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The Deep Brain Stimulation of the Pedunculopontine Tegmental Nucleus

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ABSTRACT

Objective. The aim of the present study was to describe the surgical and clinical outcomes of the implantation and stimulation of the pedunculopontine tegmental nucleus in humans. **Materials and Methods.** Fourteen patients affected by movement disorders (12 Parkinson's disease and 2 progressive supranuclear palsy) underwent surgery for bilateral or monolateral implantation of stimulating electrodes in the pedunculopontine tegmental nucleus. The correct placement of electrodes was established and verified by combining angio-CT scans with magnetic resonance imaging. Intraoperative and postoperative evaluations were made to assess the clinical effectiveness of stimulation according to different Unified Parkinson's Disease Rating Scale items and neurophysiologic parameters. **Results.** No major complications occurred following the insertion of electrodes into the pedunculopontine tegmental nucleus. Neuroimaging showed that the electrode contacts were always correctly placed below the ponto-mesencephalic line. Stimulation of the pedunculopontine tegmental nucleus improved gait, posture, and speech, and modulated reflexes integrated at spinal or pontine levels. **Conclusions.** The surgical targeting of the pedunculopontine tegmental nucleus requires a careful adaptation of the traditional stereotactic approaches owing to the high variability of brainstem anatomy from one patient to another. The insertion of the leads in the pedunculopontine tegmental nucleus as well as their activation did not appear to induce serious adverse effects. The correct positioning of stimulating electrodes in pontine structures such as the pedunculopontine nucleus was ascertained not only through neuroimaging techniques but also through intraoperative and postoperative clinical neurophysiology. The evolution of the surgical planning that we have developed emphasizes the limited value of single-unit recordings to identify the pedunculopontine tegmental nucleus and highlights the opportunities offered by functional evaluations of neurophysiologic parameters. As far as the clinical efficacy is concerned, our data suggest a promising outcome for simultaneous implantations of different basal ganglia nuclei in Parkinsonian and in progressive supranuclear palsy patients as well.

KEY WORDS: *Brainstem, deep brain stimulation, Parkinson's disease, pedunculopontine tegmental nucleus, progressive supranuclear palsy, stereotactic surgery.*

Il y a ceux qui font quelque chose.
Il y a ceux qui ne font rien.
Il y a ceux qui croient faire quelque chose.
Il y en a trois qui font quelque chose.
Il y en a dix qui font des conferences sur ce que font les trois.
Il y en a cent qui font des conferences sur ce qui disent les dix.
Il arrive que l'un des cent dix vienne expliquer la maniere de faire a l'un des trois.
Celui-ci se tait, car il n'a pas l'habitude de la parole.
D'ailleurs il a quelque chose à faire.

—Anonyme

There are those who do something.
There are those who do nothing.
There are those who want to do something and three of them do something.
There are ten of them who confer on what the three did.

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There are a hundred of them who confer on what the ten said.
It so happens that one of the hundred and ten explains the manner of the creation of the one of the three, the one who kept silent because he did not have the practice of the "word."
—Anonymous (1)

Introduction

The pedunculopontine tegmental nucleus (PPTg) is a part of the upper brainstem locomotor region that has an important role in the control of gait and muscle tone (2–6). Anatomic and electrophysiologic studies have demonstrated that the PPTg is reciprocally linked to main basal ganglia nuclei (7–13) and that descending PPTg fibers modulates the activity of reticulospinal neurons (14–26). On the basis of the results of these studies, it is conceivable that, in Parkinson's disease (PD), an inhibitory output signal from basal ganglia nuclei might be overactive, decreasing a PPTg-mediated excitation over reticulospinal nuclei, and contributing in such a way to Parkinsonian rigidity and axial deficits. Therefore, as the PPTg is located at the interface between the basal ganglia and the spinal cord, our group considers it a target for deep brain stimulation (DBS) for the neurosurgical treatment of movement disorders in PD and in progressive supranuclear palsy (PSP). We also consider the PPTg an alternative or associated target to traditional targets such as the subthalamic nucleus (STN) or the inner segment of the globus pallidus (GPi) widely used by other groups (27–30).

We performed the first human PPTg implantation (PPTg) in February 2005 (31,32), and described the surgical approach to the PPTg and the clinical outcome in previous papers (31,33,34). Furthermore, we reported that PPTg-DBS, alone or associated with standard STN-DBS, was effective in improving gait and posture as well as optimizing the drug-induced ON state. Plaha and Gill also reported a significant improvement of gait and postural instability following bilateral PPTg implantation (35). Our first reports raised a controversy (36–39) regarding the location of the human PPTg due both to a misrepresentation of our target in one of our papers and to the scanty representation of the PPTg in the widely used Schaltenbrand and Wahren's stereotactic atlas (40). A recent attempt to better localize the PPTg has been made by Zrinzo et al. (41) according to atlas-based coordinates and magnetic resonance imaging (MRI). However, the conclusions of this study were not sustained by any direct neurosurgical or neurophysiologic validation; furthermore, the illustrations provided to support the putative location of the PPTg seemed to extend the PPTg into the mesencephalon rather than in the pons.

Therefore, the aims of our present paper were: 1) to summarize our targeting techniques for the PPTg-DBS; 2) to describe the surgical outcome of the PPTg implantation; and 3) to review the clinical outcome of the PPTg-DBS.

Methods

Subjects

A group of 14 patients (12 PD and 2 PSP), 12 men and two women, ages ranging from 48 to 67 years (mean age 61.1 ± 6.9 years), received a total of 20 definitive lead implantations in the PPTg. These resulted from eight bilateral and six monolateral implantations. The first two procedures, performed in a same patient, were limited to targeting the PPTg for Intra-Operative Micro Electrode Recordings (IOMER) with high impedance tungsten electrodes (0.5–1.5 MΩ), and were not followed by permanent lead positioning into the PPTg. The bilateral PPTg implantations were associated with bilateral STN implantation in six cases and with bilateral GPi implantation in one case. The six mono and laterally implants into PPTg were associated with other DBS bilateral targets (GPi) in one patient alone. The main clinical features, the demographic details of the patients, and the type of implantations that were used are summarized in Table 1. Our protocol was approved by the local Ethical Committee and all patients, before their operations, gave informed and written consent.

