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ORIGINAL ARTICLE

Stereotactic surgery of nucleus tegmenti pedunculopontini

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Abstract

The nucleus tegmenti pedunculopontini (PPTg) is a new target for deep brain stimulation (DBS) in Parkinson's disease (PD), in particular for ameliorating postural abnormalities and gait disturbances. The objective of the study is to describe the pre-operative planning, the surgical procedures and results of the DBS of PPTg in humans. Thirteen patients were considered. The surgical approach evolved from the traditional 'indirect' method based on stereotactic ventriculography (5 patients) to a more recent 'direct' method, based on both a digital elaboration of axial stereotactic CT scan and on the 'direct' visual 3D representation of the PPTg (8 patients). No major complication occurred. The direct approach allowed to eliminate the major sources of variability caused by the use of the traditional stereotactic approach. The DBS of PPTg induced a significant amelioration of the following clinical symptoms: gait disturbances, freezing on, speech and arising from the chair. These symptoms are usually not improved by levodopa treatment. The implantation of PPTg proved safe and effective in the treatment of levodopa resistant PD patients. The classic determination of stereotactic coordinates, through a proportional system based on ventriculography, utilising as landmark the CA-CP line and the top of the thalamus, and stereotactic atlases, can hardly be applied to brainstem surgery. The 'direct' method, based on both an digital elaboration of axial stereotactic CT scan and, on the 'direct' visualisation of brainstem borders as well as on the 3D representation of the PPTg, permits a better adaptation to individual anatomic features.

Key words: *Pedunculopontine nucleus, deep brain stimulation, Parkinson's, disease, sterotactic surgery, brainstem, pons varolii.*

Introduction

Deep brain stimulation (DBS) is the first choice of treatment for patients with severe Parkinson's disease (PD) refractory to pharmacological treatments. DBS is indicated for the treatment of PD when the disease is severe, the response to drug treatment is unsatisfactory or after the appearance of severe complications of long-term levodopa uptake.[1–3] The subthalamic nucleus (STN) has become the principal target for DBS in PD, likely because the targeting of this nucleus nowadays is fully standardised and the technical variability is very low. Nevertheless, many authors are reconsidering the globus pallidus (GPi) for DBS in PD.[2,4–9]

In February 2005, we realised the first human pedunculopontine tegmental nucleus (PPTg) implantation.[5,10–12] The PPTg had been previously identified as a potential target for DBS in PD based on a bulk of experimental evidences.[13,14] Indeed, three lines of evidences suggested a role of PPTg in motor control. First, the PPTg receives fibres from the neocortical motor areas 4 and 6 and it has reciprocal connections with the inner segment of the GPi, the STN and the substantia nigra (SN). Second, the PPTg is linked to the spinal cord directly as well as indirectly by the virtue of its projection to reticulospinal neurons. Third, the PPTg is a part of the mesencephalic locomotor region from which movements are induced by electrical or chemical stimulation.[15–19] PPTg-DBS alone or associated with standard STN-DBS has been shown to be effective in improving gait and in optimising the dopamine-mediated ONstate, particularly in those patients whose response to STN-DBS alone were unsatisfactory.[20]

Thus, this article has been aimed:

- to describe our targeting technique for the PPTg;
- to compare it with the traditional conceptions in stereotaxis that we employed in the first cases presented elsewhere;[11,21]

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- to standardise the approach to PPTg, to extend its therapeutical application to the widest possible number of patients affected by movement disorders.

Materials and methods

Patients

Thirteen patients, 11 males and 2 females, age range from 48 to 70 years, mean age 61.7 ± 7.1, received a total of 21 leads implantation in the PPTg and these are resulted from 8 bilateral and 5 monolateral implantations. The main clinical features, the demographic details of the patients and the type of implantation that they received are summarised in Table I. All patients gave a written informed consent to participate in the study, and the study was approved by the local Ethical Committee.

Methods

In all cases we used the 3389 DBS leads (Medtronic® Minneapolis, USA, Neurological Division), inserted by the aid of a 3P Maranello stereotactic system (CLS Titanium Forlì, Italy). Our former surgical approach underwent a relevant technological evolution along the time.

