 0.3 to 1 MOhms at 1,000 Hz. Mapping is possible only by microrecording. This consists of precisely defining, for each nucleus, the sensorimotor region and its somatotopic arrangement and the borders of the surrounding nuclei and pathways. The sensorimotor region is delimited by recording the increases (“driving”) in neuronal discharges on passive manipulation of the limbs and during active movements. In the STN and GPi, the arm and face are in the most lateral region and the leg slightly more medial. The reverse is the case for the Vim, where the leg is lateral to the arm.

(c) Implantation of the electrode in the sensorimotor region is the ultimate goal of the procedure. There are currently two electrodes for DBS in PD; both are quadripolar but differ in the distance between active sites. The one chosen for STN stimulation has a total length of 7.5 mm and 0.5 mm between consecutive stimulation sites; the other is 10.5 mm in length and has an interval of 1.5 mm. Both models have a diameter of 1.27 mm. The electrode is placed into the intended target under X-ray control, with the beam orthogonal to the stereotactic frame.

Before definitive positioning to the skull, the electrode is connected to an external pulse generator to test the therapeutic action of stimulation and the possible occurrence of adverse effects. Some teams use antiparkinsonian effectiveness as the most valuable indicator in deciding where to definitively locate the electrode. In our experience, this is easy in patients in whom tremor is still present at this stage of the procedure, but in some of them there is little or no tremor at all as a result of the mechanical effect of the microelectrode and the stimulation electrode. In addition, the operating room setting precludes accurate evaluation of patients with bradykinesia of

the limbs or axial symptoms, or both, as main clinical features. We therefore rely more on the mapping procedure for placing the electrode and use intraoperative stimulation mainly to ensure the absence of important side effects.

Targeting the STN. The STN is an ovoid nucleus that, in humans, has a volume of about 150 to 200 mm³. The usual coordinates are 2 to 3 mm behind the midintercommissural point (AC-PC line) in the rostro-caudal plane (Y coordinate), 11 to 13 mm lateral to the intercommissural line (X coordinate), and 4 to 6 mm below this line (Z coordinate). When microrecording is used, a typical track (45 to 50 degrees with respect to the AC-PC line) toward the STN successively consists of neuronal activity in the striatum (caudate nucleus), low-amplitude fiber activity while passing through the internal capsule (anterior arm), a modest increment in activity due to medium size (50 to 200 μ Volts) fiber potentials 1 to 3 mm before reaching the STN, and a robust increment in the electrical recording on entering the nucleus (figure 1). When the cannula is more caudal, thalamic activity corresponding mainly to the reticularis nucleus is recorded for several millimeters before penetrating the fiber zone and subsequently the STN (figure 2). Therefore, the caudal approach is less convenient because it leads to greater difficulty in deciphering the dorsal boundary of the STN and because the region of the zone incerta (caudal to the STN) is abundant in neurons with large-amplitude action potentials, which may be confused with neurons of the STN. The STN is somatotopically organized. All neurons with sensorimotor responses are in the dorsolateral region of the STN (figure 3A). Therefore, movement-related neurons are very seldom in planes medial to 12 mm of the AC-PC line and in the ventral third of the nucleus. Neuronal activity in the STN in PD can be separated into three main types:^{5,6} (a) irregular discharges at a frequency of 20 to 30 Hz and periods of high-frequency firing, which may reach an instantaneous rate as high as 200 Hz. These cells are the ones most commonly recorded in the STN (65%); (b) units with a regular tonic pattern of activity, discharging at about 50 Hz; and (c) slow, rhythmical oscillatory activity with a bursting activity at about 2 Hz. Cells with the irregular and tonic patterns of discharge are found in the dorsolateral region of the nucleus and can be activated by passive or active movements. On the contrary, rhythmical cells in slow burst are more frequently found in the ventral region of the nucleus and have no sensorimotor responsiveness. In addition, in patients with tremor during the surgery, it is possible to record tremor-related neurons characterized by rhythmical oscillatory activity time-locked with the EMG discharges underlying the tremor. Once neuronal activity in the STN ceases, there is usually some 0.5 to 1 mm of electrical silence, followed by recording of the tonic high-frequency activity of the substantia nigra reticulata (SNr). Microstimulation of the STN is ac-

