

UNILATERAL SUBTHALAMIC NUCLEUS LESIONING

A safe and effective treatment for Parkinson's disease

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ABSTRACT - The present study, the largest in the literature, was performed to assess the effectiveness and safety of unilateral subthalamic nucleus (STN) lesioning for Parkinson's disease (PD). From August 1999 to September 2000, 21 consecutive patients evaluated pre- and postoperatively by a single examiner were operated. Levodopa intake and dyskinesia, Hoehn & Yahr, Schwab & England and UPDRS motor scores were recorded. Stereotactic CT and MRI and the effects of macrostimulation were used to determine STN coordinates. A single radiofrequency lesion was made (60-75°C/60"). Concomitant ipsilateral Vim/VOp lesions were made in 8 patients. Using a new technique, we were able to determine the territory of STN involved by the surgical lesion. The Wilcoxon and Mann-Whitney statistical tests were applied to evaluate the surgical results. All recorded parameters showed stable improvement after a mean follow up of 13.5 months. Recurrence occurred in two patients. Contralateral tremor arrest and decrease of rigidity and bradykinesia should be regarded as STN hallmarks to stimulation. Hyperintense lesions in the early-phase MRI seem to be a poor prognostic factor. Lateral territory lesioning correlates with better results. There was no significant difference between the cohorts with and without a Vim/VOp lesion. Dyskinesias happened in two patients (promptly abolished by a Vim/VOp lesion). Other complications were transient and/or rare. In conclusion, STN lesioning is a safe and very effective procedure to treat PD and probably an underutilized operation for those who can not afford the costs of DBS.

KEY WORDS: subthalamic nucleus lesioning, deep brain stimulation, stereotactic surgery, subthalamic nucleotomy, subthalamotomy, Parkinson's disease.

Lesão unilateral do núcleo subtalâmico: um tratamento seguro e eficaz para a doença de Parkinson

RESUMO - O presente estudo, o maior da literatura, foi realizado para avaliar a eficácia e segurança da lesão unilateral do NST (núcleo subtalâmico) para o tratamento da DP (doença de Parkinson). Entre agosto de 1999 e setembro de 2000, 21 pacientes consecutivos avaliados pré e pós-operatoriamente por um único examinador foram operados. Os seguintes parâmetros foram avaliados: dose diária de levodopa, discinesia induzida pela levodopa, estadiamento da doença, atividades de vida diária e escores motores da UPDRS. RNM e TC estereotáxicas e os efeitos da estimulação com macroeletrodo foram utilizados na determinação das coordenadas do NST. Uma única lesão por radiofrequência foi realizada (60 – 75°C / 60"). Lesão concomitante de Vim/VOp ipsilateral foi realizada em 8 pacientes. Utilizando-se uma nova técnica, foi possível estabelecer o território do NST lesado cirurgicamente. Os testes estatísticos de Wilcoxon e Mann-Whitney foram aplicados para avaliar os resultados cirúrgicos. Todos os parâmetros avaliados apresentaram melhora sustentada após seguimento médio de 13.5 meses. Recidiva ocorreu em 2 casos. Abolição do tremor e redução da rigidez e bradicinesia contralaterais devem ser considerados como "marcadores" do NST à estimulação. A presença de lesão hiperintensa na RNM pós-operatória precoce parece ser indicadora de mau prognóstico. Os melhores resultados foram obtidos com a lesão do território lateral do NST. Não houve diferença estatisticamente significativa entre os subgrupos com e sem lesão concomitante de Vim /VOp. Discinesia ocorreu em 2 casos, prontamente revertida pela lesão concomitante de Vim/VOp. Outras complicações foram transitórias e/ou raras. Concluindo-se, a lesão unilateral do NST é procedimento seguro e eficaz para o tratamento da DP, tratando-se, de uma cirurgia subutilizada para aqueles que não podem arcar com o elevado custo da estimulação cerebral profunda.

PALAVRAS-CHAVE: núcleo subtalâmico, lesão, estimulação cerebral profunda, cirurgia estereotáxica, nucleotomia subtalâmica, subthalamotomia, doença de Parkinson.

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Despite having been performed for more than 70 years¹, it was only in the last decade of the last century, after the development of non-human primate animal models of MPTP-induced parkinsonism², that the surgical treatment of Parkinson's disease (PD) abandoned the empiric field to become really scientific. Using these models it was possible to demonstrate hyperactivity in the globus pallidus internus (GPi) and subthalamic nucleus (STN) and the presence of tremor-cells in GPi and STN^{1,3-7}, validating previously proposed circuits of the basal ganglia⁸⁻¹⁰. Such knowledge made possible the comprehension of the genesis of the cardinal manifestations of PD^{1,3-7} and how to better treat them surgically¹. Besides, a new hypothesis has been advanced: the excitotoxic effect of STN glutamate on dopaminergic cells of substantia nigra pars compacta (SNc) would act as a perpetuating mechanism of dopaminergic cell death and PD progression^{3,4,7,11}.

Taking these findings all together, one could suppose that STN would be the most suitable target to treat PD^{3,4}. STN deep brain stimulation (STN-DBS) was first performed by Benabid's group in 1993^{12,13}. Since then, many groups, including his own, have replicated the excellent results initially reported^{7,14-25}. STN lesioning, on the other hand, was first reported by Obeso et al. in 1997²⁶. Probably due to the fear of producing hemiballismus, this procedure has been reported in only 21 patients all over the world^{1,3,4,7,14,17,26-30}, despite the significant improvement obtained.

The present authors, in an attempt to determine the safety and efficacy of unilateral STN lesioning, prospectively performed this procedure in 23 consecutive patients with idiopathic PD, regardless the predominant manifestations of the disease. To the best of our knowledge, the present study represents the largest series on STN lesioning for PD treatment reported in the literature.

METHOD

From August 1999 to September 2000, after informed consent, 23 consecutive patients with PD underwent unilateral STN lesioning in our two Services (Hospital das Clínicas of Universidade Federal de Goiás and Instituto do Cérebro de Goiânia). Two patients were excluded from analysis due to events not related to the operation itself, preventing an adequate evaluation of the surgical result.

Of the remaining 21 patients, all presented bilateral disease. There were 16 male and 5 female, mean age of 56 years (38 to 77 years; ≤ 60 years = 11 patients and > 60 years = 10 patients) and mean duration of the disease of 8.4 years (2.5 to 19 years; ≤ 5 years = six patients, 6-9 years = five patients and ≥ 10 years = nine patients and unknown = one patient). Three patients had been

previously operated contralaterally to the proposed surgery, with good results: Vim/VOp (intermediate ventral nucleus / posterior ventral oral nucleus) thalamotomy, one patient and campotomy, two patients.

All patients were evaluated pre and postoperatively, while "on", by a single examiner (DJS). Levodopa intake [postoperatively it was classified as: unchanged, slight reduction (33%) or significant reduction ($\geq 50\%$)], levodopa-induced dyskinesia, Hoehn & Yahr Modified Scale (H&Y), Schwab & England Scale (S&E) and UPDRS (Unified Parkinson's Disease Rating Scale) motor scores were recorded bilaterally, but only those contralateral to the surgery were considered for analysis (Table 1). Postoperatively, all patients were asked to self-report their improvement.

Indications and contraindications for surgical treatment were already reported elsewhere^{1,3,31}.

All patients were operated by one of the authors (OVF).