First period (February 2005 to April 2006; Patients no. 0 to no. 4. In this former phase, our surgical targeting was performed according to the traditional criteria, based on ventriculography, CA-CP line and top of the thalamus, with proportional system and repetitive numeric coordinates. In particular, the stereotactic planning method evolved from the application of non-telemetric ventriculography to computerised ventriculography without contrast medium.

The determination of numeric coordinates of the target was obtained by means of the 2D Maranello stereotactic planning system (CLS Titanium – Srl Forlì, Italy), modified in 2006 to adapt it to the non-invasive digital ventriculography. At that stage, the anatomic representation of the target was based exclusively on the Schaltenbrand and Wahren stereotactic atlas of human brain.[22] The coordinates were calculated indirectly because the sagittal slides of S&W do not represent the PPTg (labelled as Tg.pd.po), which appears only in two coronal sections.

In 2005 and 2006 (first phase) (Patients no. 0 to no. 4), the 3D reconstruction of the structures around the PPTg was partially completed and limited to STN, GPi, 3rd ventricle, the SN, the red nucleus, the PPD (peripeduncular nucleus) nucleus and some thalamic nuclei (CM-Pf, VPL, VIM, VOa, VOp according to the Schaltenbrand and Wahren's nomenclature[22]).

Second period (April 2006 till present; patients no. 5 to no. 12). The surgical planning was made based on the 'direct' individuation and visual representation of the PPTg coordinates. For this aim, we utilised simultaneously:

- a computerised ventriculography with classical 2D coordinates determination, performed to compare the indirect method with the direct one;
- CT scan (axial planes) with superimposition of bi-dimensional atlas slides fitted based on the clearly detectable borders of the brainstem (Fig. 1). The atlases utilised were all the main human brainstem atlases in which the PPTg is represented (Olszewski and Baxter,[12] Paxinos and Huang,[24] Schaltenbrand and Wahren[22]). On the contrary, the Afshar *et al.* probabilistic

TABLE I. Summary of demographic, clinical and surgical data of the 13 implanted patients.

				PPTg		STN		GPi		CM-Pf	
Patients	Age	Sex	Diagnosis	Monolateral	Bilateral	Monolateral	Bilateral	Monolateral	Bilateral	Monolateral	Bilateral
0	60	F	PD		○		●				●
1	62	M	PD		●		●				
2	61	M	PD		●		●				
3	67	M	PD		●		●				
4	66	M	PD		●		●				
5	62	M	PD		●		●				
6	69	M	PD		●		●				
7	66	F	PD dystonic	●				●			
8	56	M	PD dystonic		●				●		
9	49	M	PSP	●							
10	48	M	PD dystonic	●							
11	67	M	PD	●							
12	70	M	PSP	●							
Mean	61.77										
St. dev.	7.07										

PD, Parkinson's disease; PSP, progressive supranuclear palsy; PPTg, pedunculopontine nucleus; STN, subthalamic nucleus; GPi, globus pallidus internus; CM-Pf, centromedian–parafascicular complex; St. dev., standard deviation; ●, targeted and implanted; ○, targeted but not implanted.