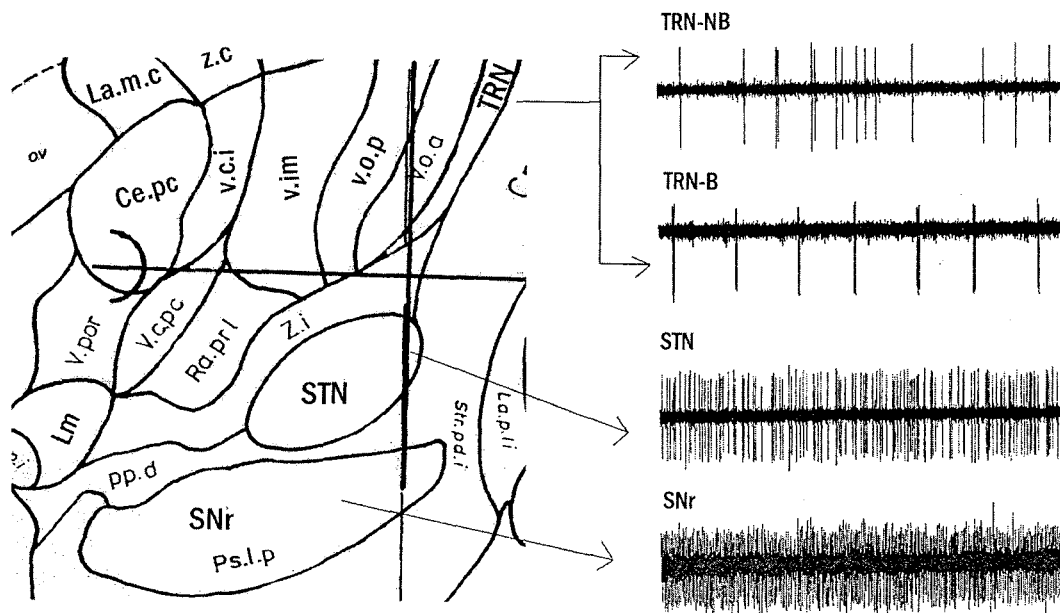


Figure 1. Single-cell recording during a typical track to target the subthalamic nucleus (STN). The microelectrode first passed through the thalamic reticular nucleus (TRN), where neurons discharge spontaneously with an irregular slow pattern (TRN-NB) but also with a bursting pattern (TRN-B). Further down, the characteristic high-frequency discharges of the STN appeared. Below the STN, neurons from the substantia nigra pars reticulata (SNr) are recorded. From Hutchinson and Lozano,¹¹ with permission.

accompanied by tremor arrest in a somatotopically organized fashion when the tip of the electrode is in a region in which tremor-related cells are present.⁷ Motor benefit may also be observed in some other parkinsonian signs, such as rigidity and bradykinesia. The most common side effects evoked by stimu-

lation in this region are tingling and cortico-spinal responses. Less frequently, oculomotor tonic responses, nausea, dysarthria, and changes in the respiratory rhythm are observed. Dyskinesias during microstimulation can be elicited. Their presence, in accord with the large experience of the Grenoble group, is an excellent sign of adequate targeting.

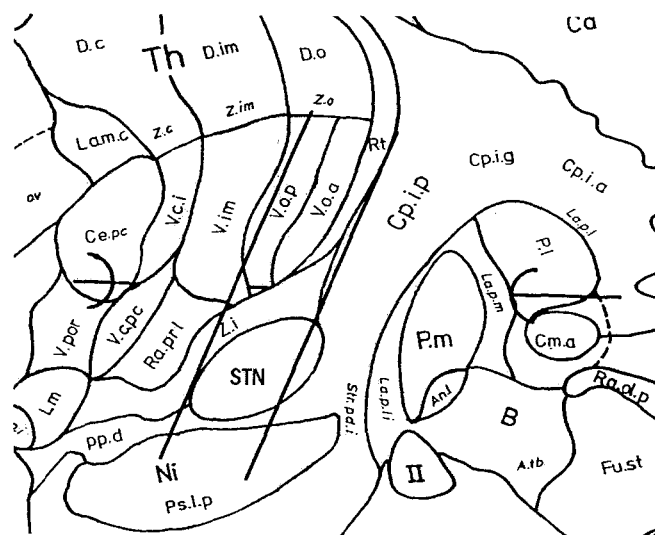


Figure 2. Stereotactic trajectory toward the subthalamic nucleus (STN) represented on a sagittal view of the Schaltenbrand and Wahren atlas with a laterality of 14 mm. Two trajectories are illustrated. The initial one was too caudal and went through a large portion of the thalamus reticular nucleus (Rt) and zona incerta (Zi). The second, more rostral one passed down the internal capsule, impinging only slightly on the Rt, and entered into the STN.