Under local anesthesia, the stereotactic frame (model MT-03B, Micromar Stereotactic System, São Paulo, Brazil) is placed parallel to the infraorbital – external auditory canal line [this line is usually parallel to the AC-PC (anterior commissure-posterior commissure) line], the box containing the MRI (magnetic resonance imaging) fiducials is adapted and an MRI (Gyroscan Nt10, 1 tesla, Philips) is performed (15 of our patients) obeying the protocol shown in Table 2, taking care to place the probable projection of the AC-PC line (usually 2 cm above the nasion) as close as possible to the center of the magnetic field. The axial slices are performed parallel to the frame and the coronal slices, perpendicular to it, the central one passing through the midcommissural point (MCP). The coordinates of AC, PC and MCP are obtained from the axial slices using the resident software of the MRI.

Fortunately, STN can usually be seen on T2-weighted coronal images. The landmarks for its identification are shown in Figure 1A. The target is chosen in its central part

Table 1. Preoperative evaluation.

	Number of patients	Range	Mean
Bradykinesia	21	1.0 - 3.5	2.5
Rigidity	20	1.5 - 3.5	2.5
Tremor	19	0.5 - 4.0	3.0
Postural disturbance	18	0.5 - 3.5	2.0
Speech disturbance	18	0.5 - 3.0	2.0
Dyskinesia	06	2.0 - 3.5	3.0
Schwab & England	21	30% - 80%	50%
Hoehn & Yahr	21	2 - 4	3
Levodopa intake (tablets/day; 1 tablet = 250 mg)	19	1 - 9	3.5

and its coordinates are obtained using the resident software of the MRI. The final coordinates we use, though, are 2 mm lateral to those obtained, in order to reach preferentially the lateral territory of STN.

Still on T2-weighted coronal images, the vertical (Fig. 2A) and horizontal (Fig 2B) diameters of STN are measured, as well as the distance of its central part from AC (number of slices posterior to AC x slice thickness = 1.5 mm) (Fig 3A and 3B), midline (laterality) (Fig 4A) and apex of the choroidal fissure (height) (Fig 5B).

The MRI box is then replaced by the CT (computed tomography) fiducials and a CT is performed (Somatom AR.C, Siemens) obtaining axial slices (thickness and gap of 2mm) parallel to the frame base (all patients underwent CT). At the end, a new topogram is performed. Comparing the angle of the gantry necessary to obtain slices parallel to the frame in both initial and final topograms, it is possible to verify if there was any movement during the exam, in which case it is repeated. The coordinates of AC, PC and MCP are derived from the resident software of the CT. Usually, CT is performed just to compare the MCP (very close to STN) coordinates so obtained with those derived from T1-weighted axial images. If there is any anteroposterior displacement of the y coordinate obtained from T1-weighted MRI, the STN y coordinate derived from T2-weighted coronal images can be corrected.

Discrepancies between MRI- and CT-derived coordinates and the final STN coordinates (place where the lesion is made) are calculated.

A software developed by the Department of Neurophysiology of the University of Toronto is fed with the CT-derived AC and PC coordinates, which, in turn, constructs a series of sagittal diagrams ruled in a millimeter grid (based on digitized plates from the Schaltenbrand and Wahren atlas)³² stretched or shrunk to match the patient's intercommissural (AC-PC) distance³³. When only CT is used to establish target coordinates, they can be easily read directly from these diagrams, usually 2-5 mm posterior, 2-4 mm below and 10-15 mm lateral to the MCP³³.

The same diagram³³ is also used to plan the best trajectory to the target: to avoid "contamination" of STN responses to stimulation with those from the motor thalamus, the electrode is commonly angled 40 to 45° anteriorly to pass exactly in front of the last structure. The mediolateral angle is usually zero.

The electrode is driven to the target along the planned trajectory through a 4 mm percutaneous twist drill hole placed just in front of the coronal suture and about 13 mm lateral to the midsagittal plane (it depends on the lateral coordinate of the target). It is 1.1 mm in diameter with a 3-mm bare tip (Diros Technology Inc., Toronto, Canada). Macrostimulation is carried out in 2-mm steps from

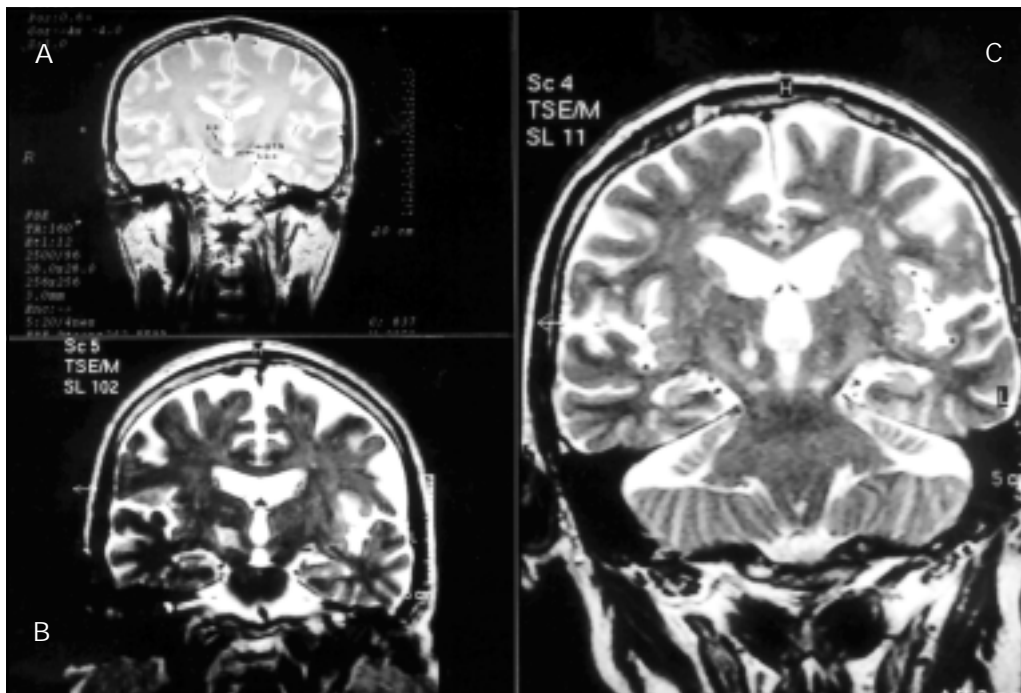


Fig 1. T2-weighted 3D coronal MRI. A- Landmarks for identification of STN (subthalamic nucleus): 14 to 18 mm posterior to AC (anterior commissure); superior and medial to the apex of the choroidal fissure; superior and lateral to SNR (substantia nigra pars reticulata); superior, lateral and anterior to RN (red nucleus); and an imaginary line passing through the lateral border of the brainstem usually crosses STN through its medial region; B- Habitual characteristics of the early-phase STN radiofrequency (RF) lesion: a three-concentric-zone image; C- Unusual characteristics of the early-phase STN RF lesion: a hyperintense image, probably correlated with a poor outcome (only our two patients harboring such a lesion presented recurrence). Reprinted under permission of Karger, Basel, from Vilela Filho O, et al.⁴.