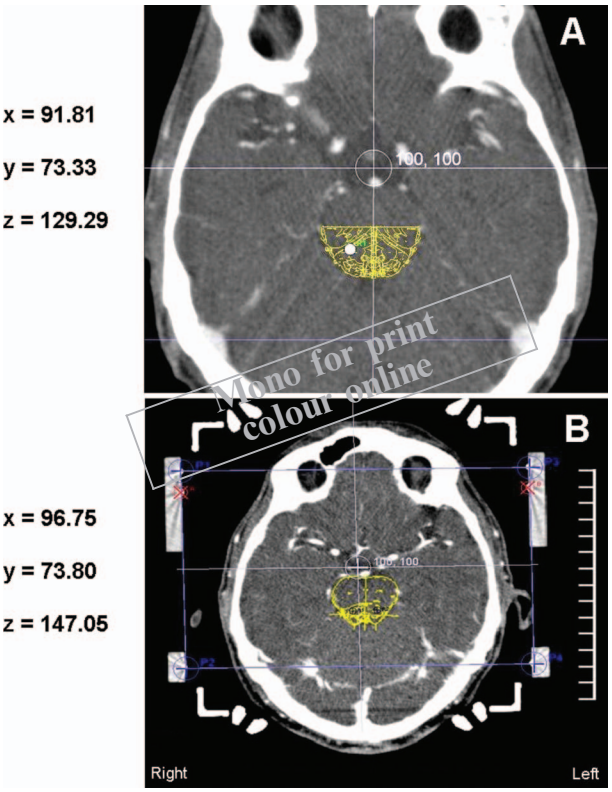

FIG. 1. Pre-surgical planning: automatic overlapping of the axial CT scans in the Fast-CT system with axial slides (sections) from two different human brain atlases. (A) overlapping of section +33 from the Paxinos and Huang's[23] atlas on the section 72 of axial CT scan. The circle on the right indicates the target, i.e the pedunculopontine tegmental nucleus. (B) Overlapping of slide Tc-3 from the Schaltembrand and Wharen's[17] atlas on the axial CT scan (in a different patient from the one represented in panel A). Numeric values of *x*, *y* and *z* coordinates are reported in the left side of the Figure.

atlas[25] does not represent and label 'directly' the PPTg. It must be kept in mind that, among these, only the Schaltenbrand and Wahren[22] is an atlas of stereotactic surgery. For this reason, the utilisation of non-stereotactic atlases in human surgery must take into account several sources of variability from an atlas to the other, deriving from the methodologies, the anatomic representations and the different enlargement of brain structures.

- The 3D reconstruction of the brainstem structures was made utilising the axial 2D representations provided by the atlases.[12,22,24] This novel tri-dimensional modelling was included into the 3D planning system, thus enhancing the precision of the pre-surgical planning and giving the chance to directly verify the spatial relationships between the leads and the target in a 3D model. Because the PTg is partially represented in the Schaltenbrand and Wahren[22] atlas exclusively in the coronal sections (Tg-pd-po, Fp 15.5–16.5), we completed the 3D reconstruction of the Schaltenbrand and Wahren[22] atlas by adding a further reconstruction of brainstem structures obtained from coronal projections. This tool allowed to overcome the dimensional and spatial discrepancies between the atlases, and permitted to produce a model of brainstem anatomy which can be fitted on the anatomical landmarks measurements made in each patient (Table II). In this way, we eliminated one major source of variability, and we avoided the effect of magnification caused by the 2D overlapping, typical of the ventriculography-based indirect method. The multi-planar reconstruction (MPR, Fig. 2) of the CT scan allowed us to chose the single axial CT slide on which the planning of the implantation should be performed (Fast TC, 3P Maranello® sterotactic system, CLS Titanium – Srl, Forlì, Italy). Eight patients (see Table I) underwent a bilateral PPTg targeting, with different time of surgery in the right and left site. The presence of a previous, monolateral implantation allowed to impose the same numeric coordinates for the contralateral lead. Moreover, it was possible to verify and quantify the differences between the planned and the real targeting performed with the direct method (Fast TC; Fig. 4). ③

As far as the trajectories are concerned, the employed angle was not different in the two periods as described in the first reports:[11,21] usually 25° in the sagittal plane and 11–18° in the coronal plane, as much parallel as possible to the floor of the fourth ventricle; thus the trajectory was preferably extraventricular. In the case of multiple implantations (STN or GPi plus PPTg), the post-operative controls showed that the trajectories of the leads in the different targets were more or less parallel to each other.

A relevant matter in the technological evolution of the targeting procedure was the implementation with 3D cerebral stereotactic angiography (in May 2007) reconstructed from the stereotactic angio-CT scan, and included into the 3D planning system (Fig. 3).

Clinical evaluations in off- and on-therapy and/or off- and on-DBS were performed in all the patients. Evaluations included video recordings (video 1), quantitative gait and axial analysis. All these evaluations were repeated in the phase test and in the follow-up.

Post-operative control CT scans (in 4 cases) and/or MRI (in 9 cases) were performed in all patients to assess the final position of the implanted leads (Fig. 5). Post-operative CT or MRI scans allowed to evaluate the spatial relationships of contact leads with some anatomical landmarks of the brainstem i.e: the ponto-mesencephalic border, the floor plane (angle) of the IV ventricle and the ventricular floor line.