We used #3389 DBS leads in all patients (Medtronic®, Minneapolis, USA, Neurological Division). After our initial implants, in which our presurgical planning was essentially based on the definition of anatomic landmarks obtained from traditional ventriculography (patients #0–4), we moved to surgical planning made on the basis of direct individuation and visual representation of the PPTg coordinates (patients #5–13). To reach our goal of direct surgical planning, we simultaneously utilized: 1) informatic ventriculography with classical two-dimensional (2D) coordinate determinations; 2) Angio-CT scan (axial planes) on which 2D atlas sections were superposed; and 3) three-dimensional (3D) reconstructions of the brainstem structures constructed utilizing the axial 2D sections provided by the atlases (Fig. 1). The 2D sections were overlapped on the brainstem borders which were clearly detectable on the CT scan (Fig. 2) and comparable with illustrations of human brainstem atlases in which the PPTg is represented, i.e., the Schaltenbrand and Wahren (40), the Olszewski and Baxter (42), and the Paxinos and Huang's atlases (43). The Afshar et al. probabilistic atlas (44) was also used; although not directly representing the PPTg, it gave us a detailed anatomic description of brainstem.

This novel tridimensional modeling was included into the 3D planning system (2D and 3D Medico-Cad, 3P-Maranello® Stereotactic System), therefore enhancing the precision of presurgical planning. This enhanced precision allowed us to directly verify, in a 3D model, the spatial relationships between the contact leads and the target. The multiplanar

TABLE 1. Summary of Demographic, Clinical, and Surgical Data of the 14 Implanted Patients

					PPTg	PPTg	STN		GPi		CM-Pf	
Patient	Age (years)	Initials	Sex	Diagnosis	Bilateral	Unilateral	Unilateral	Bilateral	Unilateral	Bilateral	Unilateral	Bilateral
0	60	NL	F	PD	○			●				●
1	62	DFC	M	PD	●			●				
2	61	CE	M	PD	●			●				
3	67	LU	M	PD	●			●				
4	66	MU	M	PD	●			●				
5	62	GS	M	PD	●			●				
6	69	IM	M	PD	●							
7	66	MA	F	PD dystonic		●			●□□			
8	56	LS	M	PD dystonic	●	(●)						
9	49	VM	M	PSP		●						
10	48	LM	M	PD dystonic		●						
11	67	GGP	M	PD		●						
12	73	AS	M	PSP		●						
13	65	AV	M	PD		●						
Mean	61.1											
SD	±6.9											

PD, Parkinson's disease; PSP, progressive supranuclear palsy; PPTg, pedunculopontine tegmental nucleus; STN, subthalamic nucleus; GPi, globus pallidus internus; CM-Pf, centromedian—parafascicular complex; SD, standard deviation; ●, targeted and implanted; ○, targeted but not implanted; □□, adverse event; (●), final configuration.

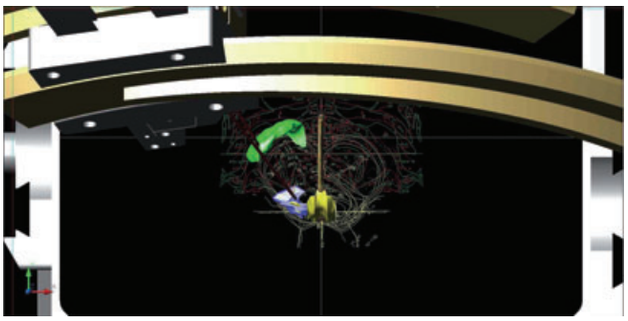

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FIGURE 1. An example of a 2D and 3D surgical overlapped planning obtained by combining original plates from the Paxinos and Huang, and Schaltenbrand and Wharen atlases. The 3D reconstruction was based according to the patient's anatomic features revealed by neuroimaging. Brown = 3rd ventricle; yellow (midline) superior and inferior collicoli; blue = pedunculopontine tegmental nucleus (PPTg) (pars disseminata); yellow (left side) = PPTg (pars compacta); green = left globus pallidus internus; dark red = leads trajectories.

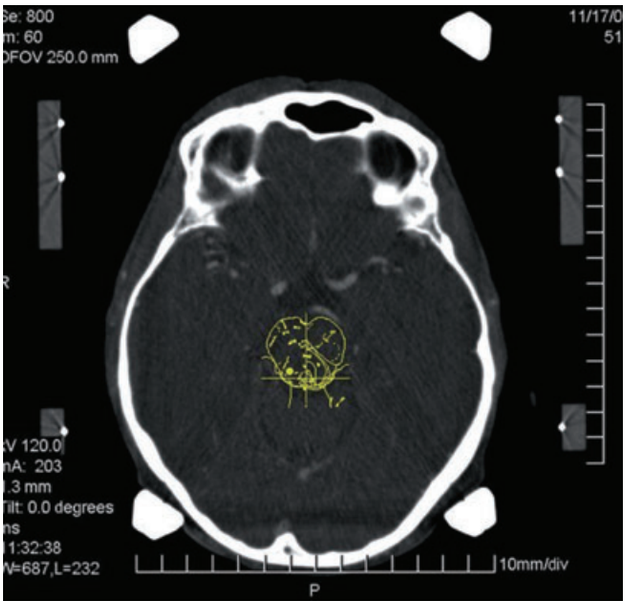

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FIGURE 2. Angio-Ct scan (TC axial plane 60) with a superimposed 2D atlas section. The Schaltenbrand and Wahren's brainstem section Tc-1,5 section is overlapped on the brainstem borders which were clearly detected in the angio-CT scan. The yellow-filled spot indicates the estimated position of the target.

reconstruction of CT scans allowed us to chose a single-axial CT section on which we could plan our implant (Fast TC, 3P-Maranello® Stereotactic System, CLS—Srl, Forlì, Italy). The angle usually employed for our trajectories, preferably and possibly extra-ventricular, was between 8° and 11° in the coronal plane and 25° in the sagittal plane, as much parallel as possible to the floor of the IV ventricle considered in the stereotactic position.

A crucial step of our targeting procedure, starting from May 2007, was the addition and inclusion into the 3D planning system of 3D cerebral angiographies reconstructed from stereotactic angio-CT scans (Fig. 3). The use of carbon tips to fix the skull to the stereotaxic frame prevented the production of artifacts on the angiogram, as these artifacts do occur when using metallic screws. This

new step gave us a reliable evaluation tool to determine whether the trajectory of our leads would come into contact and potentially damage vessels.

Furthermore, a miniaturized "frame revolver" was implanted onto the skull to directly insert the lead (Fig. 4a) in two patients instead of using the traditional 3P Maranello stereotactic apparatus. On this "frame revolver" (diameter 12 mm) was applied a microdrive (single or multiple) (Fig. 4b), designed to be integrated into a fully robotic stereotactic device, actually under construction. The miniaturized "frame revolver" was implanted with the aid of the arch of the 3P-Maranello stereotactic apparatus, which, soon after implantation, was removed. Once implanted, the microdrive guarantees a precise lowering of stimulating or recording electrodes allowing the patients to move freely about.