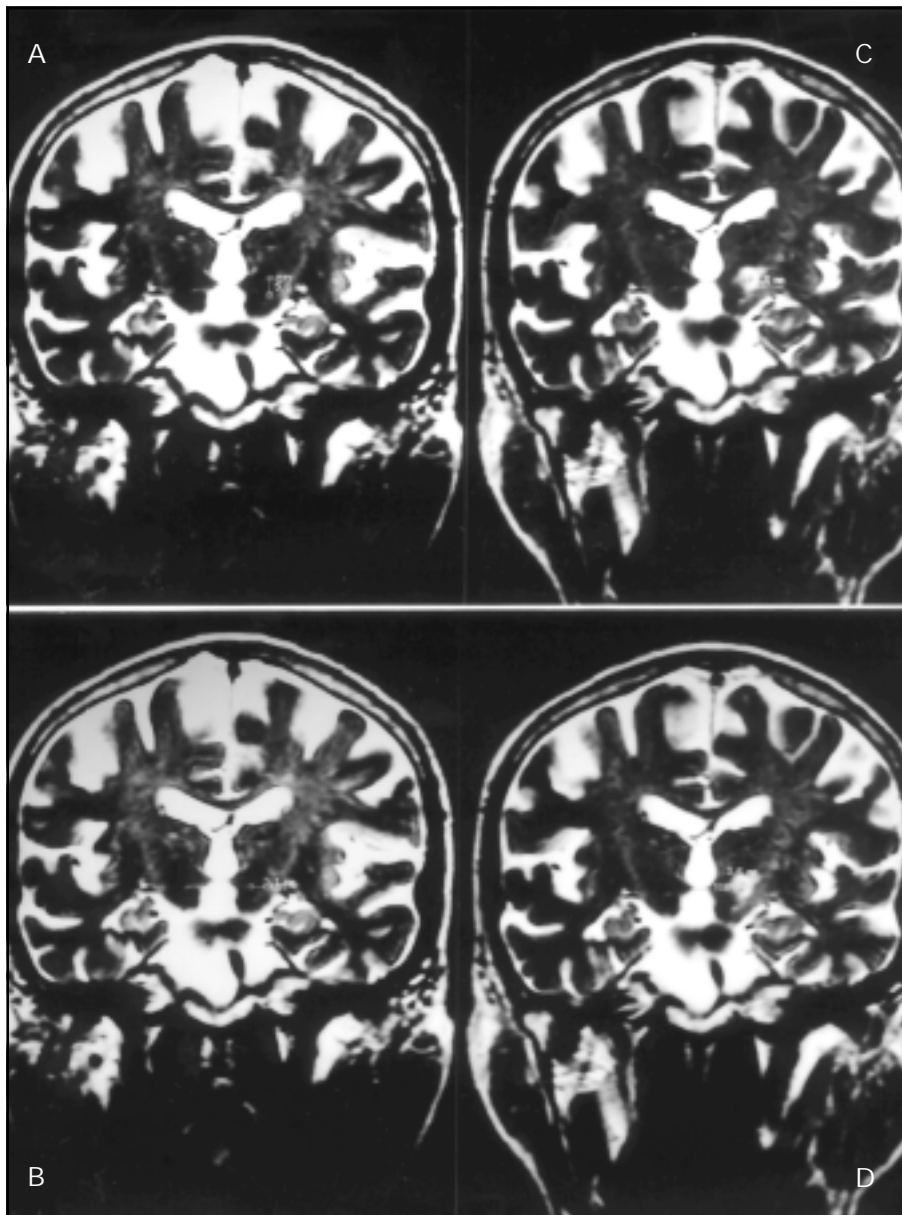


Fig 2. Pre- and postoperative MRI showing, respectively, the vertical (A) and horizontal (B) diameters of STN, and the vertical (C) and horizontal (D) diameters of the lesion.

6 mm above the target to 6 mm below it, starting, in each point, with a current of 0.5 Volt at 100 Hertz, which is increased in 0.5-Volt steps to a maximum of 3 Volts. After physiological determination of the target (point where stimulation produces the best expected responses), a single lesion is made, under careful neurological monitoring: we start with 45°C/40 seconds and, if there are no untoward effects, it is slowly increased up to 60-75°C/60 seconds, depending on the results obtained. We use a radiofrequency (RF) generator/stimulator for both stimulation and lesioning (OWL, model RFS-1, Diros Technology Inc., Toronto, Canada or MRFG-01B, Micromar, São Paulo, Brazil).

Postoperative MRI, following the same protocol and slices' orientation of the preoperative MRI, is performed usually within the first three postoperative days [(16 pa-

tients); occasionally, for financial reasons, it is performed sometime later (five patients, from 13 to 90 days after the operation)]. Using T2-weighted coronal images, the vertical (Fig 2C) and horizontal (Fig 2D) diameters of the lesion are measured, as well as the distance of its central part from AC (Fig 3C and 3D), midline (Fig 4B) and apex of the choroidal fissure (5-A). Comparing these data with those obtained preoperatively for the STN, we are able to determine the territory of STN involved by the lesion, which was classified as: lateral, medial, mixed (lateral and medial) and central. In the six patients in whom a preoperative MRI was not performed and in the patient in whom STN could not be identified, this determination was based on the comparison between the site and dimensions of the lesion and of the intact contralateral STN.

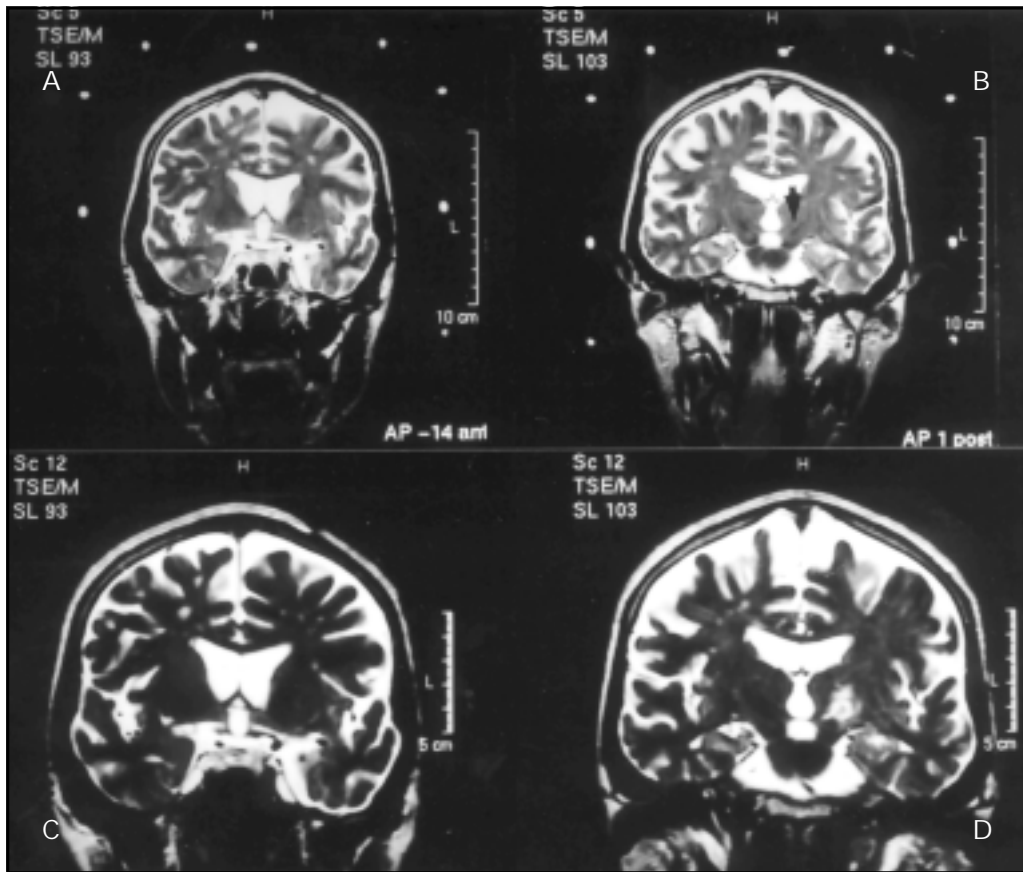


Fig 3. Pre- (upper row) and postoperative (lower row) T2-weighted 3D coronal MRI from a single patient showing exactly the same anteroposterior distance (15 mm) between STN [1 mm post (arrow in B)] or lesion [6 mm post (D)] and AC [14 mm ant (A) in the preoperative image and 9 mm ant (C) in the postoperative image]. Reprinted under permission of Karger, Basel, from Vilela Filho O, et al.⁴,

