J Neural Transm
DOI 10.1007/s00702-011-0593-x

The deep brain stimulation of the pedunculopontine tegmental nucleus: towards a new stereotactic neurosurgery

Paolo Mazzone · Stefano Sposato · Angelo Insola · Eugenio Scarnati

Received: 17 December 2010 / Accepted: 24 January 2011

Abstract The application of deep brain stimulation (DBS) to the pedunculopontine tegmental nucleus (PPTg) has required profound modifications of classic neurosurgical techniques and of the criteria for evaluation of clinical results. This review analyzes a novel method of targeting the PPTg, based on angio-computerized tomography (angio-CT) scans and the tridimensional reconstruction of nuclei and cerebral vessels, and considers the advantages of applying these methods in comparison to the more traditional approach based on reference points obtained through the evaluation of the bicommessural line. Validation of the results obtained following unilateral PPTg DBS through neurophysiological recordings and objective measurements of functional parameters suggests that the PPTg may be considered as an initial target for the treatment of motor symptoms in selected patients affected by idiopathic Parkinson's disease (PD), which, if required, could be followed by DBS of other target areas. Moreover, on the basis of the observations derived from stimulating the PPTg, the potential utility attributed up to date to intraoperative neurophysiological recordings for identifying neurosurgical targets should be revisited, and the need for changes in the intraoperative management of patients has arisen from the body of evidence accumulated over recent years. The results obtained by different groups following PPTg DBS in parkinsonian patients are not uniform, most likely due to a cautious acceptance of this methodology, the experience progressively acquired, the criteria for patient selection and to subtle differences in target location. Although the role of PPTg in PD and/or in other pathologies remains to be clarified, pursuing the traditional approach on classical basal ganglia targets may limit the perspective of DBS based on multiple implantations.

Keywords Somatosensory evoked potentials · Intraoperative microrecordings · Local field potentials · Blink reflex · Gait analysis · Jaw movements

P. Mazzone (✉)
Functional and Stereotactic Neurosurgery,
CTO Hospital ASL Roma C, Via San Nemesio 21,
00145 Rome, Italy
e-mail: stereomaz@libero.it

S. Sposato
Neuroradiology, CTO Hospital ASL Roma C,
Via San Nemesio 21, 00145 Rome, Italy

A. Insola
Clinical Neurophysiopathology, CTO Hospital ASL Roma C,
Via San Nemesio 21, 00145 Rome, Italy

E. Scarnati
Department of Biomedical Sciences and Technologies (STB),
University of L'Aquila, Via Vetoio Coppito 2,
67100 L'Aquila, Italy

Introduction

The present review aimed to summarize and critically discuss the neurosurgical and clinical experience of deep brain stimulation (DBS) of the pedunculopontine tegmental nucleus (PPTg) that we have progressively acquired since our first implantation in 2005 (Mazzone et al. 2005b, c). To the best of our knowledge at least 55 papers have been published up to date concerning the PPTg in humans, of which only 18 reported data directly related to DBS. Out of these 18 papers, only 5 papers published before 2009 and 7 published after 2009 included postoperative neuroradiological images, while only 11 reported clinical results of DBS and were accompanied by appropriate clinical

Published online: 12 February 2011

evaluations (Table 1), and 3 of these 11 papers were case reports. We have considered all of these papers in an attempt to provide an exhaustive clinical and neurosurgical discussion concerning the utility and limits of PPTg DBS in idiopathic Parkinson's disease (PD) and progressive supranuclear palsy. We believe that it is time to provide a comprehensive view of our methodological and conceptual data arising from a consistent number of patients ($N = 23$) implanted up to date in our hospital. We have included the initial six patients, to whom other authors often refer and whose aspects were studied and partially reported elsewhere. Patient 0, who was not implanted but only targeted for intraoperative microrecordings (IOMERs), is also included (Table 2, pt. 0).

This review is divided into four parts devoted to: (1) identification of the PPTg target area, (2) postoperative neuroradiology, (3) the changing role and type of neurophysiology, and (4) the clinical analysis.

Each of these items will be discussed in relation to the differences in methodology and patient selection as well as the intraoperative management related to the modifications of surgical procedures that we have introduced and assessed as our experience progressed. The differences between the PPTg and the traditional targets for PD surgery will be adequately highlighted. In particular, it will be discussed how the PPTg DBS in PD is a surgery that requires several modifications to the canonical concepts and models reserved at present for the neurosurgery of the subthalamic nucleus (STN).

Identification of the PPTg target area: differences in the brain atlases and in the neurosurgical literature

One of the canonical concepts of stereotactic surgery is identification of the target, which is considered as the anatomical site that, irrespective of the procedure adopted (lesion, stimulation, cells grafts, for example), causes a reliable clinical effect. This simple axiom can no longer be considered in its absolute meaning: it needs to be revisited in light of the growing amount of experience acquired through the use of neurostimulation techniques. If we consider the variables involved in stereotaxic surgery and the possibilities offered by modern technologies, the traditional view of a neurosurgical target may appear to be outdated. Clearly, any effort must be made to achieve the greatest perfection in the identification of a site-specific effect when dealing with neurostimulation, and, in addition, it is also crucial to understand which neuronal elements the stimulation acts on. The possibility of applying