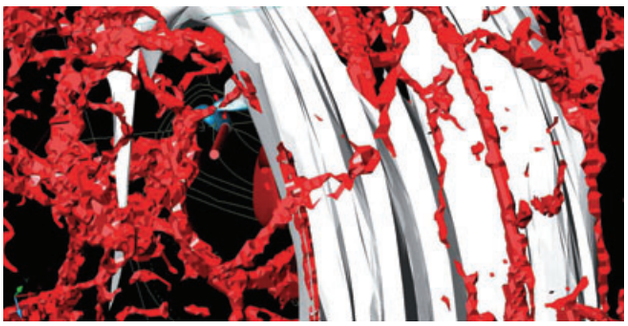

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FIGURE 3. Presurgical planning: the 3D angiography (in red) allows to evaluate the risk of conflict between leads and brain vessels. In white: 3D representation of the ventricular system; in blue: 3D reconstruction of the pedunculopontine tegmental nucleus; in dark red: the lead. In the background, the yellow lines represent the overlapped 2D sections (Tc) taken from the Schaltembrand and Wharen's atlas.

Postoperative imaging controls were performed in all patients in order to assess the final position of the implanted leads (CT scans in four patients and/or MRI in ten patients). Postoperative neuroimaging was aimed at evaluating the spatial relationships of contact leads with some anatomic landmarks of the brainstem, i.e., the pontomesencephalic border, the floor plane of the IV ventricle (VFL) and the fastigial floor line.

Electrode implantation was followed by a 15-day test period. During this test period, neurophysiologic recordings were performed using the contact leads. The clinical evaluations, using the Unified Parkinson's Disease Rating Scale (UPDRS) (45), were performed during off-and-on DBS. The neurophysiologic recordings, performed using routine electrophysiologic techniques, included somatosensory evoked potentials (SSEPs), blink-reflex, Hoffman (H)-reflex, and polysomnography. Speech was investigated in six patients, under differing DBS conditions, according to a linguistic task aimed to evaluate phonology, lexica semanties, morphology, and synthax (grammar) as described elsewhere (46). Different configurations of the DBS were tested, i.e., monopolar vs. bipolar, high frequency (HF) vs. low frequency (LF), and continuous vs. cyclic. The comparison between the clinical efficacy of HF (80 Hz) and LF (25 Hz) DBS was performed by means of Student's two-tailed *t*-test, with post-hoc Bonferroni's correction for multiple comparison, with a level of significance of $p < 0.01$. Clinical evaluations were also repeated during the follow-up period.

Results

The anatomic variability of individual landmark measurements and the stereotactic coordinates of the implanted electrodes are reported in Table 2. When evaluating the

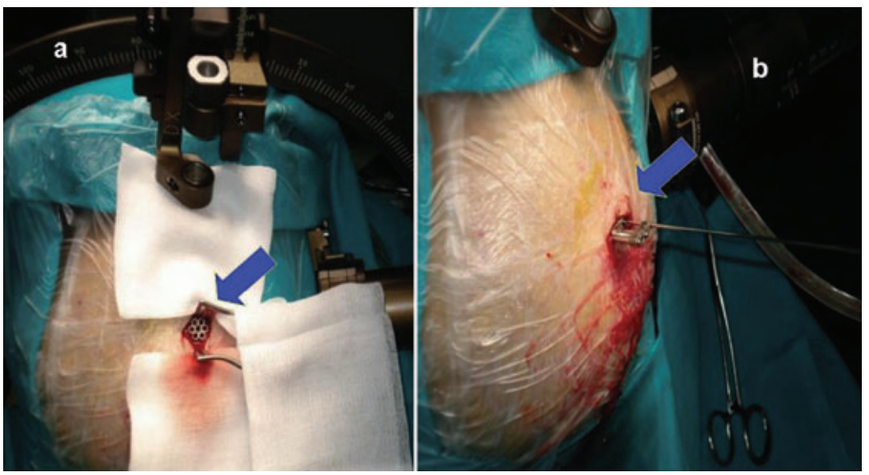

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FIGURE 4. (a) The "frame revolver" applied to the skull (12 mm of diameter) (blue arrow). (b) The microdrive directly implanted on frame revolver in some patients, holding the inserted stylet (blue arrow).

Pearson's correlation coefficients, by comparing the anatomic measurements of the brainstem and the x, y, and z stereotactic coordinates, we noticed that the VFL angle was the most important parameter influencing the values of the accuracy of the stereotactic coordinates. Postoperative CTs and/or MRIs confirmed the correct placement of the leads in the pons in all patients. Examples of postsurgical neuroimaging are shown in Figure 5.

The clinical follow-up lasted from one to more than 24 months in our patient population. None of the implanted patients showed major adverse events during the surgical procedure. Transient and clinically unremarkable

TABLE 2. Measurements of Anatomic Landmarks in the 14 Implanted Patients, Values of x, y, and z Coordinates and Displacement From Midline, in the 14 Patients Considered

	Midbrain				Coordinates			
Patient	Height	FFL height	MWP	VFL angle (degrees)	X	Y	Z	Midline displacement
0	10.0	18.9	26.6	35	90.0	83.9	144.7	–12
1	14.1	22.3	26.6	35	90.6	82.1	136.4	–13
2	14.3	23.4	26.4	39	85.5	85.5	153.1	–13
3	12.4	20.1	10.1	33	90.4	78.5	143.6	–13
4	10.4	15.2	27.9	26	86.0	77.2	122.6	–11
5	15.5	23.4	17.0	24	90.2	87.2	137.9	–10
6	14.5	19.2	15.9	4	93.0	81.5	131.9	–10
7	16.0	20.9	22.9	9	93.3	76.9	103.6	–8
8	9.3	14.0	24.5	23	91.8	75.2	130.1	–8
9	14.1	30.8	35.5	22	91.1	70.7	124.4	–7
10	10.6	24.9	24.8	18	91.4	69.8	140.0	–7
11	14.6	18.1	28.6	16	88.0	66.0	139.0	–7
12	10.2	26.5	23.4	19	92.4	69.0	127.0	–7
13	8.8	21.5	16.3	26	90.0	64.0	140.0	–7
Mean	12.49	21.36	23.86	23	90.3	77.2	133.4	–9.7
SD (±)	0.85	4.59	6.44	10	2.4	6.8	12.5	2.5

All values are expressed in mm.
FFL, fastigial floor line; FFL height, distance between FFL and top of Midbrain; MWP, maximus width of pons; VFL, ventricular floor line; SD, standard deviation.