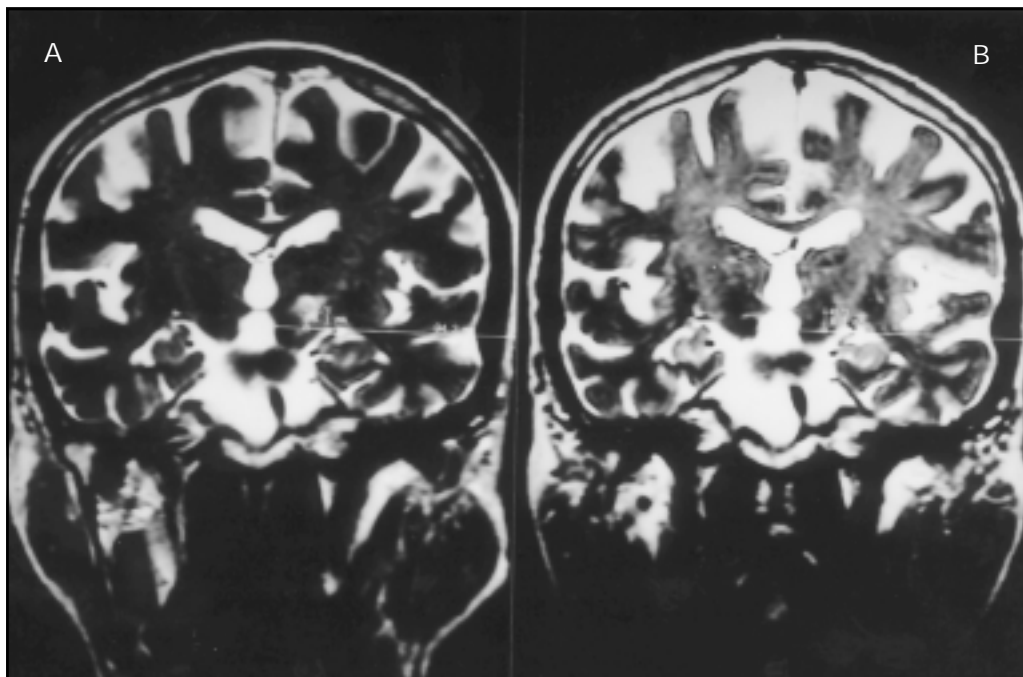


Fig 4. Post- and preoperative T2-weighted 3D coronal MRI from a single patient showing exactly the same height (6.1 mm) of the lesion (A) and STN (B) in relation to a horizontal line passing through the apex of the choroidal fissure. Reprinted under permission of Karger, Basel, from Vilela Filho O, et al.⁴.

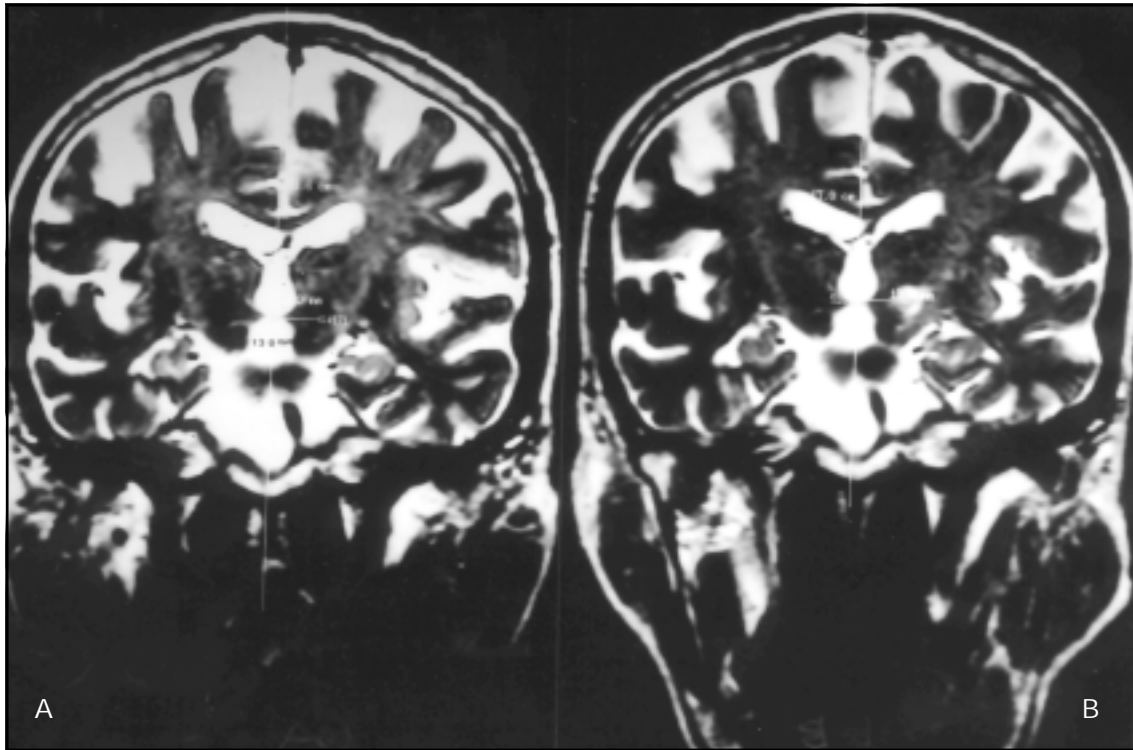


Fig 5. Pre- and postoperative T2-weighted 3D coronal MRI from a single patient showing the laterality of STN [13 mm (A)] and lesion [13.8 mm (B)] in relation to a vertical line passing through the center of the 3rd ventricle. Note that the laterality of the lesion is slightly greater, in order to involve the lateral region of STN, place of its somatosensory territory. Reprinted under permission of Karger, Basel, from Vilela Filho O, et al.⁴.

A concomitant Vim/VOp lesion (usually 7 mm anterior to PC and 2 mm above and 15 mm lateral to the AC-PC line) was performed in eight patients (residual tremor, six patients; surgery-induced dyskinesia, two patients) where macroelectrode stimulation produced tremor arrest (residual tremor) or increased dyskinesia (ballism and chorea) with a current of 0.5-2 Volts at 100 Hertz. The same lesioning parameters used for STN were used for Vim/VOp.

To have a more objective and global evaluation of the postoperative improvement, we have created three indices, expressed in percentage: overall improvement index (OII), appendicular improvement index (AII) and midline improvement index (MII). The MII is obtained by adding the percentages of speech and postural disturbances improvement and dividing this sum by the number of these manifestations presented by the patient. The AII is expressed by dividing the sum of the percentages of improvement of tremor, rigidity, bradykinesia and levodopa-induced dyskinesias by the number of these manifestations presented by the patient. Finally, the OII is obtained by adding the percentages of improvement of tremor, rigidity, bradykinesia, levodopa-induced dyskinesias, speech disturbance, postural disturbance, S&E, H&Y and the percentage of reduction of levodopa intake and dividing this sum by the number of these manifestations presented by the patient.

The Wilcoxon test was used to assess the general impact of surgery on all recorded parameters. The Mann-Whitney test was applied to evaluate the significance of

sex, age, duration and stage (H&Y) of the disease on the OII, AII and MII and to compare the impact of the different territories of STN involved by the lesion and the cohorts with and without a Vim/VOp lesion on all recorded parameters, including OII, AII and MII.