Table 1 Summary of studies published up to date on PPTg DBS in humans

Authors and year	No of patients[a]	Pathology	Type of report	Neuroradiology	Lead
Mazzone et al. (2005a)	3	PD	S, C	+	3389®
Mazzone et al. (2005a, b)	2	PD	S, N	–	3389®
Plaha and Gill (2005)	2	PD	S, C	+	3387®
Stefani et al. (2007)	6	PD	S, C	+	3389®
Lim et al. (2007)	1	PD	N	+	3387®
Mazzone et al. (2008a, b)	13	PD–PSP	S, C	+	3389®
Weinberger et al. (2008)	7	PD	S, N	–	3389®
Mazzone et al. (2009)	14	PD–PSP	S, N, C	+	3389®
Piallat et al. (2009)	2	PD	S, N	+	3389®
Ostrem et al. (2010)	1	PPFC	C	+	3389®
Shimamoto et al. (2010)	4	PD–AP	S, N	+	3389®
Ferraye et al. (2010)	6	PD	S, C	+	3389®
Moro et al. (2010)	6	PD	C	+	3387®
Yeh et al. (2010)	8	PD–PSP	S, N	–	3387®
Thevathasan et al. (2010)	11	PD	C	–	3387®
Wilcox et al. (2010)	1	PPFG	C, I	–	3387®
Schweder et al. (2010a, b)	1	PD	I	–	3387®
Mazzone et al. (2011)	23	PD–PSP	S, N, C, I	+	3389®

S surgery, *N* neurophysiology, *C* clinical analysis, *I* instrumental analysis, 3389®/3387®, Quadripolar lead from Medtronic Inc., Minneapolis, USA, Neurological Division; *PD* Parkinson's disease, *PSP* progressive supranuclear palsy, *PPFG* progressive freezing gait disorder, *AP* atypical parkinsonism

[a] Studies conducted on the patients reported in more than a paper are not included

Table 2 Patients features

Pts.	Age at surgery sex (years)	Diagnosis	Duration of symptoms (years)	Other targets	PPTg
0	*60F*	*PD*	*10*	*STN-CM/Pf*	*10 MERs*
1	*62M*	*PD*	*12*	*STN Bilat*	*Both*
2	*61M*	*PD*	*13*	*STN Bilat*	*Both*
3	*67M*	*PD*	*16*	*STN Bilat*	*Both*
4	*66M*	*PD*	*10*	*STN Bilat*	*Both*
5	*62M*	*PD*	*9*	*STN Bilat*	*Both*
6	*69M*	*PD*	*10*	*STN Bilat*	*Both*
7	66F	PD dyst	13	GPi(R*)	R
8	56M	PD dyst	5	GPi Bilat	L
9	49M	PD	11	–	R
10	48M	PD dyst	10	–	R
11	67M	PD	8	–	R
12	70M	PSP	8	–	R
13	65M	PD dyst	16	GPi Bilat	R
14	58M	PD dyst	5	GPi Bilat	R
15	62M	PD	11	–	R
16	53M	PD	10	–	R
17	54M	PD	5	–	R
18	78M	PD	34	–	R
19	56M	PD	7	–	R
20	47M	PD	4	–	R
21	63M	PD	9	–	R
22	56M	PD	10	–	R
23	69M	PD	10	–	R

Italic entries represent first group of patients implanted bilaterally in STN and PPTg. Non-italic entries represent patients implanted after 2007

* Adverse event

DBS to the PPTg region has prompted a consistent effort to identify the most appropriate site of stimulation and to standardize coordinates, as happened years ago when STN surgery was introduced.

It should be considered that until 2005, when we first began neurosurgery experience with the PPTg, there was limited knowledge of planning and a scanty awareness of the anatomical problems that could accompany stereotactic surgery of the brainstem. This limitation was essentially caused by the fact that this cerebral region was not among the targets usually used in neurosurgery (Talairach et al. 1957). At that time reconstructions of the brainstem based on the overlapping of stereotactic atlases and magnetic resonance imaging (MRI) were difficult, but they became even more complicated when an automatic superposition of stereotactic plates over MRI images was attempted (Niemann et al. 1999). Furthermore, at the same time landmarks that did not find large applications later on, such as the fastigium point, were considered (Afshar et al. 1978). Previous experience of electrode implantation in the Koelliker–Fuse area (Young et al. 1992), borrowed from pain neurosurgery, seemed to confirm even at that time that the application of traditional stereotactic methodologies, such as ventriculography, evaluation of the bicommessural line (Ca–Cp line), standardized coordinates and neurophysiological recordings, did not allow the exact anatomical localization of the target in the brainstem to be ascertained. Young et al. (1992) illustrated a plain postoperative X-ray, but it was not easy to detect the correspondence between the lead position and the target in the area considered in that image.

Moreover, the partial representation of the PPTg in the only stereotactic surgical atlas reporting this nucleus (Schaltenbrand and Wahren 1977) was read by some authors in a contradictory manner (Zrinzo et al. 2007a). Only after 2007 it was realized that the Schaltembrand and Wharen's atlas was of limited value for identifying the PPTg, especially when compared to other atlases, which, although stereotactic (Paxinos and Huang 1995) were not intended for neurosurgery and/or were only based on the cytoarchitecture of the brainstem (Olszewski and Baxter 1982). Furthermore, the nomenclature, abbreviations and acronyms used by various authors to indicate the PPTg were not standardized and did not help to produce an unambiguous reference for the target: nucleus tegmenti pedunculo-pontinus (Tg.pdpo) (Schaltenbrand and Wahren 1977); pedunculopontine nucleus (PPN) (Lavoie and Parent 1994; Pahapill and Lozano 2000) or PPT (http://

www.brainmaps.org); PPTg (Olszewski and Baxter 1982; Paxinos and Huang 1995). The compromise adopted by Stefani et al., who in recent papers (Ceravolo et al. 2010; Peppe et al. 2010) called the PPTg the "caudal pontine representation of PPN" is also inappropriate. Indeed, such an arbitrary definition has no anatomical or cytoarchitectonic background and may further confound the reader since the two abbreviations are used in the literature and even in the popular Wikipedia to indicate the same structure.