TABLE 3. Configuration of PPTg-DBS During the Test Phase and Follow-up

			DBS parameters						
Patient	Implant	PPTg	Contacts	Voltage (V)	Pulse width (µsec)	Frequency (Hz)	Continuous	Cyclic (in follow-up)	Follow-up (months)
0	STN+CM-Pf bilateral	Bilateral	n.a.	n.a.	n.a.	n.a.	n.a.		
1	STN bilateral	Bilateral	$0^{(-)}$ $1^{(+)}$; $4^{(-)}$ $5^{(+)}$	1.5–2.0	60	25	+	+	>24
2	STN bilateral	Bilateral	$0^{(-)}$ $1^{(+)}$; $4^{(-)}$ $5^{(+)}$	1.5–2.0	60	25	+		>24
3	STN bilateral	Bilateral	$0^{(-)}$ $1^{(+)}$; $4^{(-)}$ $5^{(+)}$	1.5–2.0	60	25	+	+	>24
4	STN bilateral	Bilateral	$0^{(-)}$ $1^{(+)}$; $4^{(-)}$ $5^{(+)}$	1.5–2.0	60	25	+		2
5	STN bilateral	Bilateral	$0^{(-)}$ $1^{(+)}$; $4^{(-)}$ $5^{(+)}$	1.5–2.0	60	25	+	+	18
6	STN bilateral	Bilateral	$0^{(-)}$ $1^{(+)}$; $4^{(-)}$ $5^{(+)}$	1.5–2.0	60	25	+	+	18
7	GPi dx	Unilateral	$1^{(-)}$ $3^{(+)}$	2.0–2.5	60	25	+		12
8	GPi bilateral	Unilateral (initially bilateral)	$1^{(-)}$ $2^{(+)}$	2.0–2.5	60	25	+		8
9		Unilateral	$2^{(-)}$ $3^{(+)}$	2.0–2.5	60	25	+		12
10		Unilateral	$1^{(-)}$ $2^{(+)}$	2.0–2.5	60	25	+		12
11		Unilateral	$1^{(-)}$ $2^{(+)}$	2.0–2.5	60	25	+		12
12		Unilateral	$1^{(-)}$ $2^{(+)}$	2.0–4.0	60	25	+		11
13		Unilateral	$3^{(-)}$ $2^{(+)}$	2.0–2.5	60	25	+		1

PPTg, pedunculopontine tegmental nucleus; DBS, deep brain stimulation; STN, subthalamic nucleus; CM-Pf, centromedian—parafascicular complex; n.a., data not available; GPi, globus pallidus internus.

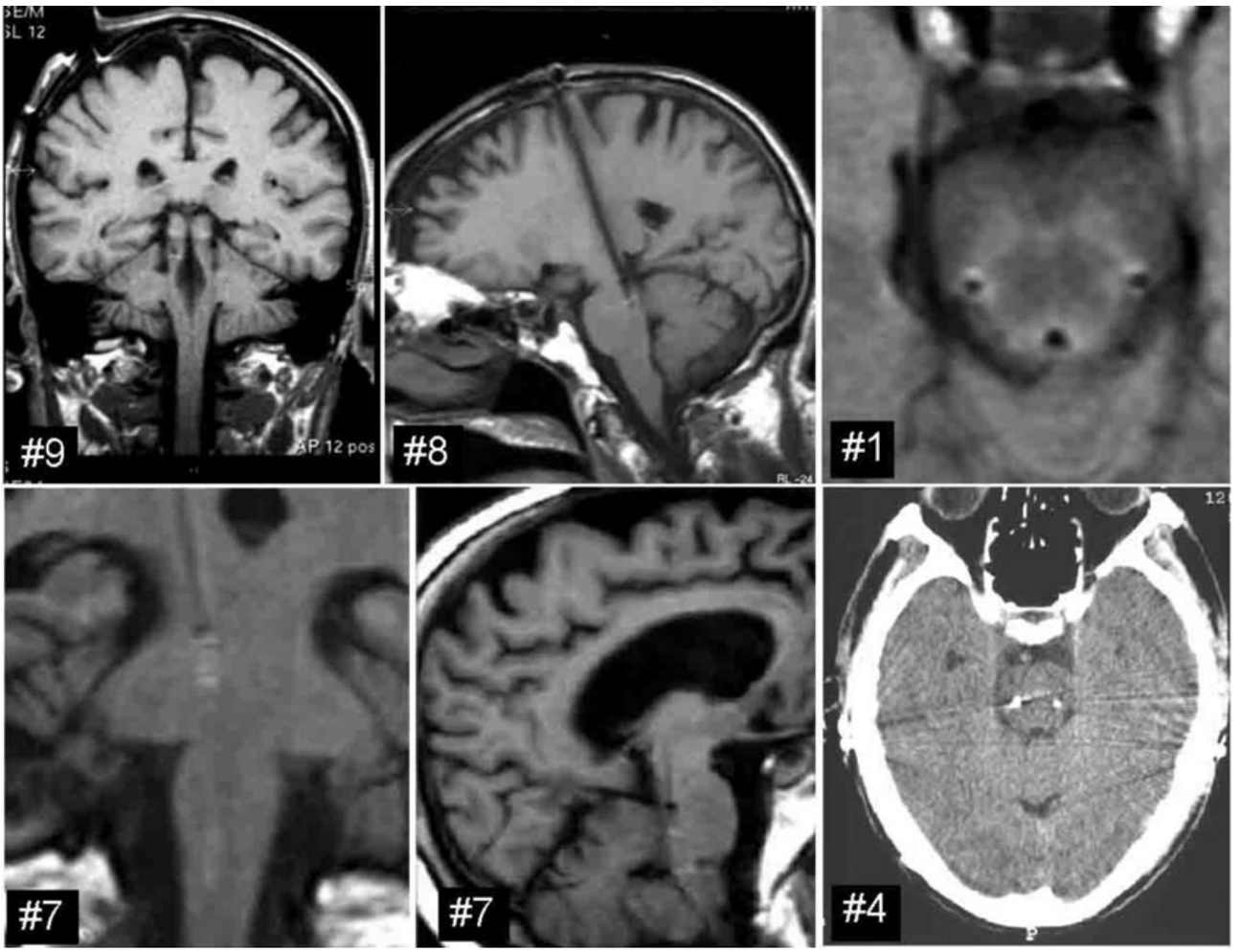

FIGURE 5. Postoperative magnetic resonance imaging control scans from patients #1, #7, #8, and #9 and postoperative CT control scan from patient #4 (lower right panel).

paresthesias occurred in three patients during the implantation procedure, likely as a consequence of the mechanical stimulation of the medial lemniscus. In all patients the intraoperative activation of DBS resulted in paresthesias, whose intensity, extension, and distribution varied according to the contacts employed, the voltage, and the rate of stimuli and to the proximity of the lead to the medial lemniscus as well.