RESULTS

Parallelism between the frame base and AC-PC line:

The orientation used for frame placement enabled us to establish a parallelism between the frame and the AC-PC line in 15 out of 21 patients; in the other six patients, AC and PC appeared in adjacent axial slices.

Identification and diameters of STN on T2-weighted

3D coronal images: STN identification was possible in 14 out of 15 patients. Its mean horizontal and vertical diameters were, respectively 6 mm (4-9.2mm) and 5 mm (3.4-6.4 mm).

Discrepancy between CT and MRI-derived coordinates

and final STN coordinates: The mean x, y and z coordinate discrepancies were, respectively: a. CT: 0.9 mm (0-3 mm), 0.6 mm (0-2 mm), and 1.6 mm (0-5 mm); b. MRI: 0.7 mm (0-2 mm), 0.9 mm (0-5.2 mm), and 1.1 mm (0-2.3 mm).

It can be observed that MRI seems to be more precise for the acquisition of x and z coordinates and CT, for the y coordinate.

Table 2. MRI protocol.

	T1-weighted spin-echo sagittal sequence	T1-weighted turbo field echo 3D axial sequence	T2-weighted fast field echo 3D coronal sequence
Field of view	260 mm	260 mm	260 mm
Rectangular field of view	100 mm	100 mm	100 mm
Repetition time	550 ms	20 ms	1500 ms
Echo time	16 ms	6.9 ms	50 ms
Turbo factor	————	30 ms	11 ms
Number of signal averages	2	1	2
Matrix size	256 x 256	256 x 256	256 x 256
Slice thickness	6 mm	2 mm	1.5 mm
Interslice gap	0.6 mm	0 mm	0 mm
Flip angle	90°	30°	70°

Effects of macroelectrode stimulation and number of tracks: At the target, stimulation produced pronounced alleviation or elimination of contralateral rigidity, bradykinesia and tremor in all patients presenting these manifestations and, in one out of six patients with levodopa-induced dyskinesia, it produced dyskinesia.

One to five tracks were necessary for target confirmation (mean = 2.2); a single track was enough in 9 out of 21 patients.

STN coordinates in relation to the midcommissural point (MCP): The most prevalent coordinates were: 12.5 mm lateral, 4 mm inferior and 3.5 mm posterior to the MCP.

Lesion diameters and aspects on T2-weighted coronal images: The mean horizontal and vertical diameters of the lesion were, respectively, 4.7 mm (2-8.7 mm) and 4.8 mm (2-7.5 mm).

According to their aspect in the postoperative T2-weighted images, the lesions were classified as: hyperintense (four patients) (Fig 1B), hypointense (one patient; MRI performed three months after the procedure), two-concentric-zone lesion (hypointense inner zone and hyperintense outer zone; five patients), three-concentric-zone lesion (hyperintense inner zone, hypointense middle zone and hyperintense outer zone; ten patients) (Fig 1C) and unseen (one patient; MRI performed 61 days after the operation).

The whole core of hyper- and hypointense lesions was considered when measuring their diameters. With regard to the two- and three-concentric-zone lesions, the outer zone, considered by some as a mere edema³⁴, was not included in the measurement.

Territory of STN involved by the lesion: The STN territory involved was: lateral (three patients), medial (four

patients), mixed (nine patients) and central (two patients). It was not possible to establish this relationship in three patients: in one patient, the lesion could not be seen in the postoperative MRI and in two patients, the established protocol was not obeyed in the postoperative MRI.

It is worth mentioning that the STN lesion extended to SNR (substantia nigra pars reticulata) in one patient, to SNR and zona incerta in one patient and to the zona incerta in nine patients; in other nine patients, the lesion did not extend beyond the limits of STN.

Sex, age and duration of the disease: There was no statistically significant difference (Mann-Whitney: $\alpha > 0.05$) in clinical outcome by sex. However, there was a non-statistically significant (Mann-Whitney test: $\alpha > 0.05$) tendency for better results in those patients aged 60 years or less than in those older than 60 [E 60 years (n = 11): OII = 61.4%, AII = 78.3% and MII = 64.1%; ≥ 60 years (n = 10): OII = 55.3%, AII = 77% and MII = 49.1%] and in those patients presenting PD for six to nine years (n = 5; OII = 67.7%, AII = 80.4% and MII = 77.6%) than in those presenting it for less than six years (n = 6; OII = 49.7%, AII = 68.7% and MII = 43.3%) or more than nine years (n = 9; OII = 58%, AII = 81.2% and MII = 51.9%).

Impact of surgery: All recorded parameters were significantly improved, as seen in Table 3. Some points, though, deserve further comments.

In one patient with a 50% initial relief of the tremor, curiously, the improvement continued and the long-term follow up relief was of 85.7%.

The H&Y improved by 0.5 in five patients, 1 in eleven and 1.5 in one; four patients remained unchanged. The patients with H & Y = 3 or 3.5 (n = 10; OII = 63.8%, AII = 82.4% and MII = 67.5%) did better than those with H & Y

Table 3. Impact of surgery.

	Mean score		Improvement	Number of asymptomatic patients	Number of unchanged patients	Wilcoxon test
	preop	postop				
Bradykinesia	2.5	1.0	68.2%	0	0	$\alpha < 0.0001$
Rigidity	2.5	0.5	83.9%	11	0	$\alpha < 0.0001$
Tremor	3.0	0.5	84.9%	11	0	$\alpha < 0.0001$
Postural disturbance	2.0	1.0	66.5%	0	3	$\alpha < 0.001$
Speech disturbance	2.0	1.0	44.2%	0	4	$\alpha < 0.01$
Dyskinesia	3.0	1.0	74.2%	1	0	$\alpha < 0.05$
Schwab & England	50%	75%	52.3%	0	1	$\alpha < 0.0001$
Hoehn & Yahr	3	2 – 2.5	23.4%	0	4	$\alpha < 0.0001$
Daily levodopa intake (tablets / day)	3.5	1.7	42.6%	0	4	$\alpha < 0.001$

< 3 (n = 6; OII = 54.2%, AII = 71.8% and MII = 60%) and H & Y = 4 (n = 5; OII = 52.9%, AII = 75.5% and MII = 34.3%); this difference, however, was not statistically significant (Mann-Whitney test: $\alpha > 0.05$).

Due to intolerance, two of our patients were not using levodopa. The degree of reduction was slight (33%) in two, significant ($\geq 50\%$) in thirteen and none in four patients. The patients were able to decrease levodopa intake since the early postoperative phase.

Patient's self-evaluation: The mean self-reported improvement was 84% (80-100%, 18 patients; and 40-60%, 3 patients).

Overall (OII), Appendicular (AII) and Midline (MII) Improvement Indices: The OII, AII and MII were, respectively, 58.5%, 77.7% and 57.3%.

STN x Combined STN + Vim/VOp lesions: There was no statistically significant difference in any evaluated parameters between these two cohorts (Mann-Whitney test: $\alpha > 0.05$).

Lesioned STN territory x Results: The Mann-Whitney test showed no statistically significant difference between the lateral and mixed subgroups ($\alpha > 0.05$); however, tremor, OII and MII were better improved by lateral than medial lesions ($\alpha < 0.05$) and tremor, OII and S&E were better improved by mixed than medial lesions ($\alpha < 0.05$). These findings suggest that lesioning of the lateral territory (the mixed lesion includes the lateral territory) is important to achieve the best results.

Follow-up and Recurrence: All patients were followed for a minimum of 9 months and a maximum of 22.5 months (mean follow-up of 13.5 months) by a single examiner, a neurologist with expertise in movement

disorders (DJS). Only six patients were followed for less than one year.