Results

None of the patients implanted in the PPTg showed major adverse events, neither during the surgical

procedure, nor in the follow-up. In particular, no sexual impairment was reported. Transient paresthesias occurred in most patients either during the implantation or at the beginning of the stimulation, presumably as a consequence of electric or mechanical stimulation of the medial lemniscus.

The measurements of brainstem landmarks, performed in the pre-surgical planning phase, demonstrate the extremely high degree of inter-individual variability in the brainstem anatomy (Table II). This variability is even more likely in middle-aged or elderly patients, and in patients affected by progressive degenerative diseases,[26] in particular in progressive supranuclear palsy (PSP). This is the main reason for which we chose to shift from the 'indirect' targeting to a system based on a 'direct' 3D representation of the PPTg.

TABLE II. Measurements of anatomic landmarks in the 13 implanted patients.

	Midbrain				
Patients	Height (mm)	FFL height (mm)	MWP (mm)	VFL angle (degrees)	VFL-QL angle (degrees)
0	10	18.9	26.6	35	165
1	14.1	22.3	26.6	35	145
2	14.3	23.4	26.4	39	142
3	12.4	20.1	10.1	33	160
4	10.4	15.2	27.9	26	147
5	15.5	23.4	17	24	152
6	14.5	19.2	15.9	4	159
7	16	20.9	22.9	9	143
8	9.3	14	24.5	23	157
9	14.1	30.8	35.5	22	144
10	10.6	24.9	24.8	18	153
11	14.6	18.1	28.6	16	145
12	10.2	26.5	23.4	19	152
Mean	12.77	21.36	23.86	23	151
St. dev.	2.36	4.59	6.44	10	7

FFL, fastigial floor line; FFL height, distance between FFL and top of midbrain; MWP, maximus width of pons1; VFL, ventricular floor line; St. dev., standard deviation.

The displacement from the midline, which expresses the laterality of leads respect to this landmark, underwent a slight variation after the first 3 patients, then it was stable, with a mean value of 8.1 ± 4.0 mm. It must be considered that in the first three targeting procedures, based on the traditional or CT ventriculography, the displacement from the midline was greater, because it included the thickness of the 3rd ventricle.

The main issue in approaching the axial planning was a careful choice of an axial section corresponding to the z coordinate of the target. In the 'direct' approach, this CT section corresponded to an axial plane located 5 mm below the ponto-mibrain border, which crossed a point in the midsagittal plane placed 7 mm in front of (lateral to) the wall of the pontine tegmentum. Because the cranio-caudal extension of the PPTg is located from 3 mm above and 2 mm below the ponto-mesencephalic border, the length of intercontact distances (7.5 mm) ensures the optimal targeting for DBS in the PPTg.

It must be noted that we abandoned, at a very early stage of the second phase, the frame repositioning system, because the metallic screws produced