At the beginning of their experience with the PPTg some authors (Zrinzo et al. 2007a, b) identified it as the griseum circumflexum brachii conjunctivi (Gr.cf.b.cj., Area U from Ziehen), as reported in the Schaltenbrand and Wahren's atlas, whereas others (Yelnik 2007) attributed the effects resulting from the stimulation of the PPTg in our first implanted patients to the peripeduncular nucleus (PPD). This latter interpretation certainly arose from a poor consideration of the postoperative neuroradiological images published in our first paper (Mazzone et al. 2005c) and from an inappropriate drawing derived from the Schaltembrand and Wharen's atlas (Stefani et al. 2007). The drawing that appeared on page 1599 of that paper was certainly incorrect and rightly questioned (Yelnik 2007; Zrinzo et al. 2007b); therefore, we provided further details of the correct location of the targeted area (Mazzone et al. 2007a, b). It should be kept in mind that the Schaltembrand and Wharen's atlas does not represent the Tg.pdpo either in sagittal slides or in axial slides, and that there is a gap between the suprapontine (midbrain) and the Tc 0 axial slides. Furthermore, in the coronal plane, only two slides include the Tg.pdpo (Fp-15.5 and -16.5), represented above the Gr.circ.b.cj. These discrepancies have been highlighted and thoroughly discussed in our recent paper (Mazzone et al. 2008b).

A crucial advance in the correct localization of the PPTg was provided by 3D reconstructions of the nucleus (Mazzone et al. 2008a). At that time a 3D reconstruction of the whole brainstem already existed (Afshar and Dykes 1982) but it did not include the PPTg. Our reconstruction was made on the basis of slides from different atlases, despite the inconsistencies that can be observed in these atlases as far as the position of the pars compacta of the PPTg (Fig. 1A-e) is concerned. Other authors (Piallat et al. 2009) also presented a 3D reconstruction, that seemed to be based on another very complex and multifactorial atlas

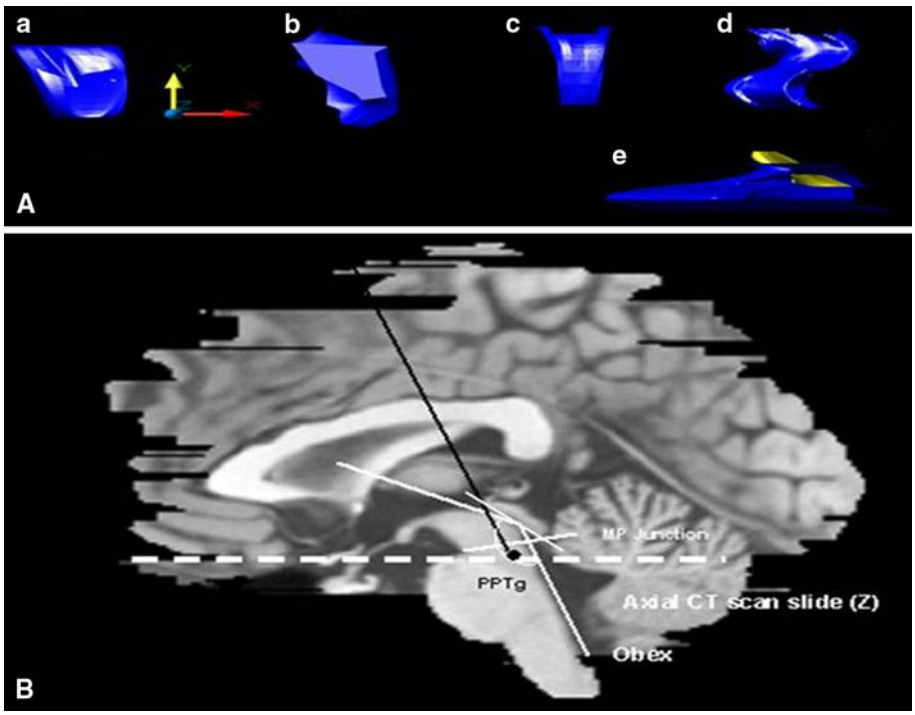

Fig. 1 **A** Tridimensional reconstruction of PPTg in coronal view according to: *a* Olzsewski and Baxter's human cytoarchitectonic atlas (1982); *b* Schaltenbrand and Wharen's human stereotactic surgical atlas (1977); *c* Paxinos and Huang's (1995) monkey and human (*d*, *e*) stereotactic atlases; *e* sagittal view of PPTg (*yellow* pars compacta). **B** Anatomical references for stereotactic determination of PPTg. The *white line* connecting the obex to the floor of IV ventricle makes an angle with the *white inclined line* of the midbrain tegmentum which is different from the angle formed with the *white line* representing the quadrigeminal plate; *the dashed line* represents the angio-CT scan slide in which the *Z* coordinate can be established; the *short continuous white horizontal line* represents the midbrain–pontine (*MP*) junction. The *black dot* represents the PPTg position below the MP junction whereas the *black continuous line* represents the ideal lead trajectory in the lateral projection

(Yelnik et al. 2007). Undoubtedly, in the future the data provided by tractographic studies may be proven useful for facilitating target localization (Aravamuthan et al. 2007, 2008; Schweder et al. 2010a). In any case, the debate prompted by our first implantations has been important for raising interest in the functional neurosurgery of the PPTg, as also shown by the impact of our results and methods in the Meeting held in Oxford in 2008, and by the number of PPTg implantations performed by other groups after our initial study (Table 2).