The recurrence rate was approximately 10% (two patients), and was taken into account when we calculated the percentage of improvement of all recorded parameters. It occurred within the first postoperative month in both patients, being only partial for tremor and rigidity, but complete in one of the cases of bradykinesia.

The other patients have maintained their improvement stable during the whole follow-up period.

Complications: There was no mortality, infection, epilepsy or cognitive impairment in our series.

Hemiballismus occurred in one patient, and mild to moderate hemichorea, in another patient soon after the end of very successful operations. Both patients were treated with a Vim/VOp lesion performed in the same surgical procedure, with immediate and complete resolution of their dyskinesias. So, in our series, the incidence of surgery-induced dyskinesia was approximately 10%.

There was a 5% incidence of impairment of previous speech disturbance (partial recovery), transient (24 hours) impairment of previous postural disturbance, hypotonia (partial recovery), and asymptomatic intracerebral (frontal) hematoma.

Transient confusion (less than 48 hours) happened in eight patients (38.1%): six of them were submitted to STN lesioning (with extension to the zona incerta in three), and two underwent STN + Vim/VOp lesioning. The medial territory was involved in seven of the patients in whom the lesion could be detected by the postoperative MRI.

DISCUSSION

Why STN?

As mentioned before, non-human primate animal models of MPTP-induced parkinsonism² demons-

Table 4. Improvement following STN lesioning and STN-DBS ("on" state).

	Vilela Filho & Silva	Alvarez et al.	Gill & Heywood	DBS (various groups)
Bradykinesia	68.2%	marked	All	50-71% (57.2%)
Rigidity	83.9%	marked	patients	52-65% (59%)
Tremor	84.9%	marked	showed	80-86% (82.6%)
Postural disturbance	66.5%	marked	improvements	49-58% (53.5%)
Speech disturbance	44.2%	NM ^a	in	NM
Dyskinesia	74.2%	unchanged	parkinsonian	41-83% (61%)
Schwab & England	52.3%	marked	symptoms	30-45% (38.3%) ("off")
Hoehn & Yahr	23.4%	NM		NM
Daily levodopa intake reduction	42.6%	59% after 1 year in 5 patients	NM and 100% ^b	37-56% (45.6%)
Global improvement	58.5%	39%	NM	10-41% (23.6%)
Patient's self-evaluation	84.0%	NM	NM	NM
Increase of "on" state	NM	52.7%→93.7%	NM	26%→52%
Decrease of "off" state	NM	NM	NM	30%→6%
Follow-up (months)	9-22.5	12-24	NM	Varied

a - NM, not mentioned; b- NM in their second report on 10 patients and complete withdrawal of levodopa in their initial report on two patients.

trated hyperactivity of the STN and GPi. Such hyperactivity induces hypoactivity of the motor thalamus and so, of the motor and pre-motor cortex, causing bradykinesia^{1,3,5-7}. Hyperactivity of STN may also activate the nucleus tegmenti pedunculopontis pars compacta (TPC), which, in turn, excites the nucleus reticularis gigantocellularis, site of origin of the reticulospinal tract (RST). The RST is inhibitory for the I-B spinal cord interneurons, which, in turn, inhibit α -motor neurons^{1,3,6}. It has been shown that those interneurons are hypoactive in PD^{1,3,5,6}. This hypoactivity may then induce hyperactivity of α -motor neurons, the pathophysiological substrate of rigidity, according to one of the accepted hypotheses^{1,3,5,6}. Tremor cells have also been found in STN. Some authors have even suggested that the Vim/VOp tremor cells represent nothing more than the transmission of the activity of STN cells to the motor thalamus^{1,3,7,15,17}. So, STN seems to be involved in the genesis of the main manifestations of PD. In fact, inactivation of STN has a profound benefic effect on practically all manifestations of the disease, both in humans and MPTP monkeys^{1,3,4,7,12-30,35,36}. Another important aspect is the STN location within the basal ganglia circuitry: through its projections to the GPi,

SNR and brainstem, it is in a unique position to influence the entire output of the basal ganglia^{1,3,5,7-10}.

We have stated before that the current knowledge of basal ganglia functioning, which is based on MPTP monkey models and on the subsequent observations in humans, validated previously proposed circuits and physiology of the basal ganglia. However, there is one point deserving further comments: considering the indirect basal ganglia circuit, the STN would be hyperactive in PD due to hypoactivity of GPe (globus pallidus externus). Nevertheless, it was demonstrated experimentally that the GABA level at the GPe-STN pathway terminals is normal and not diminished, as expected⁷. Besides, GPe lesioning increases STN activity only by 19.5%, while SNC lesioning increases it by 105.7%, suggesting that STN hyperactivity would be secondary to the reduced levels of dopamine in the terminals of the SNC-STN pathway⁷. Interestingly, however, one of the researches going on at one of the authors (OVF) laboratory is on the effect of bilateral stereotactic lesioning of the GPe in intact Wistar rats (unpublished data): the preliminary results have consistently shown bradykinesia of such magnitude as to interfere with

the animals' feeding; some of them lost 50-100 g in five days. These findings, obviously, are completely opposite to those aforementioned.

The STN presents four distinct territories⁷, with different functions and connections: a-) the dorso-lateral sensorimotor territory receives afferents from GPe, motor and premotor cortex and projects to GPe and putamen, being rich in kinesthetic and voluntary cells and, in cases of PD, also of tremor cells; the upper limb is represented in its lateral part and the lower limb, in its medial part; b-) the ventrolateral associative territory, which projects to GPI, SNR and caudatum; c-) the ventromedial limbic territory, which projects to the ventral pallidum; and d-) the dorsomedial oculomotor territory. Considering this anatomofunctional distribution, it is our opinion that the best STN region to be targeted is the lateral one. Furthermore, contrarily to Vim/VOp (the limits of GPI can be partly identified on IR MRI images), STN can almost always be directly seen in MRI studies^{3,4,14,30}, which makes its targeting easier and independent of other landmarks commonly used in stereotactic surgery, such as AC and PC. Not less important, if STN hyperactivity really plays any role in the perpetuation of SNC dopaminergic cells death, its inactivation may have a protecting effect on PD progression^{3,4,7,11}.

Vim/VOp thalamotomy or stimulation is usually indicated when the tremor is the most disabling manifestation of PD^{1,31,37}. However, even if bradykinesia is not a significant feature by the time of surgery, with the progression of the disease it will eventually become, and then, even without tremor, the patient will find his/her limb useless due to the bradykinesia.

GPI lesioning or stimulation is a very effective procedure to treat bradykinesia, rigidity and levodopa-induced dyskinesia^{1,3,31,38}. However, both procedures are effective only while the patients are "off", doing almost nothing when they are "on", except for the elimination or alleviation of the dyskinesias^{1,3,20,38}. The levodopa intake is also not affected by these procedures^{1,3,7,19}. Many authors have claimed the successful control of tremor with these operations^{31,38,39}. In our hands, though, just mild to moderate tremor can be adequately controlled. Finally, the visual response, a very important guide for these operations, is only very rarely elicited by stimulation. Even after identification of the optic tract by microelectrode recording, stimulation at the same site still only rarely elicits visual responses (Jerrold Vitek, MD, personal communication). Those who use macrostimulation as the only means of physiological exploration, then, are at a greater risk to lesion the optic tract, despite

its low incidence in the majority of the series, including our own.

For all these reasons, STN seems to be the best target to treat PD.

Stimulation or Lesioning?