The clinical response to DBS was evaluated during two distinct periods: a test period ("acute" DBS, immediately after surgery) and a follow-up period ("chronic" DBS, ranging from one to 24 months after surgery). The optimal frequency of DBS was assessed taking into account five items of the UPDRS-III scale including: 18 = speech; 27 = arising from the chair; 28 = posture; 29 = gait; 30 = postural stability. When compared with HF stimulation, LF stimulation resulted in a striking amelioration of UPDRS-III sub-items (Fig. 6).

In the test period, the following parameters of stimulation were identified as optimal for best clinical results: bipolar contacts $0^{(-)}$ $1^{(+)}$ and $4^{(-)}$ $5^{(+)}$); 60 msec pulse width; 25 Hz frequency; and an amplitude of 1.5–2 V. These stimulation parameters were consistently maintained throughout the clinical testing phase. A summary of the DBS parameters established in the testing phase and applied during the follow-up period is shown in Table 3.

In four patients (patients #1–4), during the follow-up period, the continuous DBS of the PPTg was alternated with a cyclic stimulation, applied during the night time. This pattern of stimulation did not change the overall clinical effectiveness.

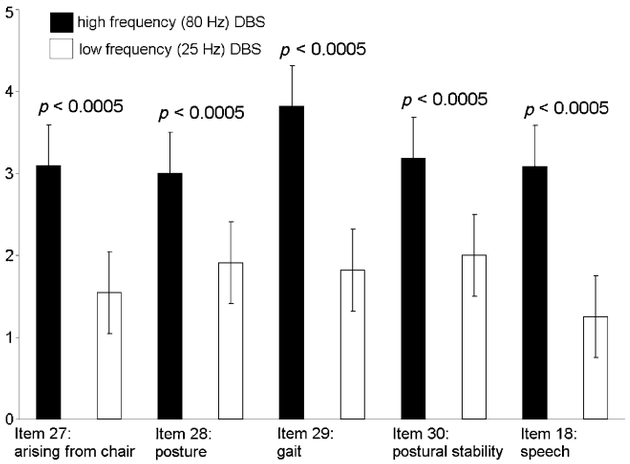

FIGURE 6. Comparison of Unified Parkinson's Disease Rating Scale—III subscores in the pedunculopontine tegmental nucleus implanted patients ($N = 13$) during deep brain stimulation at either high frequency (80 Hz, black columns) or low frequency (25 Hz, white columns). The bars indicate the standard deviation.

The proximity of the PPTg target with the medial lemniscus (Fig. 7) allowed us to record field SSEPs from the lead contacts. The peculiarity of this evoked response was helpful in assessing the proper positioning of the lead. Furthermore, the use of SSEPs allowed us to measure the distance of the contact leads from the obex (Fig. 8). During sleep stages, variations of electroencephalogram patterns [4] specifically occurred in NREM II and IV stages (Fig. 9) [5] without change of breathing patterns. In the awake condition, short periods of apnea rarely occurred.

The amplitude of the H-reflex increased during PPTg-DBS while the threshold to elicit this response was significantly lower than in the PPTg-DBS off-condition (Fig. 10). Such an effect recalls the increase of H-reflex amplitudes recorded many years ago in an animal preparation in which stimulation of the ventral root was preceded by single stimuli applied to the PPTg region (47). Finally, the prepulse inhibition of the R2 component of the Blink reflex could be restored during the DBS of the PPTg ipsilateral to the orbitofrontal muscle stimulated (Fig. 11).

As far as speech is concerned, a reduction of agrammatic errors, i.e., substition of free and inflectional morphemes, [6]

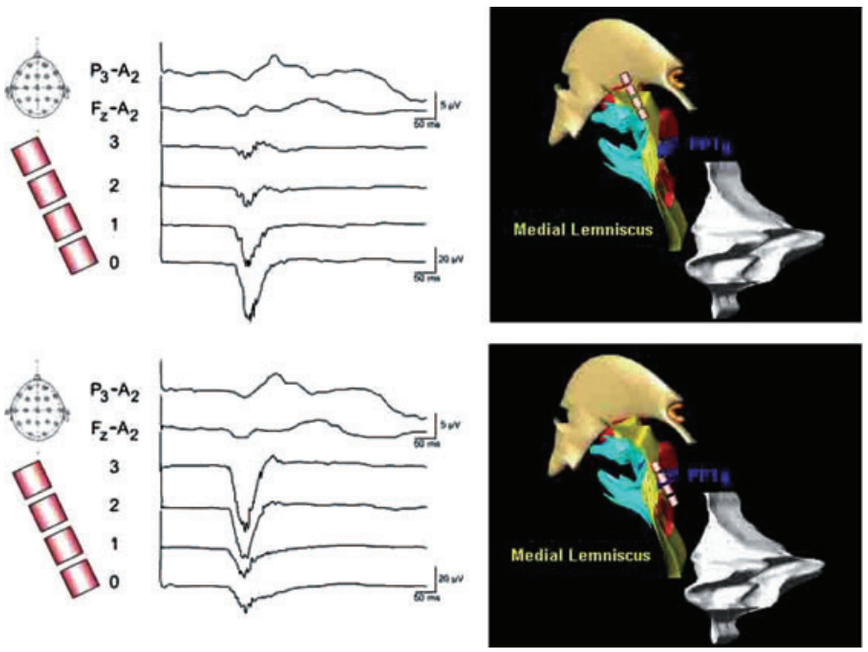

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FIGURE 7. Modification of the intraoperative somatosensory evoked potentials (SEPs) in accordance with the position of the electrode contacts [10] in the brainstem. On the left: SEP recordings, the first two traces are recorded from the scalp, the four lower traces correspond to the deep brain stimulation electrode (respectively, contacts 0, 1, 2, and 3). On the right: 3D representation of the targets. Upper panel: contacts are *above* the medial lemniscus (ML), the peak amplitude of the SEP is reached in the bottom trace, corresponding to the contact 0, which is close to the ML. Lower panel: contacts are within the pedunculopontine tegmental nucleus, *below* the ML, the peak amplitude of the SEP is reached in the middle (3rd) trace, corresponding to the contact 3, which is close to the ML.