In forming a conclusion we can affirm that at the beginning of 2009, although on the one hand, there was a general agreement on our approach and results (Muthusamy et al. 2007), on the other hand the criticism expressed by some authors (Yelnik 2007; Zrinzo et al. 2007a; Ferraye et al. 2009) still remained conjectural and was based only on our initial patients. In a successive series operating on 14 patients we introduced new reference points that can be anatomically measured (Mazzone et al. 2008b, 2009). These points take into consideration the extreme anatomical variability of the brainstem from patient to patient. This variation decreases the importance of the Ca–Cp line as a reference point (Niemann et al. 1999; Mazzone et al. 2008b) although this line continues to be utilized by some authors (Zrinzo et al. 2008; Piallat et al. 2009; Shimamoto et al. 2010). Thus, the pontomesencephalic junction, the obex, the pediment and the inclination of the aqueduct with respect to the floor of the fourth ventricle, as well as the position of the quadrigeminal plate and the width of the pons, acquire a crucial importance in the neurosurgery of the PPTg (Fig. 1B). In this context the traditional proportional allocation scheme (Talairach et al. 1957) loses its role as a reference for neurosurgical planning, although it remains valid for traditional targets such as the STN and, in general, for other basal ganglia targets (Mazzone 2003; Mazzone et al. 2005a, 2009) (Fig. 1b). In other words, the planning for PPTg implantation must be individualized from patient to patient according to direct radiological identification of the target and not merely based on numerical coordinates obtained through the classical proportional schema hinged upon Ca–Cp line evaluation.

Thus, it is difficult to understand why some neurologists in a rudimentary description of the neurosurgery of PPTg reported generic numerical coordinates for the PPTg in some studies (Pierantozzi et al. 2008; Peppe et al. 2010; Stefani et al. 2010), while accepting our innovative principle in others (Ceravolo et al. 2010) in spite of the fact that in the patients examined the PPTg was always targeted by the same neurosurgeon using the same technique.

The region including the PPTg may be further characterized according to an analysis of local field potentials (LFP), since the best clinical outcome found in our patients correlated with the recording through the implanted lead of well-defined and consistent physiological oscillations (Androulidakis et al. 2008). The occurrence of these signals may be considered indicative of the proper localization of the lead contacts in the PPTg area. Contrary to the ventriculographic planning carried out in four of the first five patients operated on, planning of the PPTg in our last 18 patients (Mazzone et al. 2008b, 2009, 2011) was made on the basis of angio-CT scan by integrating four different systems (Fig. 2), i.e.:

1. Axial, sagittal and coronal multi planar reconstruction (MPR) processing by angio-CT scans (Fig. 2a).
2. Angio-CT scan slide (Z) for the determination of *X* and *Y* coordinates (Fast-Tc, Maranello Stereotactic System, CLS Titanium, Forlì, Italy) (Fig. 2b).
3. Tridimensional planning of different structures and 2D slides. (3D Maranello Stereotactic Planning System, CLS Titanium, Forlì, Italy) (Fig. 2c).
4. Vessels reconstruction and avascular trajectory planning (Fig. 2d).
5. Tridimensional virtual surgery (Fig. 3a).

The angio-CT scan offers the advantage of being less affected by magnification, distortion and artifacts and it permits a clear, direct overlap between the axial slides of atlases also taking into account the variability in the brainstem anatomy from patient to patient. Hence, the lead trajectory that can be established on the basis of angio-CT scan assures that no vessel conflict occurs. In our experience such a trajectory must be extraventricular, intrapeduncular and intra-axial (Mazzone et al. 2008b, 2009) In a recent paper the authors (Khan et al. 2010) proposed an intraventricular access and trajectory, but we believe that such a choice may be critical, because a more vertical trajectory may have an impact with the red nucleus and with the nuclei of cranial nerves III and IV. Thus, we agree with the criticism expressed in the commentary by E.R. Gross that accompanied the above-mentioned paper, and with the concerns of other authors (Zrinzo et al. 2009) who reported frequent and significant medial displacement of the lead as it transgressed, with an oblique angle, the ependymal lining.