Targeting the GPi. The GPi is a banana-shaped structure surrounded by the globus pallidum externum (GPe) dorsolaterally, the internal capsule caudally and the optic tract ventrally. The estimated volume of the GPi in humans is about 500 mm³. The usual coordinates are 20 to 21 mm lateral to the intercommissural line (AC-PC line) (X coordinate), 5 to 6 mm above the intercommissural line (Z coordinate), and 3 mm in front of the mid-intercommissural point in the rostrocaudal plane (Y coordinate).

A typical recording track (45 to 50 degrees with respect to the AC-PC line) toward the GPi begins with striatal neuronal activity (figure 4). Typically, it is characterized by scarce spontaneous activity but by activity provoked by movements of the microelectrode, which triggers high-frequency action potentials for a short period of time. The striatum (putamen in this instance) is separated from the GPe by "border" cells. These are large neurons with high-amplitude (300 to 400 μ V), wide-duration action potentials and discharge at a low frequency with a tonic pattern.² Neuronal activity in the GPe consists of two distinct patterns of spontaneous activity. There are slow bursts (around 10 Hz) of high frequency discharges ("burster" neurons) and units that discharge with an irregular pattern, characterized

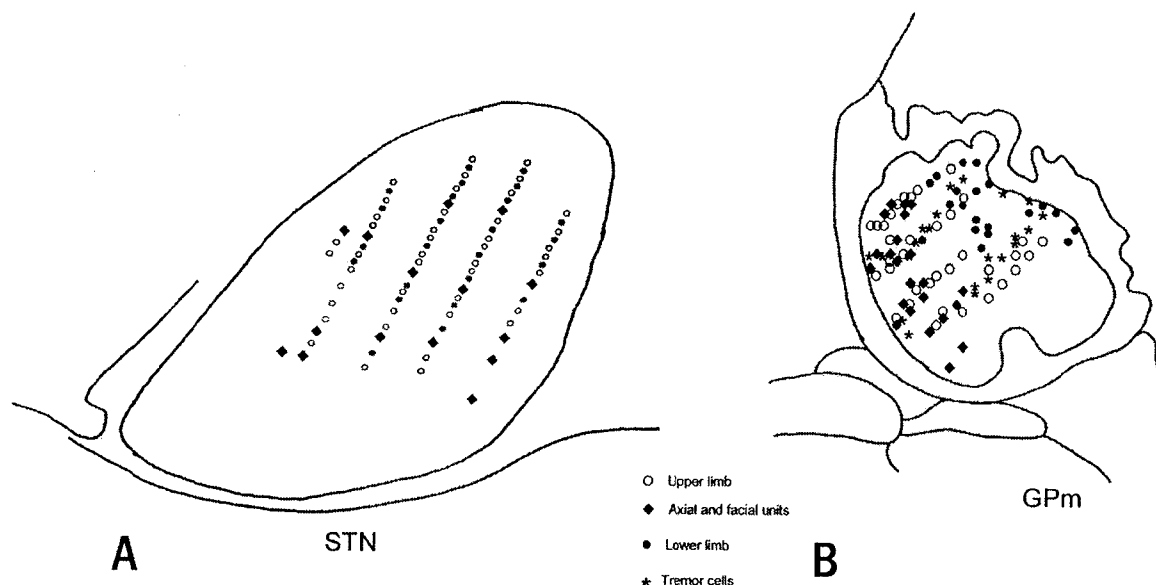


Figure 3. Schematic representation of the somatotopic arrangement of the subthalamic nucleus (A) and globus pallidus internum (B) in Parkinson's disease. The sensorimotor region in both nuclei lies in the lateral portion; also note that the somatotopic organization is similar, with the leg dorsal and medial with respect to the arm and face.

mainly by high-frequency activity and variable periods of silence or "pause."