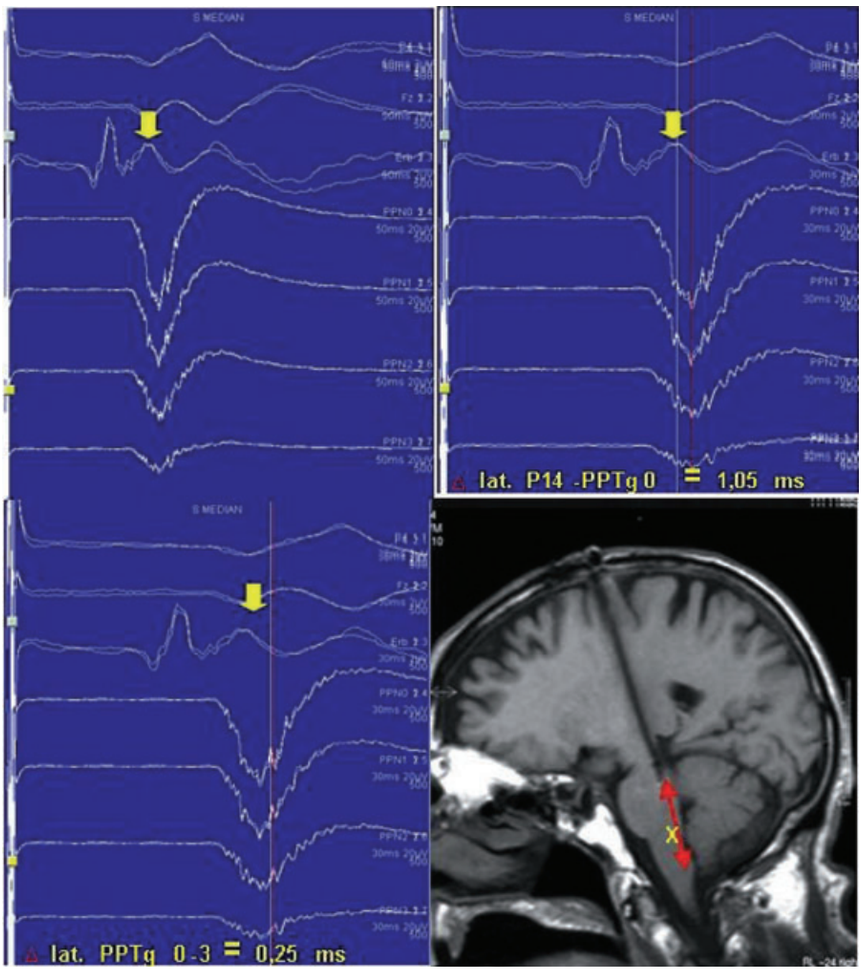

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FIGURE 8. The use of somatosensory evoked potentials (SEPs) to measure the distance of contact leads from the obex. The yellow arrow indicates the P14 wave. The difference (Δ) of the latency of the P14 recorded from contacts 0 (1.05 msec) and from contacts 0 and 3 (0.25 msec) of the lead implanted into the pedunculopontine tegmental nucleus (PPTg) is known. Taking into account that the distance of the four contacts is 7.5 mm, we can calculate the distance between the obex and the contacts. In such a way it is possible to evaluate whether the lead has been correctly positioned in the PPTg, whose spatial representation in the axial plane is comprised between plates from +31 to +36 mm from the obex according to the Paxinox and Huang's atlas. In the case illustrated in this figure, the contact 0 is located at 31.5 mm from the obex, as confirmed by the RMI.

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was found when stimulating the PPTg alone or in combination with the STN (Fig. 12).

Discussion

The extension of our initial experience from six to 14 patients, including 20 implantations in the PPTg, supports and adds new original data to our preliminary results (31,34), demonstrating that DBS implantation within the PPTg is a safe and effective DBS target in patients suffering from severe motor disorders such as those occurring in advanced stages of PD and in PSP. However, in order to render the targeting of the PPTg a precise, reliable, and reproducible procedure, we must take into account the inter-patient anatomic variations of the brainstem and to integrate these variations within the representations of brain structure provided by several atlases. The ability to include within the planning phase of the procedure a 3D reconstruction of brain vessels using stereotactic angio-CT scans (48), as reported previously, allows us to evaluate the risk of lead-vessel conflicts and greatly improves the safety of the procedure.

In the traditional surgical approach to DBS targets such as the STN, IOMERs are considered helpful to identify the target itself according to peculiar discharge patterns of