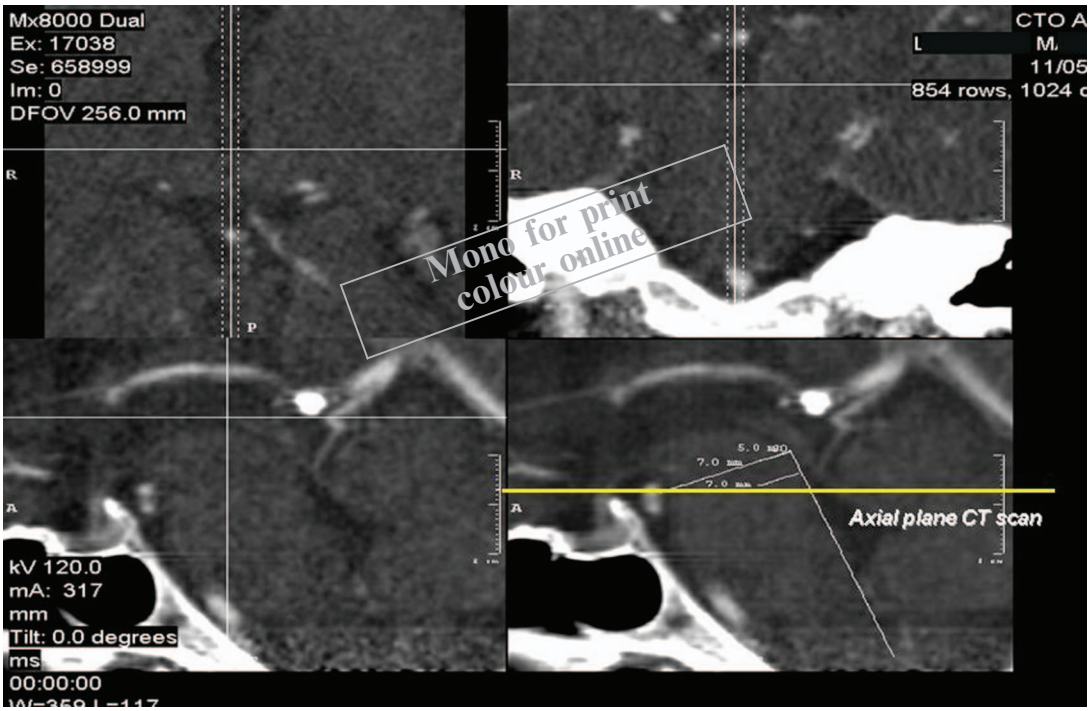

FIG. 2. MPR CT scan. In the lower right panel, the obliquous white line indicates the VFL, the white line perpendicular to VFL represents the pons-midbrain border in the midsagittal plane. The yellow line represents the CT scan axial section chosen for the planning, which is located 5 mm below the pons-midbrain border.

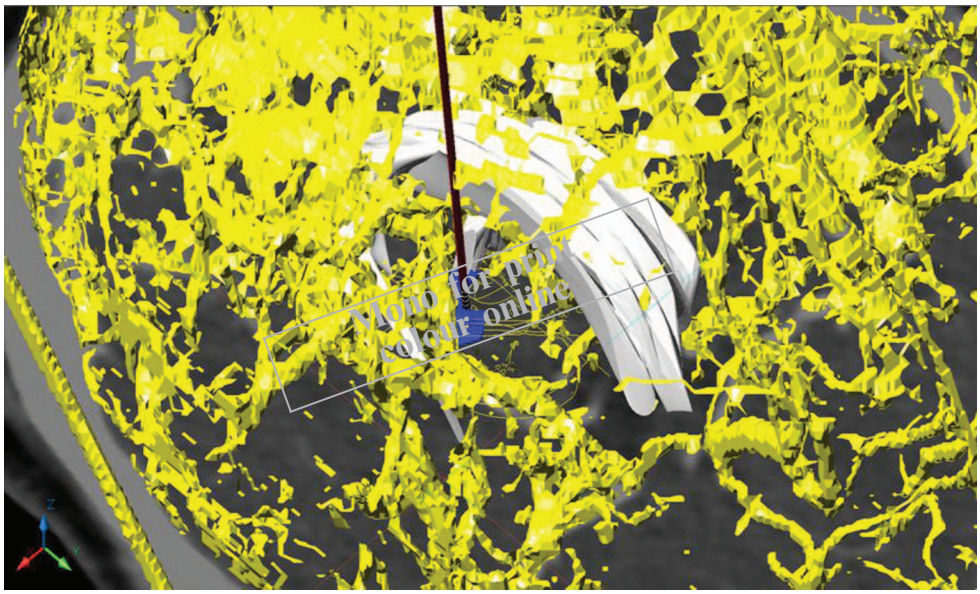

FIG. 3. Pre-surgical planning: stereotactic 3D computerised angiography (in yellow) allows to evaluate the risk of conflict between the leads and the brain vessels. In white, 3D representation of the ventricular system; in blue, 3D reconstruction of PPTg; in dark red, the lead.