But how to best manipulate this target: by stimulation or lesioning? Actually, there seems to be no doubt about it. Mainly due to its lower neurological morbidity and reversibility, stimulation is always preferred to lesioning. On the other hand, the former presents a number of mechanical complications, a much higher incidence of infection (around 8%), a high cost and the necessity to change the generator every four to seven years^{1,7,31,33}; such shortcomings do not occur when lesioning is chosen. Another point that should be kept in mind is the difficulty to perform deep brain stimulation (DBS) in third world countries, the majority of the countries of the world, due to its high cost. So, maybe the best answer to the initial question is to try to perform DBS in the dominant brain hemisphere and lesioning in the other one; if impossible, bilateral lesioning may be contemplated, but avoiding mirror lesions, which carry an increased risk of complications. STN lesioning in one side and GPI or Vim/VOp lesioning (depending on the main manifestations of the disease) in the other side can be a reasonable solution. Finally, it is worth mentioning that Gill & Heywood have performed bilateral dorsolateral STN lesioning without significant side-effects^{29,30}.

Safety and Efficacy

The next important and inevitable questions are: is STN lesioning safe? How effective is this procedure compared to STN-DBS? The present work was carried out in an attempt to answer these questions. Since the initial report from Benabid et al. on STN-DBS in 1993^{12,13}, many groups^{7,14-25} have started similar trials, reproducing the excellent results originally described by Benabid and his colleagues.

The results of these groups^{7,14-25} showed that STN-DBS produced a mean improvement of the UPDRS motor scores of 53.8% (41-62%) in the "off" state and of 23.6% (10-41%) in the "on" state. There was a substantial increase of the "on" period (from 26 to 52%, in one study¹⁸) and a significant decrease of the "off" period (from 30 to 6% in the same study¹⁸). Other data from these reports are shown in table 4 and compared with three series of STN lesioning.

Lesions of the STN, mainly vascular in origin (hemorrhages and infarcts), have always been associated with the appearance of hemiballismus. For this very reason, avoidance of STN lesioning has been considered a dogma in basal ganglia surgery. In fact, lesioning of STN is regarded as one of the most consistent animal models for movement disorders.

Aziz et al.⁷, Guridi et al.³⁵, and Bergman et al. (cited by the previous authors^{7,35}) performed STN lesioning in MPTP monkeys obtaining marked improvement of the parkinsonian manifestations; surgery-induced dyskinesia (transient or permanent), though, was not an infrequent complication. Limousin et al.²³ treated three parkinsonian patients with STN-DBS. One of them presented hemiballismus, which disappeared by changing the parameters of stimulation. In another paper, Limousin et al.²⁴ induced hemiballismus by STN-DBS in two parkinsonian patients in the "off" state, without previous levodopa-induced dyskinesia; the parameters of stimulation to produce anti-parkinsonian effects and hemiballismus, though, were completely different.

The aforementioned experiments show that STN lesioning may be a very effective procedure to treat PD, that dyskinesias are not a rule after this procedure, despite their significant incidence, and that STN-DBS may also produce dyskinesias.

Some reports on surgical treatment of PD using targets in the subthalamic region (campotomy and subthalamotomy) showed that the dyskinesias are relatively infrequent complications, even when the STN itself was inadvertently lesioned^{28,35}. Additionally, other publications demonstrated the significant improvement presented by parkinsonian patients who suffered from vascular lesions in the STN^{28,40}.

Considering all these findings, Obeso et al.²⁶ first reported, in 1997, the results of STN lesioning in five patients with PD.

Currently, according to a wide review of the literature^{1,3,4,7,14,17,26-30}, there are apparently only three groups performing STN lesioning: one group, composed of three subgroups, led by Alvarez, Obeso and DeLong^{7,14,17,26-28}; another group, led by Gill & Heywood^{29,30}; and finally, our group, led by Vilela Filho & Silva^{3,4}.

Alvarez et al.^{27,28} reported the results of unilateral STN lesioning in 11 patients [this series, apparently, compiles the patients previously reported by Obeso et al.²⁶ (five patients), Rodriguez et al.¹⁷ (7 patients) and Starr et al.¹⁴ (one patient)]. CT was used

to obtain the target (dorsolateral STN) coordinates, commonly 2-3 mm posterior, 11-13 mm lateral and 5-6 mm below the MCP. Physiological exploration was performed through semi-microrecording and stimulation. A 4-mm in diameter radiofrequency lesion was performed (60°C/30 seconds). All patients underwent an early postoperative CT; only three patients, however, underwent a postoperative MRI (11 months after surgery), which showed the STN lesion extending 1-2 mm above. The authors did not mention the responses to stimulation. A mean of 8.6 tracks was performed per patient. Dyskinesias occurred in the contralateral limbs during lesion-making in five patients and subsided after 1-12 hours. Postoperative chorea of the contralateral leg happened in one case and disappeared after five days. Another patient developed persistent disabling contralateral hemiballismus (started on the 7th postoperative day), which was completely resolved by a medial pallidotomy one year after the first operation. No other complications were mentioned. A marked amelioration of parkinsonian features was observed in all patients the day after surgery or even in the operating room in those with tremor as a major manifestation. The follow-up varied from one to two years. There was a significant reduction in the UPDRS motor scores both in the "off" (50%) and "on" (39%) states; a similar effect was observed for the UPDRS ADL scores. Both contralateral (mainly) and ipsilateral rigidity and bradykinesia were significantly improved; the ipsilateral amelioration, however, lasted just one year. Contralateral tremor was significantly improved in all and eliminated in five out of eight patients. Midline manifestations were also significantly ameliorated. No recurrences were described. All patients remained stable during the whole follow-up period.

Gill and Heywood³⁰ performed a total of 15 STN lesions in 10 patients: unilateral in five and bilateral in other five patients (performed simultaneously in three out of these five patients). High resolution MRI, apparently in conjunction with ventriculography, was used to establish target coordinates (dorsolateral region of STN). Physiological exploration was performed with macroelectrode stimulation: currents of 0.5-2 Volts at high frequencies were used and the optimum site for radiofrequency lesion (3-4 mm in diameter) placement was determined considering the point where the best improvement of tremor, rigidity and bradykinesia was achieved by stimulation. Adequate lesion placement was confirmed postoperatively in all patients with a further MRI. One patient presented small-amplitude involuntary

movements affecting the distal lower limb, "which the patient did not notice herself". There were no other side-effects. Postoperatively, all patients showed improvements in parkinsonian symptoms. In their first report²⁹ of two patients (included in the aforementioned report, we suppose) submitted to bilateral dorsolateral STN lesion, the UPDRS "off" motor score improved from 50 to 16 (68%) in one patient and from 64 to 16 (75%) in the other; both patients were discharged without levodopa and dopamine agonists presenting no noticeable "off".

We performed a trial of unilateral STN lesioning in 23 patients with PD. The last patient of this initial trial was operated in September 2000. Two patients were excluded from analysis^{3, 4}.

Frame placement parallel to the infraorbital-external auditory line enabled us, like Starr et al.¹⁴, to establish a parallelism between the frame and AC-PC line in the majority of the cases, which made the calculation of the target coordinates easier and faster. We were unable to identify the STN on T2-weighted coronal images in only 1 out of 15 patients; the same happened to Starr et al.¹⁴ in one out of six patients. In our hands, T2-weighted coronal images were at least as accurate as CT axial slices to obtain STN coordinates. Other authors, targeting other structures, have reached similar conclusions⁴¹.