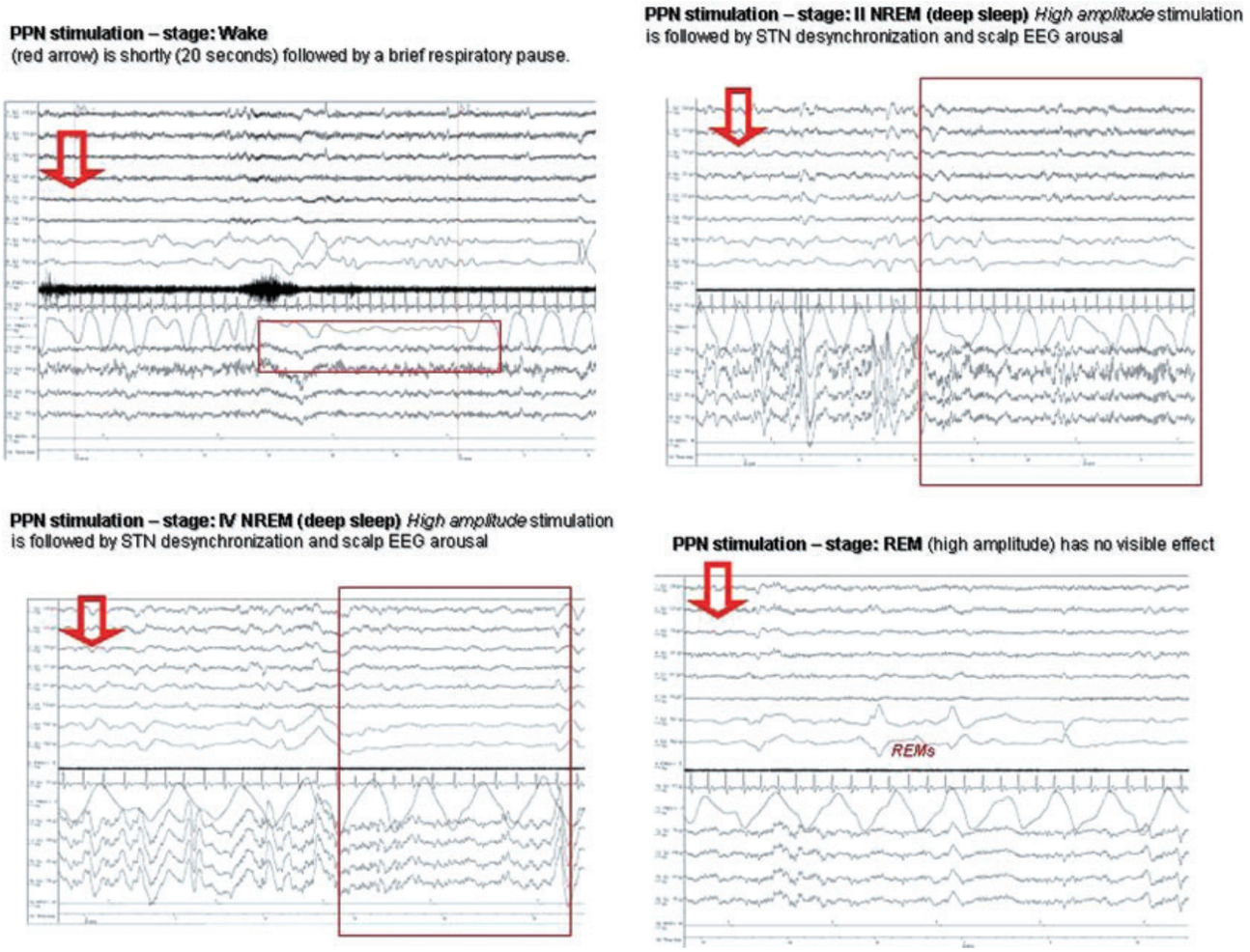

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FIGURE 9. The variation of electroencephalogram (EEG) patterns during different states of sleep (8 patients—14 bilateral 2 monolateral pedunculopontine tegmental nucleus [PPTg] investigated): Awake, II NREM Sleep, IV NREM Sleep, REM Sleep. The PPTg-DBS produce a clear arousal phenomenon on Scalp and subthalamic nucleus (STN) (globus pallidus internus) traces during NREM state and no modification in REM state, although increase in voltage of deep brain stimulation (DBS).

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STN neurons in neurodegenerative disorders (49,50). On the contrary, IOMERs recorded in two of our patients and in a presumed PPTg region investigated by Weinberger et al. (51) did not provide useful data helping us define the boundaries of the PPTg for neurosurgical purposes. Rather, intraoperative and immediately postoperative evaluations of neurophysiologic events assume more relevant significance. In particular, because of the proximity of the PPTg to the medial lemniscus and of the modification of the blink reflex, whose R2 component is integrated at pontine levels (52,53), the features of SSEPs represent unequivocal physiologic landmarks to identify the correct implanting of the PPTg DBS lead.

The postoperative evaluation, taken over a period lasting medially 15 days, allowed us to perform longitudinal clinical, electrophysiologic, and neuroradiologic assessments. In this way, it was possible to determine the correct position of the leads and define the stimulation parameters which produced the best, and better tolerated, response.

Among the first six patients who were bilaterally implanted, in the follow-up phase (as long as 24 months) none complained of autonomic adverse side-effects because of either the mechanical presence of the lead in the PPTg region or to the start of DBS. Some patients reported a behavioral change for the better and a subjective mood improvement. However, no overt changes of sexual habits or of activities of daily living have been observed until now in our patients. However, given that the PPTg is involved also in non-motor functions (54–56), likely through fibers directed to thalamic and limbic

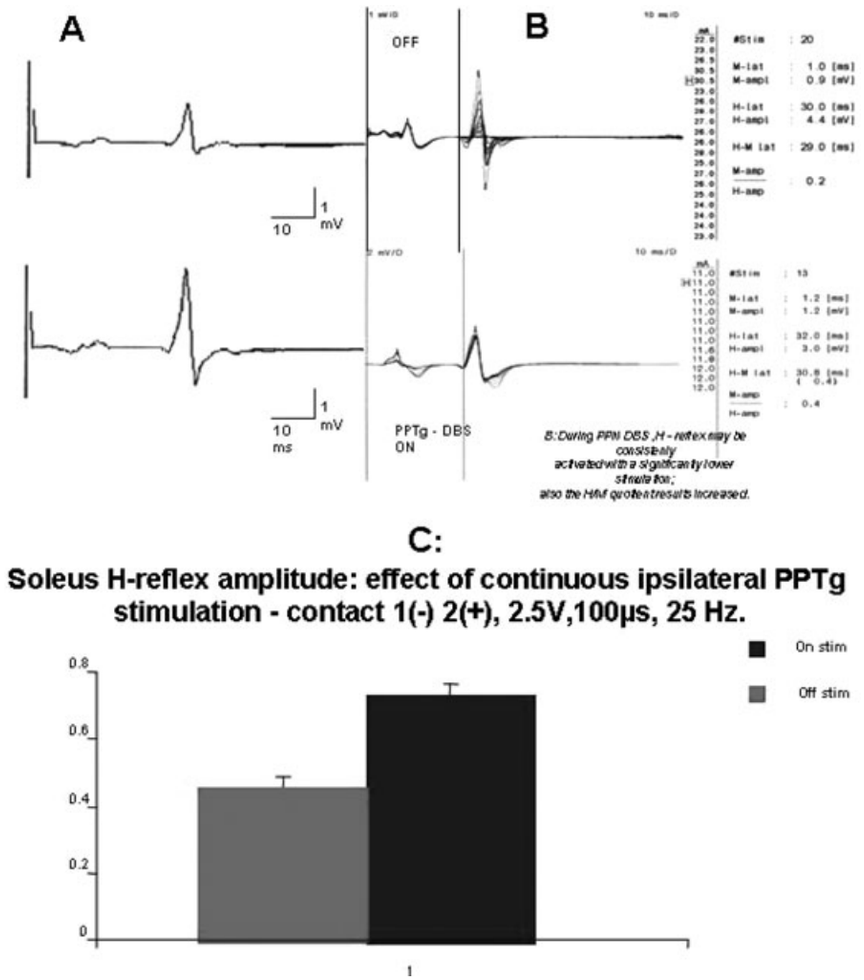

FIGURE 10. The variation of the soleus H-reflex in off- and on-PPTg-DBS. (a) During pedunculopontine tegmental nucleus (PPTg) stimulation at 25 Hz and 2 V the amplitude of the H-reflex wave was doubled compared with the stimulation off. (b) During PPTg stimulation it was possible to elicit the H-reflex at a lower stimulus intensity (13 mA) in comparison with the PPTg-off condition (20 mA). Numeric values of latencies, amplitude, and ratio of M/H responses are directly reported in the picture. (c) Histogram showing the soleus H-reflex amplitude recorded while stimulating the PPTg using contacts 1–2 (2.5 V, 25 Hz, 100 µs). (d) H/M ratio during PPTg stimulation off and on condition.

structures, the behavioral consequences of PPTg-DBS need to be further investigated with specific neuropsychologic and cognitive tests.

Polysomnographic recordings showed a cortical arousal in response to PPTg-DBS during the slow-wave sleep, which is explainable by the involvement of PPTg neurons in sleep mechanisms (57–59). Language was improved by PPTg DBS as far as grammar processing was involved using the tests employed. This is in line with the participation of basal ganglia in aspects of speech and language (60–62), though the study needs to be implemented in a larger number of patients and under different stimulation targets.