The GPe is separated from the internal segment of the globus pallidum (GPi) by a lamina of white matter approximately 1 mm thick. It is recognized by a suppression of the previous neuronal activity and the recording of border cells in its vicinity. In the GPi, neurons have a tonic pattern of discharge with a

higher frequency than the GPe (about 82 Hz in patients with PD), and some units fire in synchrony with tremor (figure 4). Below the pallidal complex and separated by 1 to 2 mm of silence or fiber activity corresponding to the ansa lenticularis, the optic tract is found. There is usually no spontaneous activity recorded from the optic tract, although sometimes monophasic spikes corresponding to fibers can be

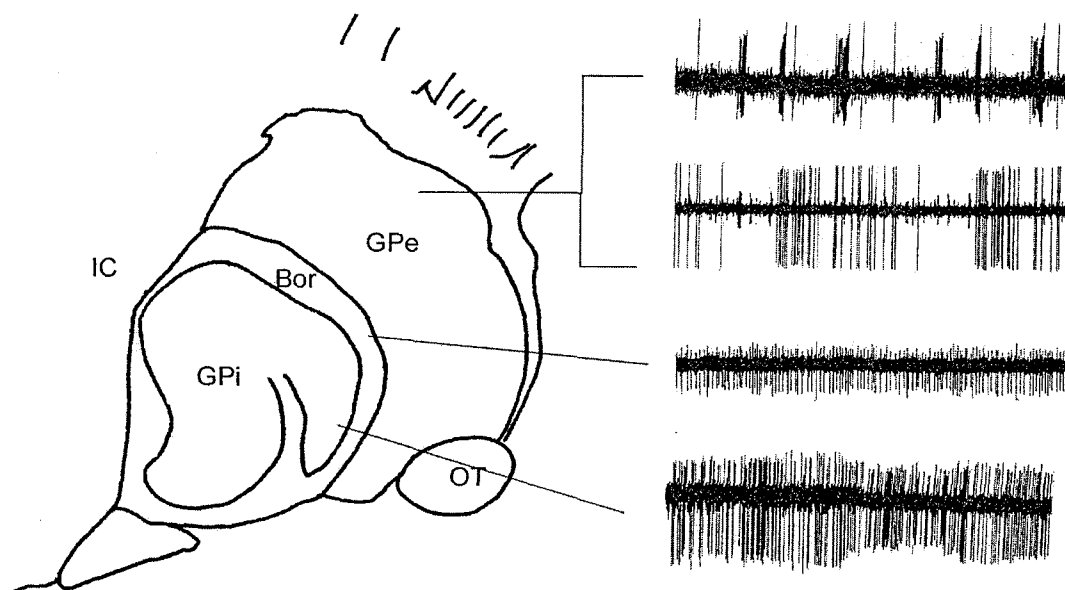


Figure 4. On the left, a characteristic single cell recording of a typical track targeting the globus pallidus internum (GPi). The microelectrode passed successively through the striatum, globus pallidus externum (GPe), lamina where border cells are recorded, and finally entered into the GPi, where a high-frequency tonic neuronal activity is recorded. In this example, tremor-related cells (bottom) are also shown to discharge in phase with the tremor in the hand recorded with the accelerometer. On the right, the trajectory followed by the microelectrode is depicted on a sagittal view of the Schaltenbrand and Wahren atlas. Note the ventral position of the optic tract (OT) with respect to the GPi. From Hutchinson and Lozano,¹¹ with permission.

found. When the microelectrode is near (approximately 500 μm) or within the tract, flash stimulation of the retina evokes a volley of action potentials that can be clearly recognized through the loudspeaker. In addition, microstimulation evokes visual sensations at currents of less than 20 μAmp .

The sensorimotor region of the GPi lies in the rostralateral half of the nucleus. The somatotopic organization of the GPi has now been analyzed in detail.⁸ The leg lies dorsally, the face ventrally, and the arm in between. Most neurons corresponding to the arm and face are in the lateral planes (21 mm or more), whereas neurons for the leg are more evenly distributed from planes 18 to 23 approximately (figure 3B). Tremor-related neurons are also present in the GPi.⁹ In general, they maintain a somatotopic distribution similar to the one described above for kinesthetic responses.

Accuracy of targeting the STN and GPi. Guridi et al.⁸ implanted 36 stimulators in the STN in 20 patients and 21 stimulators in the GPi in 11 patients. The theoretic versus the final coordinates for placement of the stimulators were compared. The theoretic coordinates were calculated by MRI according to the method described above, and the final coordinates were defined as those corresponding to the point at which the electrode was located by microrecording. For each stimulator, the analysis was made in the X and Y coordinates, taking into account the difference in millimeters between the calculated and the real position of the electrode. According to theoretic calculations and experimental data,¹⁰ the electrical field generated by the stimulation with the implanted electrode (common parameters 2.6 to 3.6 Volts, 60–90-ms pulse width, and 130–160 Hz) has a radius of 1.5 mm. We assume that a difference of more than 1.5 mm between the theoretic and the final electrode position would have led to placement of the stimulator off target and is considered for the purpose of the analysis as a *targeting error*. In patients in whom the bilateral implant took place the same day, the degree of symmetry between final electrode placements was also analyzed.