Hutchison et al.¹⁵ also obtained tremor arrest by STN stimulation, but did not consider this finding as an STN "marker", contrarily to Rodriguez et al.¹⁷. Benabid's group⁴⁰ suggested that the STN hallmark to stimulation is the decrease of wrist rigidity. Stimulation-induced dyskinesia is also thought to be a useful "marker" of STN^{23,24,28}. Unfortunately, Alvarez et al.²⁸ did not comment on their results with STN stimulation. Our experience with intraoperative STN stimulation showed that tremor arrest (curiously, for some reason that we fail to recognize, the latency for STN stimulation-induced tremor arrest was usually greater than that observed for Vim stimulation) and a pronounced decrease of the bradykinesia and rigidity in both contralateral limbs occurred in every patient harboring such manifestations. For this reason, all these findings should be regarded as hallmarks to STN stimulation. Stimulation-induced dyskinesia, though, happened in only one of our patients, for which reason we can not comment on its value as an STN "marker".

Using macroelectrode stimulation, we performed a mean of 2.2 tracks to determine the final STN coordinates, which were usually 3.5 mm posterior, 4 mm inferior and 12.5 mm lateral to the MCP, a bit posterior and superior to those reported by Alvarez et al.²⁸.

Postoperative MRI, performed in all our patients to assess the accuracy of lesion placement and its aspect and dimensions, could not detect any lesion in one of them (the MRI could only be performed 61 days after the operation), despite the excellent results obtained. Likewise, Krauss et al.³⁴ performed late MRI (usually six months after the operation) in 32 out of 36 patients who underwent medial pallidotomy; no lesion could be observed in three of them.

Using a method first described by our group, we were able to determine the STN territory involved by the lesion. The best results were obtained when the lateral territory was involved, in keeping with the knowledge that the STN sensorimotor territory is located in its dorsolateral region and that the STN efferents to GPi and SNr originate from its ventrolateral part⁷. Our point-of-view, then, differ a bit from other authors^{28,30}: we think that both dorsolateral and ventrolateral territories should be lesioned to achieve the best results and not only the dorsolateral territory. Alvarez et al.²⁸, despite having performed postoperative MRI in only 3 of their 11 patients, and Gill and Heywood³⁰, despite the fact of not using any measuring method to confirm their assumption, claimed that the lesion was placed in the dorsolateral STN.

The MRI aspect of a radiofrequency lesion was first described by Tomlinson et al., cited by Krauss et al.³⁴, in patients submitted to ventrolateral thalamotomy. Krauss et al.³⁴ reported a somewhat similar result in patients who underwent medial pallidotomy. The acute-phase aspect on T2-weighted MRI images was of a three-concentric-zone lesion: a hyperintense inner zone, a hypointense middle zone (thought to represent hemorrhagic coagulation necrosis) and a hyperintense outer zone (thought to correspond to edema), involved by additional perilesional edema, with a signal not as intense as the lesion outer zone; the late-phase aspect was of a hyperintense lesion. We observed two other types of acute-phase lesions: hyperintense and two-concentric-zone (corresponding to the middle and outer zones of the three-concentric-zone lesion) lesions. Interestingly, the two patients with acute hyperintense lesions (fig. 1C) did not present the same degree of improvement of the other patients. We also observed another type of late-phase lesion: hypointense lesion, seen in only one patient who presented a very good result. The dimensions of our lesions were a little bit larger than those reported by Alvarez et al.²⁸ and Gill and Heywood^{29,30}.

Surgery-induced dyskinesia occurred in 10% of our patients. Such incidence was similar to that repor-

ted by Gill and Heywood (1 out of 10 patients³⁰) and by Alvarez et al. (1 out of 11 patients with persistent hemiballismus and 6 out of 11 patients with transient dyskinesia^{27, 28}). Since both our patients underwent Vim/VOp thalamotomy in the same surgical procedure, achieving complete and immediate relief of their dyskinesias, we do not know if they would be transient or persistent.

It has been suggested²⁸ that the low incidence of dyskinesia following STN lesioning is due to its upward extension towards the zona incerta, interrupting the pallido-thalamic pathway, and thus mimicking the effect of medial pallidotomy, which is well-known to abolish dyskinesias both in humans and monkeys. This hypothesis is not supported by our findings: the STN lesion extended to the zona incerta in only ten of our patients, including the patient who developed hemichorea; on the other hand, none of the nine patients with lesions restricted to the STN presented dyskinesia (in the patient who developed hemiballismus, the postoperative MRI, unfortunately performed only two months after the operation, did not show either the STN or the Vim/VOp lesions). Another possibility is that the threshold to induce dyskinesia in patients with PD is greater than in normal individuals, which is in keeping with some experimental data showing that dyskinesias are induced more frequently in normal than in MPTP monkeys submitted to kainic acid lesion of the STN²⁸.

The only other complication that deserves some attention, due to its high incidence, is the fortunately only transient confusion, presented by eight of our patients. In all cases (seven patients) in which the lesion could be identified by the postoperative MRI, there was at least a partial involvement of the medial region of the STN, where its limbic territory is located. On the other hand, seven other patients with medial territory involvement (medial and mixed lesions) did not present any confusion. In conclusion, all patients with transient confusion presented at least partial medial territory involvement, but not all patients with medial territory involvement presented transient confusion.

We have created three new indices, the overall improvement index (OII), the appendicular improvement index (AII), and the midline improvement index (MII), which, in our opinion, provide a more objective and precise assessment of the patient's response to the instituted treatment than the other scales currently available³. The version here presented is the first one, and it is our intention to better elaborate it in the near future.

In our series, all recorded parameters were significantly and greatly improved by the operation (Tables 3 and 4). Contrarily to Alvarez et al.²⁸, though, the improvement was observed soon after the procedure and only in the opposite hemibody and midline; reduction of levodopa intake was possible since the early postoperative period; and the levodopa-induced dyskinesias were substantially reduced. There were neither statistically significant differences between the cohorts with and without a Vim/VOp lesion nor sex-related differences. Although not statistically significant, there was a strong tendency for patients who were 60 or less years old, in stages 3 and 3.5 of the H&Y and with PD for six to nine years to present better results than the other patients. The latter finding is particularly interesting, since there is no agreement in the literature about the ideal time to indicate surgery. Finally, our patients self-reported their improvement as a mean of 84%.

Contrarily to Alvarez et al.^{27,28} and Gill and Heywood^{29,30}, who did not mention any recurrence, we have observed a 10% recurrence rate in our patients, followed up for 9 to 22.5 months. Since the early-phase postoperative MRI showed a hyperintense lesion (Fig 1C) in the two patients with recurrence, one could speculate if this finding may represent a poor prognostic factor.

Aziz presented orally his experience with STN lesioning for PD during the 13th Meeting of the World Society for Stereotactic and Functional Neurosurgery, in 2001. Only a short-term relief of the manifestations of the disease was observed in his series. The early-phase postoperative MRI aspect of the RF lesions produced, however, was of the hyperintense type and not of the expected three-concentric-zone type. This finding gives support to our hypothesis that the presence of hyperintense lesions in the early postoperative MRI correlates with a poor surgical result and can be regarded as a poor prognostic factor.

In general, our results compare favorably with those of STN-DBS and with the two other series on STN lesioning (Table 4).

In conclusion, STN lesion is a very effective and safe operation, with a low recurrence rate and an acceptable complication incidence. The most feared complication, dyskinesia, can be successfully treated in the same surgical procedure or later by lesioning another target, Vim/VOp (in our series) or GPI (as reported by Alvarez et al.²⁸), without increasing the incidence of complications.

Only after proving its safety and good and stable results in patients followed up for more than one year, we restarted to perform STN lesioning. Since February 2001, 11 other patients have been operated, with results somewhat similar to those already described.

In an attempt to avoid any misunderstanding with other operations previously performed in the subthalamic region, like campotomy and subthalamotomy, we would like to suggest another term for the relatively new procedure here reported: lateral subthalamic nucleotomy.

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