The individualized trajectory that we adopted was made on the basis of a 3D reconstruction of vessels and after having studied the spatial arrangement of the veins of the cortical and ventricular walls and their relationships with the cerebral peduncles (Fig. 2d). Indeed, after adopting such a trajectory, the lead contacts can be allocated in different regions of the pontine tegmentum and may therefore induce different results as a consequence of the distribution of the electrical field (Fig. 6). In our planning, the axial plane of the CT scan, which represents the *Z* coordinate of the PPTg, was chosen 5 mm below a line traced perpendicularly to the floor of the IV ventricle, at a

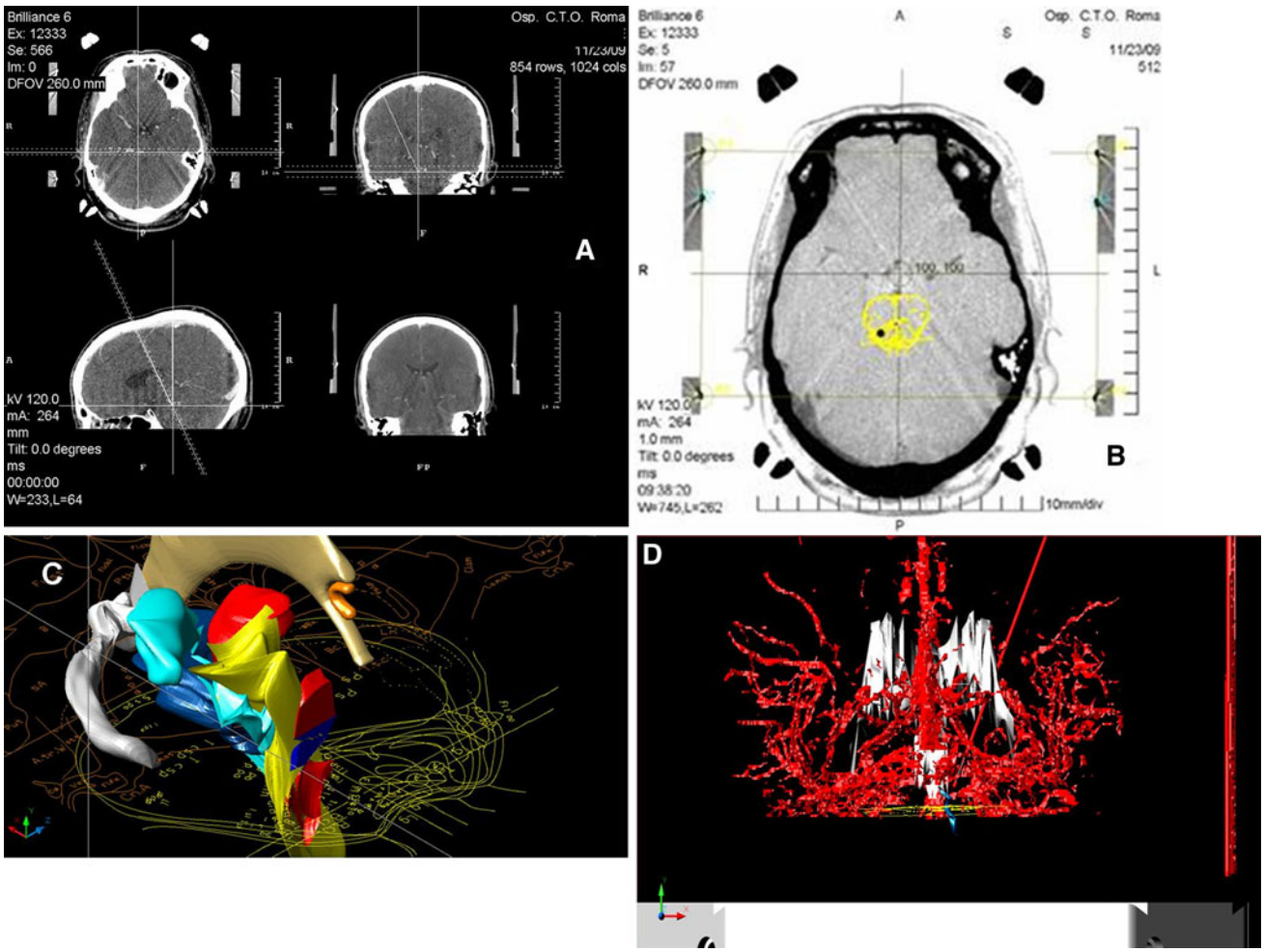

Fig. 2 **a** Angio-CT scan: multi planar reconstruction for the direct determination of PPTg coordinates and former choice of trajectory with angio-planning in 2D slides. The lower coronal and sagittal CT slides were cut along the trajectory planes. **b** Angio-CT scan: direct individualized determination of *X* and *Y* values by overlapping atlas slides on the angio-CT scan slide (*Z* plane chosen on the basis of the distance from the obex. Fast-Tc, Maranello Stereotactic System®, CLS Titanium, Forlì, Italy) **c** Tridimensional planning of different structures and 2D slides, based on 2D from the Schaltembrand and Wharen's atlas. (Axonometric projection. Maranello Stereotactic System®, CLS Titanium, Cesena, Italy). *Light brown* III ventricle, *white* anterior commessure, *gold brown* posterior commessure, *ciano* STN (*upper*) PPD (*lower*), *yellow* medial lemniscus, *red* red nucleus (*top*). Area parabigemina cuneiformis (A.pbg) (*middle*) and area U (*bottom*) (Gr.cf.b.cj), *light blue* substantia nigra (LN), *dark blue* PPTg (Tg.pdpo). The abbreviations are as in the Schaltembrand and Wharen's atlas. **d** Vascular planning: coronal projection. Maranello Stereotactic System®, CLS Titanium, Cesena, Italy. *Red* vessel reconstruction from angio-CT scan, *dark red* lead, *white* ventricular system, *dark blue* locus coeruleus, *silver* stereotactic frame. PPTg not represented

reference point located 31 mm above the obex but with a certain variability due to individual anatomical differences from patient to patient (Table 48 slide +31 in Paxinos and Huang's atlas) (Fig. 1B). This axial plane is generally tangential to the posterior clinoid process. In the lateral position the landing point is 7 mm anterior to the quadrigeminal plate, whereas the laterality is determined directly on the axial slides in a site (Fig. 1B) that corresponds to the region where the major afferents from the inner segment of the globus pallidus (GPi) run (Muthusamy et al. 2007; Aravamuthan et al. 2007, 2008).