STN implants ($n = 36$). Twenty-five electrodes were located more than 1.5 mm away from the intended target either in the X (four cases) or Y coordinates (eight cases) or even in both coordinates (13 cases). This represents a 69.44% inaccuracy of the classic stereotactic method with regard to physiologic evaluation. Such a deviation becomes particularly important when the mismatching between the theoretic and actual coordinates is greater than 3 mm ($n = 16$, 44.44%). This means that the electrical field generated by the electrode would have not reached any portion of the area physiologically defined as optimal.

For the X coordinate (figure 5A), the mean deviation of the theoretical target was 1.52 mm (range 0–4). Twelve electrodes were placed in the theoretic coordinates (targeting deviation 0). The final position

in 11 stimulators was medial (mean deviation 2.13 mm, range 1–4) to the intended target and in 13 cases it was lateral (mean deviation 2.42 mm, range 1–4). Overall, in this coordinate there was a targeting error in 17 electrodes.

For the Y coordinate (figure 5B), the mean deviation was 2.31 mm (range 0–7). Targeting deviation was 0 in 6 implants. There was an anterior deviation (mean error 2.63 mm, range 1–6) in 22 implants and a posterior deviation (mean error 3.18 mm, range 1–7) in eight procedures. The total number of cases with a deviation greater than 1.5 mm was 21.

Bilateral targeting. In 18 electrodes corresponding to nine patients with bilateral implants performed in the same surgical operation, we found a targeting error in seven procedures for the first side and six for the second side.

GPi implants ($n = 21$). Sixteen stimulators were placed at a point more than 1.5 mm away from the calculated coordinates either in the X coordinate (three cases) or the Y coordinate (10 cases) and even in both coordinates (three cases). This represents a 79% of mismatching between the theoretic and real targets. In nine cases (42.85%), the distance between the real and the theoretic coordinates was more than 3 mm, indicating again that the electromagnetic field would have not reached the intended target.

The mean deviation between the theoretical and the final position of the electrodes was 1.5 mm (range 0–3.5) in the X coordinate (figure 6A), always in the lateral direction. In 11 procedures there was no targeting deviation. In six cases there was an error greater than 1.5 mm, therefore regarded as targeting error. For the Y coordinate (figure 6B), the mean deviation was 2.35 mm (range 0–7). There were four electrodes with no targeting deviation. In two implants the deviation was anterior (mean deviation 3 mm, range 1–5) and in 15 it was posterior (mean error 2.9 mm, range 1–7) to the final location. There were 13 instances of target error in this coordinate.

Bilateral targeting. Twelve stimulators were implanted on the same day in six patients. Targeting errors occurred in five instances on the first side and two on the second side.

Conclusions. Microrecording is probably the most accurate if not the only approach to defining the boundaries of the STN and GPi and their sensorimotor region, which in theory coincide with the ideal coordinates to locate the stimulation electrode for DBS in PD.¹¹ This technique has a high degree of accuracy and prolongs the overall duration of the procedure only by a fraction of time. In fact, the extra time consumed by intraoperative mapping is probably compensated by a more precise electrode placement and by avoiding the hazards of making several penetrations with the macroelectrode or even not being able to find the target by relying solely on macrostimulation. The latter approach, the use of stimulation as the only physiologic assessment, may