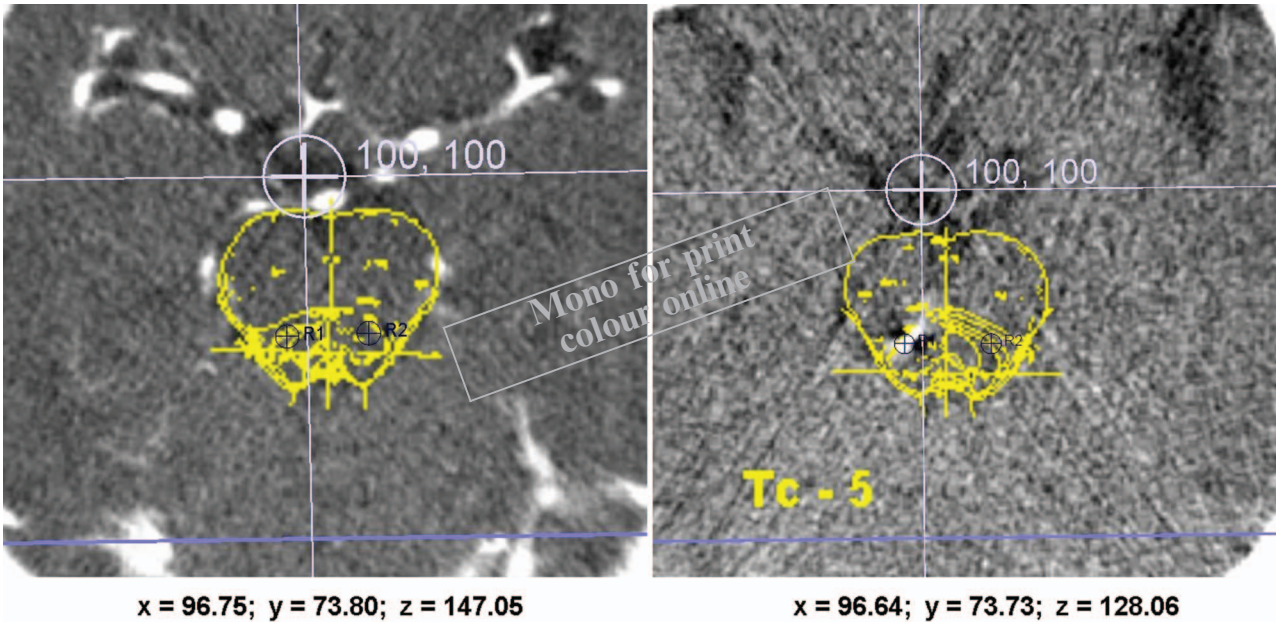

FIG. 4. Comparison between planned and realised coordinates of implanted lead in the PPTg.

artefacts which impaired the quality of mathematical processing of the safety 3D angiograms.

Post-operative control CT scans and/or MRIs are shown in Fig. 5.

Discussion

The extension and improvement of our initial experience to 13 patients, including 21 implantations, allows to confirm our previous suggestions,[11,20,21] and demonstrates that the implantation of the PPTg is a safe and reproducible approach for DBS in patients suffering with movement disorders (PD or PSP patients). The targeting of the PPTg can be rendered a precise, reliable and reproducible procedure, but it is necessary needs to take into account the individual anatomic variations of the brainstem in each patient, and to combine them with the representations of brain structure provided by in the atlases and/or by neuroimaging.[12,22,24,25] According to this view, the easiest and most reliable method to reach the PPTg comes from the possibility to overlap the theoretical anatomy to the individually defined boundaries in the axial plane. The indirect approach, based on the determination of coordinates with ventriculography and on the use of bicommissural landmarks, may reveal of poor precision and reliability in the stereotaxis of brainstem, because of the high inter-individual variability of the subtentorial structures.[15,26,27] If this variability is not taken