The lead crossing the medial lemniscus (ML) allows to record intraoperatively the somatosensory evoked potentials (SEPs), whose characteristics permit to confirm the position reached by the lead (Mazzone et al. 2007a, 2008b, 2009; Insola et al. 2010) (Fig. 3a). The planning system that we applied in recent years has produced some differences in the final lead position in our last 18 patients in comparison to the first 5 patients implanted in 2005 and 2006. Indeed in the initial 5 patients, the lead reached the pontine wall in a rather lateral position while in the recent 18 patients the lead penetrated the pons more medially and reached the lower part of the PPTg pars compacta (Fig. 4a, slide 3) (Mazzone et al. 2008a, b, 2011), i.e. in the region in which the PPTg is close to the locus coeruleus (Aravamuthan et al. 2008) (Fig. 4a, slide 2).

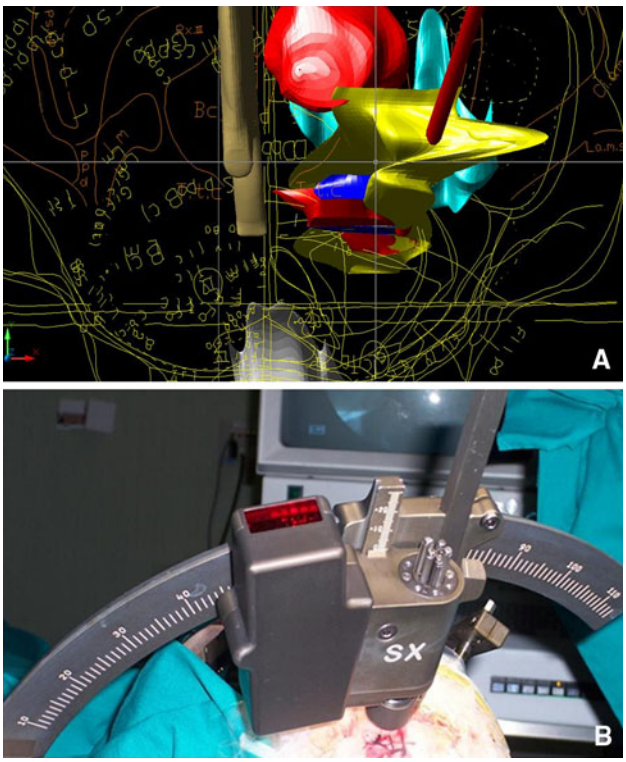

Fig. 3 **a** Tridimensional virtual surgery. Axial projection. 3D Planning Maranello Stereotactic System®, CLS Titanium, Cesena, Italy. *Light brown* III ventricle, *cyan* PPD (*bottom*), *yellow* medial lemniscus, *red* red nucleus (*top*) and Tg.pdpo (*bottom*) (PPTg), *dark blue* area parabigemina cuneiformis (A.pbg) and area U (Gr.cf b.cj) (*bottom*): *dark red* lead, *white* IV ventricle. The abbreviations are as in the Schaltembrand and Wharen's atlas. **b** Robotized multitrack device. The progression of the leads (steps from 1 mm to 1 μm) is done through a remote infrared controller. The device in the figure is mounted on the stereotactic hemiarch. Maranello Stereotactic System® (CLS Titanium, Cesena, Italy)

From the above description, it can be seen that our targeting procedure for the DBS of the PPTg has been subjected to a progressive refinement that has also taken into account the different sites that could have been stimulated by other groups. Thus, a profound conceptual challenge to the traditional stereotactic methodology has been launched. As a result, the reference points or lines traditionally used for the proportional representation of targets has assumed a limited utility or no utility at all in determining the position of targets in the brainstem; rather, the direct determination of coordinates as can be established on neuroimages, appears to be more reliable.

The most important conclusion that emerges from the above data is that when dealing with the PPTg it is more correct to refer to the landing point of the lead in the pontine part of the nucleus. The PPTg area, as reported by Androulidakis et al. (2008) may serve as a neurophysiological reference region rather than a surgical landmark. The definition of the PPTg area given by these authors fits well with the concept of the targeted area as a discrete region, densely populated by nuclear formations which establish diffuse connections with other parts of the brain and which may be affected to different degrees by different neurodegenerative pathologies (Braak et al. 2004; Hawkes et al. 2010). The delivery of electrical stimuli (Fig. 5) in such a region may induce physiological and clinical effects that may vary from subject to subject according to the disease progression, site of DBS and lead trajectory. Moreover, the type and configuration of lead contacts add another source of variability which may explain the different results reported in the literature. Such effects are not necessarily linked to electrical changes in the cellular elements in the stimulated region since these effects may be also observed in PD in spite of the degeneration and loss of PPTg neurons that occurs with this disorder (Braak et al. 2004; Hawkes et al. 2010). Thus, the planning method, the relationship between DBS and the PPTg area, and the mechanism of action of stimulation need to be reconsidered according to the concepts of where, how and why. Such a revision, as will be discussed later in this paper, must also carefully examine which types of physiological intraoperative recordings are really useful for the success of the targeting procedure and which are safe for the patients. Finally, the results of DBS applied to other conditions besides PD, as in some psychiatric disorders and Alzheimer's disease (Lipsman et al. 2010; Laxton et al. 2010) may be ascribed to the different mechanisms of action of DBS and to the different pathways involved in each condition. Thus, the concept of a specific action of DBS being confined to the stimulation site can no longer be accepted in its simplistic enunciation. As a consequence, perseverating with traditional methodological approaches and considering old concepts as immutable, may limit the development of new neurosurgical strategies and may lead to the acceptance of surgical results that in some circumstances may be unsatisfactory.