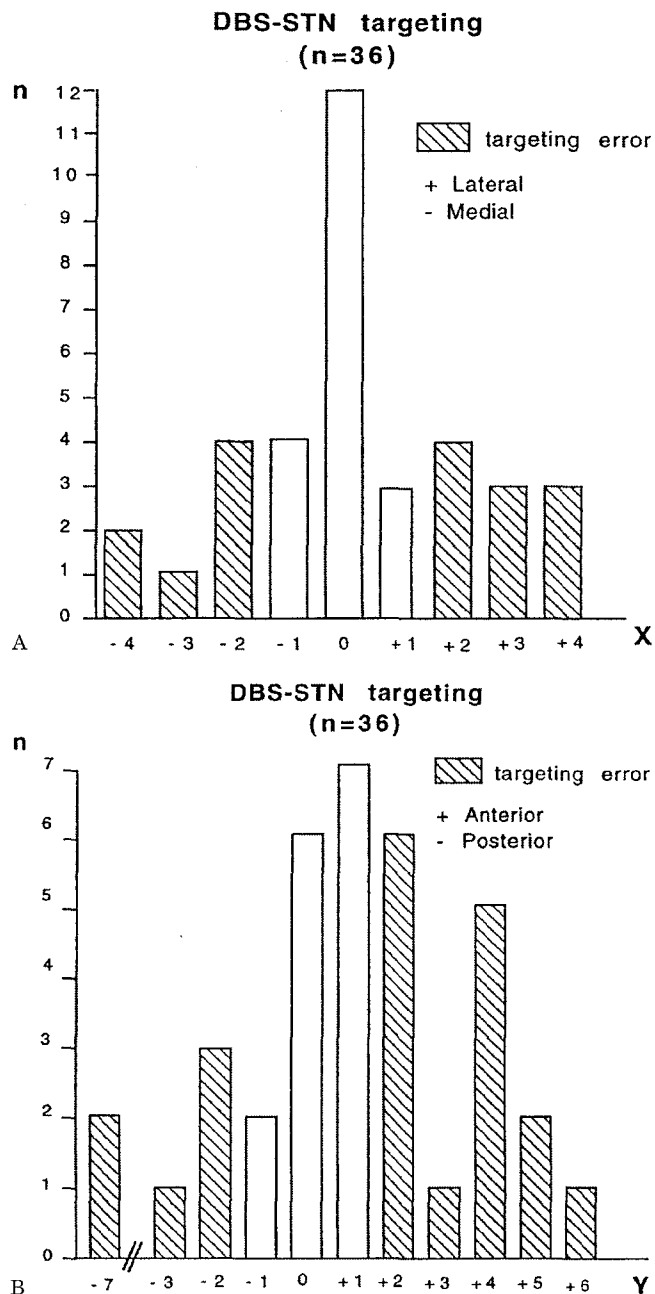


Figure 5. Diagram showing the deviation expressed in mm between the final and the theoretic points for placing the stimulator in the X (A) and Y (B) coordinates of the STN. Shaded bars represent the cases in which the deviation is greater than 1.5 mm, corresponding to targeting error.

be particularly compromising when the condition of the patient during surgery does not allow his or her collaboration, or when there is a preponderance of symptoms that are impossible to assess during the intervention (e.g., gait, axial symptoms).

It must be admitted that the above considerations involving the best methods to target the basal ganglia are still a matter of debate, particularly with regard to DBS. The table summarizes the main pros and cons of both methodologies. The data presented