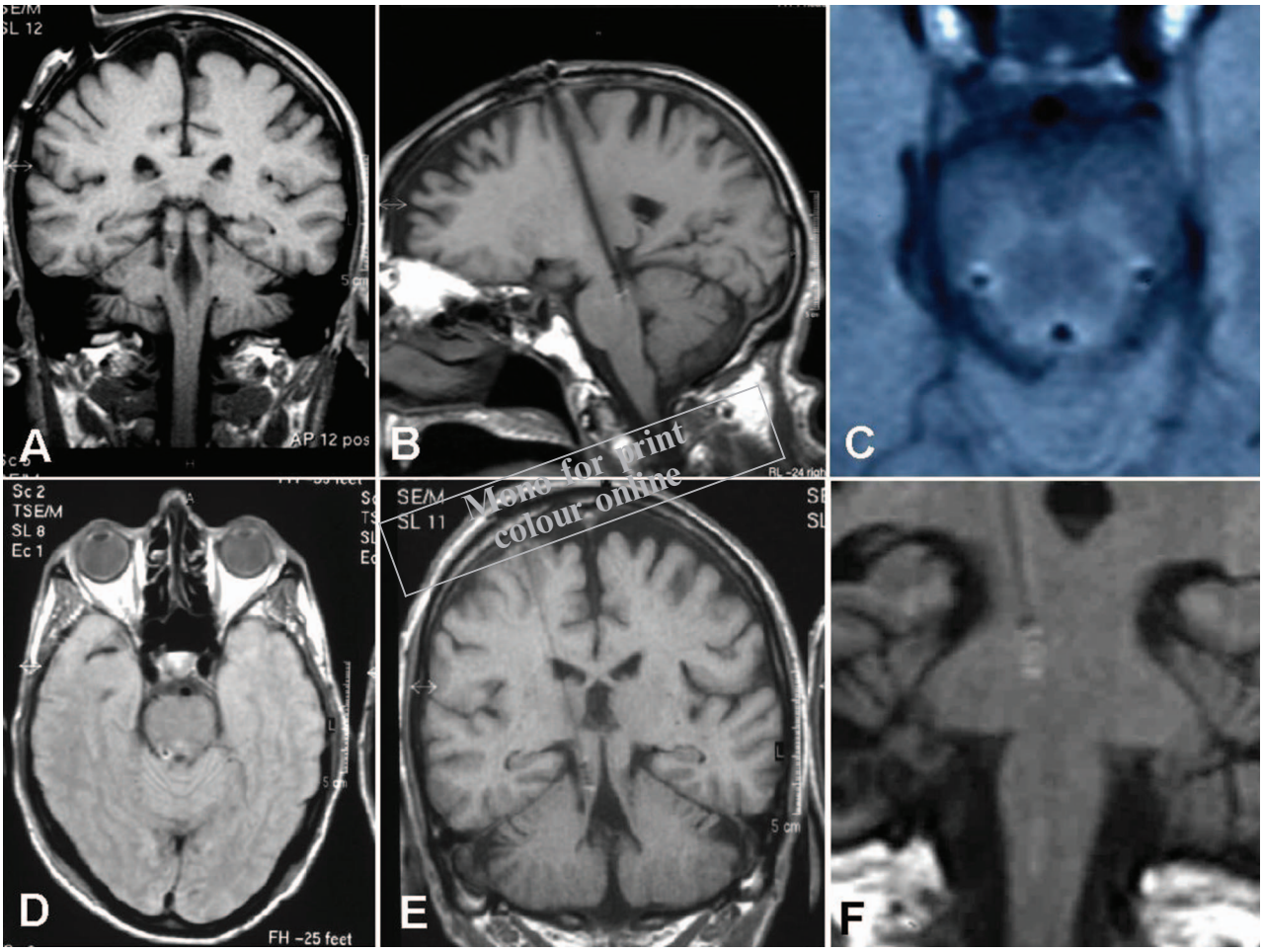

FIG. 5. Post-surgical neuroimaging (CT scan or MR imaging), evidencing the implanted leads, with distal tips located in the pons.

into account, it can easily lead to subjective misunderstandings of the targeting assessment.

On the other hand, the PPTg should be further considered as a functional area of the reticular activating system, rather than *only* an anatomically defined entity. The Schaltembrand and Wharen[22] atlas simply places it in the two coronal planes (Fp 15.5–16.5, 1 mm) but does not represent it in the sagittal and axial planes. The spatial expression of these coronal sections does not fully include the region of the lamina quadrigemina and the pontine-midbrain tegmentum. Also in the cytoarchitectonic atlas of Olszewski and Baxter[12] (see Table XXX to XXXIV) and in the Paxinos and Huang atlas[24] (see Table +31 to +36), the PPTg is in close anatomic relation with many other neuronal aggregates and fibre tracts which have different functions. In agreement with this view, the dimensions of the stimulating electrode does not fit with a strictly selective targeting of the nucleus. In the determination of the 2D coordinates, according to the proportional scheme[28,29] utilised in our 3P Maranello stereotactic system, the automatic overlapping of sagittal sections of the Schaltembrand and Wharen[22] atlas caused a certain degree of caudalisation of the target. On the contrary, some authors reported that, after the automatic overlapping of brainstem structures with MRI, the target appeared to be cranialised.[26] These discrepancies among the brainstem atlases, patient's individual anatomy, neuroimaging techniques employed in the planning and the automatic overlapping system may potentially account for variable degrees of distortion and approximation in the coordinate determination. The simultaneous, integrated utilisation of several atlases (based on different approaches to human anatomy) linked to multimodal neuroimaging techniques (CT, MPR, angioCT), can lead to a reliable, reproducible and unquestionable, surgical planning.