Postoperative neuroradiology

The PPTg is not easily visible on low tesla routinary MRI, whereas the ML and the superior cerebellar peduncle can be visualized. However, under stereotactic conditions the visualization of these structures is difficult because of artifacts related to the presence of stereotactic tools.

The right methodology for proving that a correct targeting has been performed requires appropriate CT or MRI documentation of the implanted leads (Mazzone et al. 2008a, b, 2009, 2011) and comparisons that can consequently be made between the position of lead tip and the reference points. The first neuroimaging data showing the position of the leads in the PPTg in a parkinsonian patient were presented at the Meeting of the World Society for Stereotactic

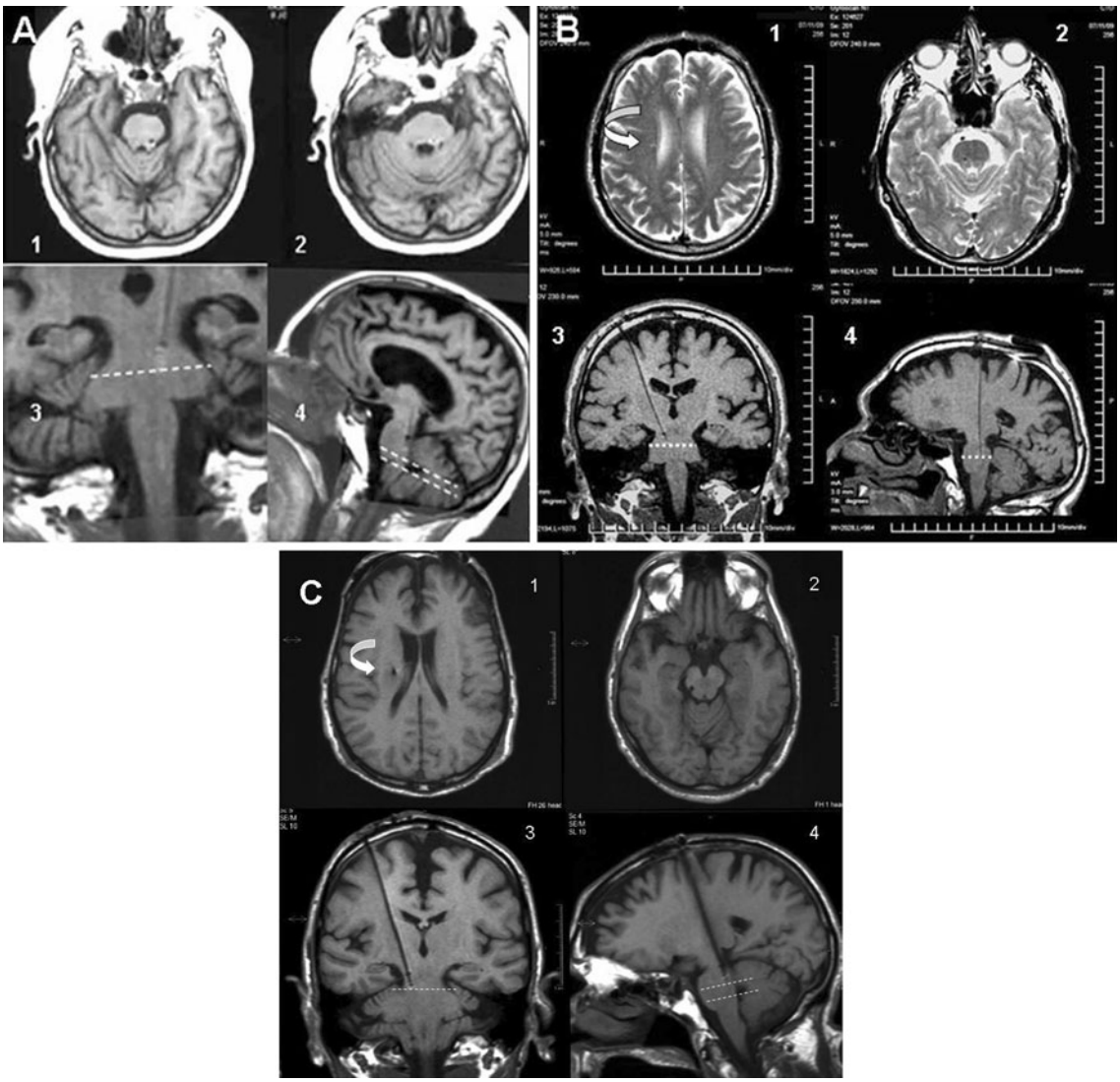

Fig. 4 **a** Full MRIs with lead artifacts noticeable in different projections: axial (*1*, *2*), coronal (*3*) and sagittal (*4*). Patient implanted in the left PPTg. The lead tip reaching the *dashed line* in *3* and *4* appears to be located in the deeper part of the PPTg, close to the locus coeruleus area (*2*). **b**, **c** Full MRIs of others two patients, who were implanted in the right PPTg. In *1* the extraventricular position and trajectory of the lead are evident (*white arrow*). The lead tip is noticeable inside the PPTg in the axial slide (*2*), and in the sagittal (*3*) and coronal (*4*) slides (*dashed lines*)