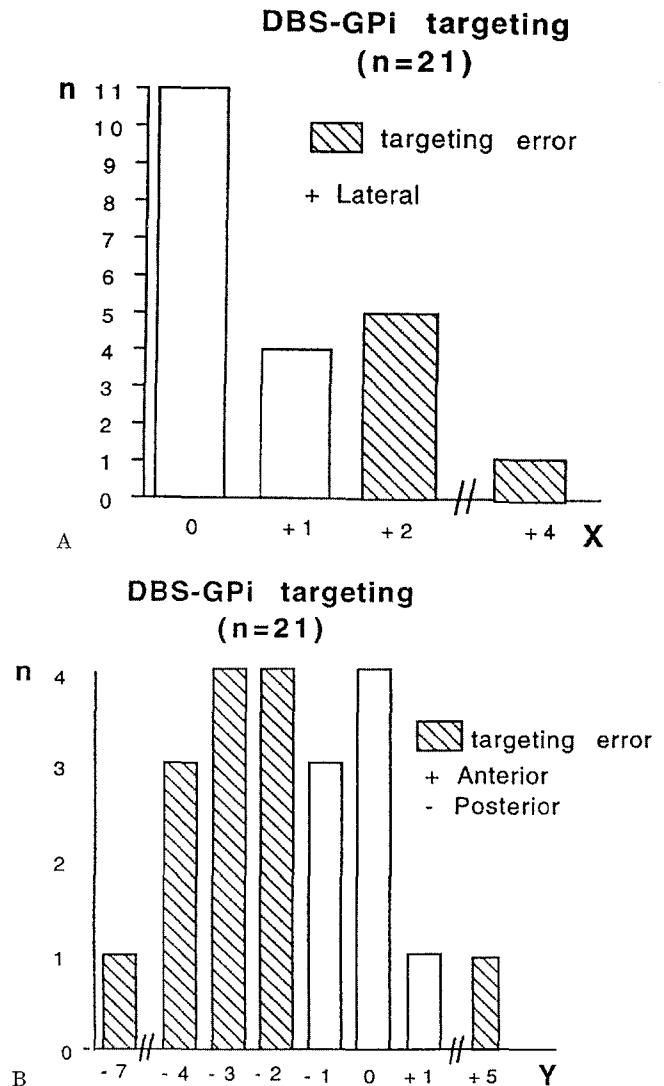


Figure 6. Diagram showing the difference expressed in mm between the actual and theoretic points for stimulator placement in the X (A) and Y (B) coordinates when the GPi is targeted. The cases in which the deviation is greater than 1.5 mm (targeting error) are represented in shaded bars.

in this article suggest that targeting by imaging alone may have an error rate as high as 75% of the implants. However, in the majority of cases (64.28% for the STN), the initial track was within the targeted nucleus even when the final coordinates did not generally coincide with those chosen initially. The crucial point in this regard is defining how precise electrode location must be to achieve the best results. The stimulation electrode generates an electromagnetic field that impinges on a relatively large volume in a current-dependent fashion.¹² This can be taken to suggest that getting into the targeted nucleus is sufficient to guarantee clinical benefit. Data to support or negate this assertion are not available. However, we believe that optimal location of the sensorimotor region by microrecording has a number of benefits. First, it considerably reduces or avoids the

Table Microelectrode recording and stimulation for physiologic localization in stereotactic surgery

	Electrical stimulation		Microelectrode recording	
	Macrostimulation	Microstimulation	Low Impedance	High Impedance
Safety	High	High	High	High
Speed of exploration	Rapid	Medium	Medium	Slow
Radius of current spread	To 3 mm	? to 1 mm		
Dependence on patient cooperation	High	High	Low	Low
Ability to record and stimulate with same tip	No	Yes	Yes	Yes
Ruggedness for repeated use	High	High-medium	High-medium	Medium
Sophistication of back-up equipment and activities	Low	Medium	Medium	Medium
Ability to detect somatotopy	None	Low	Medium	Exquisite
Variety of structures identified	High (includes fibers)	High	Low (excludes fibers)	Low (excludes fibers)
Ability to functionally compartmentalize identified structures (e.g., ventrobasal complex)	No	No	Medium	High
Ability to identify nearby structures	Good	Poor	None	None
Risk for technical problems, cost	Very low	Medium	Medium	Medium-High
Difficulty in solving problems of anatomic-physiologic variation	Medium	Medium	Medium	High

exhausting and frequently difficult task of intraoperative clinical evaluation. This contributes to shortening the entire duration of surgery. Second, it makes programming of the active leads simpler and quicker in the postoperative period. Third, it tends to reduce the electrical current needed for achieving adequate clinical results, avoiding stimulation of the adjacent structures and the associated adverse events. Fourth, the need for small current amplitude leads to longer battery life and reduces the long-term cost of the technique. Therefore, an increasing number of centers accomplish their surgical DBS protocol for PD with microrecording.¹³⁻¹⁶ The present experience by several groups indicates that a significant benefit on the parkinsonian signs was achieved with DBS of the STN or GPi, without important adverse events. This is a crucial point, because the major argument against microrecording is the risk for bleeding, which increases with the number of passes into the brain. In a recently finalized multicenter study evaluating the effect and safety of DBS of the STN and GPi, it was found that patients with intracranial hemorrhages had a higher mean number of penetrations than those without bleeding.¹⁷ However, an increased number of passes into the brain is also directly related to poor targeting by imaging, less surgical experience, and prolonged intraoperative time, all of which are also factors to consider in relation to intracranial bleeding.¹⁸

In conclusion, microstimulation and microrecording probably represent the more accurate method for placement of stimulation in the surgical treatment of PD,^{2,4,11,19} optimizing the clinical response to DBS. However, this method does involve more complex

and demanding technical arrangements than macrostimulation alone.²⁰ In the near future, imaging techniques will improve tremendously, which will help ensure an excellent stereotactic definition of the basal ganglia nuclei. Whether or not this will negate the need for sophisticated electrophysiologic intraoperative assessment remains to be determined by appropriate clinical trials.

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