The trajectory of the electrodes was designed to keep the leads aside from the nuclei of the III and the IV cranial nerve (at whose level the PPTg is localised), and to avoid the risks of neurological damage, as described by Tailairach and Tournoux.[28,29] This is the reason for which we chose an extra-ventricular and oblique trajectory to approach the PPTg.

In our pre-surgical planning, we realised that the main source of inter-individual variability was the slope of the ventricular floor line. Indeed, when evaluating the Pearson's correlation coefficients between anatomic measurements of the brainstem and the x, y and z stereotactic coordinates, we noticed that the VFL angle was the major parameter influencing the values of the stereotactic coordinates accuracy.

TABLE III. Values of *x*, *y* and *z* coordinates, and displacement from the midline, in the 13 patients considered.

Patients	Coordinates			Midline displacement
	x	*y*	*z*	
0	90.0	83.9	144.7	−12
1	90.6	82.1	136.4	−13
2	85.5	85.5	153.1	−13
3	90.4	78.5	143.6	−13
4	86.0	77.2	122.6	−11
5	90.2	87.2	137.9	−10
6	93.0	81.5	131.9	−10
7	93.3	76.9	103.6	−8
8	91.8	75.2	130.1	−8
9	91.1	70.7	124.4	−7
10	91.4	69.8	140.0	−7
11	88.0	66.0	139.0	−7
12	92.4	69.0	127.0	−7
Mean	90.3	77.2	133.4	−9.7
St. dev.	2.4	6.8	12.5	2.5

All values are expressed in mm.

The inter-individual anatomic variability causes, therefore, the risk of a mismatch between the planned and the realised position, not only depend on the stochastic fluctuations invariably associate to a stereotactic procedure. The direct approach if on the one hand contributes to reduce this fluctuations, whereas the other gives the possibility to include in the planning the 3D angiographic (Fig. 3) reconstruction, thus greatly increasing the safety of the planned targeting.

Therefore, we believe that it is hazardous and potentially dangerous for patients to transfer the concepts derived from classical stereotactic experiences realised on STN and GPi implantations[2,3,30,31] to the brainstem surgery, in particular for pontine nuclei. This is even more evident if we consider that the lead is larger than the spatial expression of the nucleus in coronal (Schaltenbrand and Wahren:[22] only 1 mm), axial (Paxinos and Huang:[24] 5 mm) and sagittal planes (3D planning of 3P Maranello System), as observed in the overlapping data.

After initial experiences with bilateral lead implantation, most of our clinical and neurophysiological evidences suggest that a monolateral implant activation, followed by a cyclic stimulation, can be equally effective and less hazardous.[20,21]

Conclusions

The surgery of PPTg represents a potentially new approach to DBS for the treatment of movement disorders, alone or combined to a classical DBS target (GPi or STN). The necessity to find a way to the human pons makes it necessary to progressively adapt the stereotactic surgical technique, and finally to develop a conceptually novel approach. The classic rigid traditions are based on the brain atlases. CA-CP line and determination of coordinates of the thalamic top cannot be fitted in this domain. In addition, it has traditional approach sometimes 'per sé' may be potentially dangerous and useless.

In the future, the introduction of microarrays or microprobes[32] will allow to overcome these limitations, and will contribute to overcome the present technological limits. The value of PPTg surgery relies in the definition of a new approach to human brainstem; this achievement must now be considered independent from any therapeutic indication, clinical results, neurophysiological findings and specific anatomic localisation.

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