The implantation of the electrode *per se* in the DBS-off condition induced physiologic modifications such as reappearing of the blink reflex. LF stimulation was more effective than HF in improving the clinical parameters considered. This is in accordance with the reports of Jenkinson et al. (63–65) who observed similar effects in non-human primates. A crucial difference in the stimulation of PPTg when compared with stimulation of the STN is the frequency of stimulation, which in the case of the PPTg appears to be optimal at 25 Hz.

In four patients, during the follow-up phase, cyclic stimulation was tested, in particular during the night sleep. This pattern of stimulation, which was tested in patients with multiple and bilateral implantations (STN or GPi + PPTg), did not show significant clinical differences when compared with the continuous stimulation protocol.

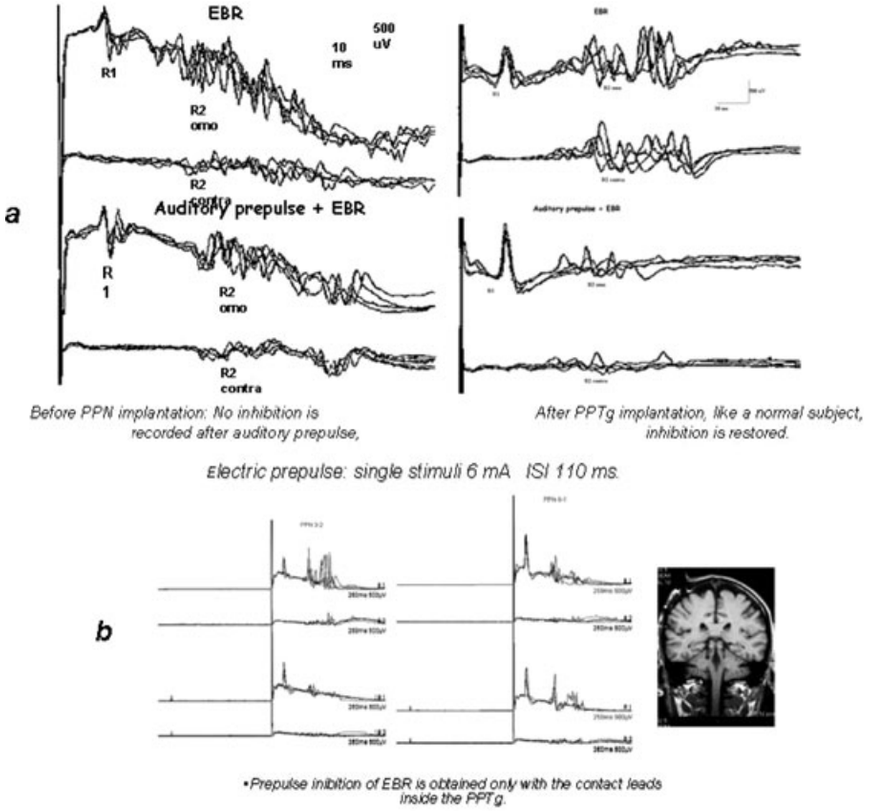

FIGURE 11. (a) Modifications induced by PPTg-DBS on the blink reflex. The prepulse inhibition of the R2 component of the blink reflex is restored with the mechanical insertion of the leads. The prepulse inhibition is restored with low intensity and short delay only with the contacts inside the nucleus. PPTg, pedunculopontine tegmental nucleus; DBS, deep brain stimulation.

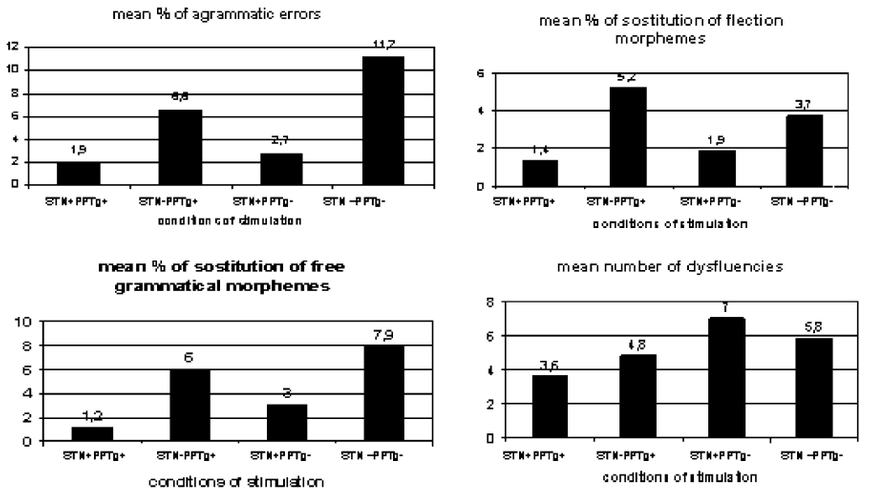

FIGURE 12. Evaluation of pedunculopontine tegmental nucleus (PPTg) stimulation on speech: the hystograms represent the effects on different evaluated items. The effects of the PPTg-DBS are represented alone or combined with the STN-DBS. The improvement of performances during PPTg-DBS was homogeneous, except in one patient. DBS, deep brain stimulation; STN, subthalamic nucleus.

In patients with multiple implantation (STN or GPi + PPTg), the simultaneous stimulation of both targets was more effective in ameliorating Parkinsonian symptoms and in reducing motor disabilities and drug requirements than when only one target was stimulated. In the past, stimulation of a single target such as either the STN or the GPi resulted in effective amelioration of motor symptoms and severity of PD for a period of at least three to four years, but a certain decline of effectiveness in the off-drug state has been observed, requiring a frequent adjustment of stimulation and medication (66). The choice of multiple targets, and in particular the association of PPTg-DBS to traditional targets, might help overcome these limitations. Of course, more prolonged follow-up studies in a larger cohort of patients might clarify this issue.

Conclusions

Targeting procedures for implantation of the PPTg requires an accurate adaptation of traditional approaches employed to date in stereotactic neurosurgery of the basal ganglia owing to the interindividual anatomic variability of brainstem. PPTg-DBS appears to be safe and effective in ameliorating specific symptoms of PD, in particular speech, gait, and posture. Careful clinical examinations of patients supported by neuroimaging studies must be carried out to identify those who are selectively eligible for PPTg-DBS. Moreover, the potential for multiple implantations needs to be further investigated in view of the promising clinical perspectives of this approach as suggested by comparing our previous results on other targets (67–69) with the actual ones involving the PPTg.

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Dedication

During the preparation of this manuscript a tremendous earthquake devastated the City and the University of L'Aquila, Italy, leaving hundreds of victims. We wish to dedicate this paper to all the students who have lost their lives in this great tragedy, hoping that this University may return to its splendor as soon as possible.

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