and Functional Neurosurgery held in Rome. A report which appeared simultaneously (Plaha and Gill 2005) with our former paper (Mazzone et al. 2005b), was corroborated by MRI in which it was possible to detect two cannulae that referred to the PPTg on the basis of Nieuwenhuys et al.'s atlas (Nieuwenhuys et al. 1988). In the coronal projection, the two cannulae showed a mesial position with respect to the theoretical location of the nucleus that can be inferred in Paxinos and Huang's atlas. In the same paper the MRI axial slides included both the lower and upper parts of the PPTg and presented superimposed drawings in white. The cannulae did not demonstrate artifacts and were intended to indicate the position for placing the leads. Moreover, the MRI sagittal projections, which in our experience are of the utmost importance for the identification of lead position and trajectory, were not represented. Thus, the relationships between the lead contacts, the pontine tegmentum and the pontomesencephalic border were difficult to establish from the documentation provided. The lack of adequate MRI or CT documentation in recent neurological reports (Plaha and Gill 2005; Weinberger et al. 2006, 2008; Thevathasan et al. 2010) (Table 1) limits the interpretation of results reported in these papers. Any reconstruction of a realized lead trajectory cannot elude the need for appropriate neuroimages, even if enriched by aesthetic drawings (Plaha and Gill 2005; Stefani et al. 2007; Khan et al. 2010). It was only after 2009 that postoperative neuroradiological images substantiated by a detailed description of the surgery began to appear in

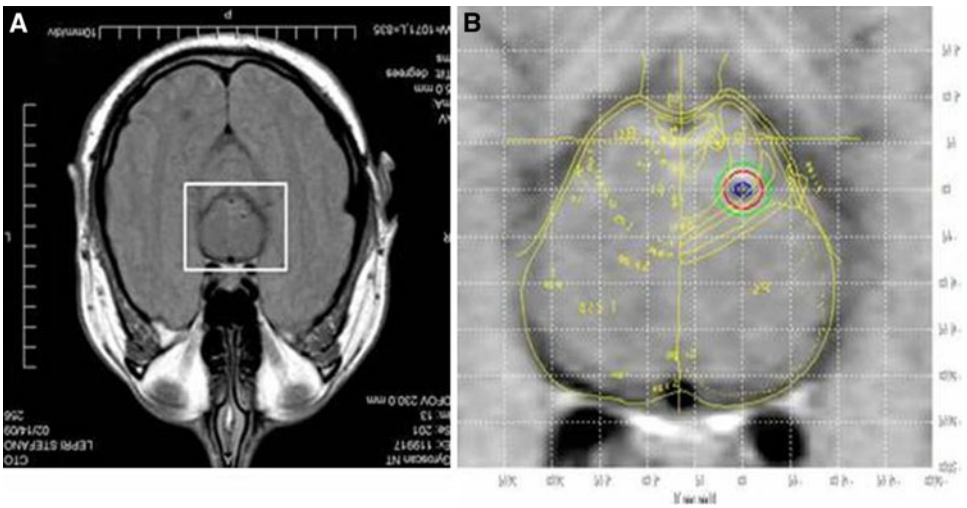

Fig. 5 **a** Axial view at the level of the 3389® lead distal tip (the MRI slide was taken parallel to the midbrain-pons junction). **b** Reconstruction of the electric field with respect to the PPTg and surroundings structures (*yellow* Tc-5 slide from the Schaltenbrand and Wharen's atlas). Contacts configuration 0^{-}, 3^{+} *blue circle* 1,000 V/m; *red circle* 200 V/m; *yellow circle* 100 V/m. Simulation was performed by the Comsol Multiphysics 3.3 software using an electrostatic approximation and assuming the brain tissue near the electrode as an homogeneous material with isotropic resistivity and no voltage dependent nonlinear effect (Hemm et al. 2005). Courtesy of Dr. G. Vagliasindi, DIIES Catania University, Sicily

the reports provided by several groups. For stereotactic neurosurgeons or neuroradiologists it would be inappropriate to make any further comment on the basis of presumed positions of leads merely documented through drawings or nonstereotactic CT scan or MRI slides (Khan et al. 2010; Stefani et al. 2010) or in patients who where not subjected to implantation (Zrinzo et al. 2008). In the paper by Stefani et al. (2007), a CT scan showing a good position of leads in the PPTg was provided, but unfortunately it was misunderstood because of an incorrect drawing also included in that paper. In fact, the CT scan showed the real and correct postoperative position of the stimulating leads, but more attention was given to the erroneous drawing that was incorrectly included in the paper. This misunderstanding could be obvious until the presentation of a more advanced planning for PPTg implantation that resulted from our efforts over recent years (Mazzone et al. 2008b, 2009, 2011). In every case, it was only in 2007 that postoperative MRI slides were published by other groups (Lim et al. 2007; Stone et al. 2009) that began to present their results and plannings as shown in Table 1.

Some authors (Piallat et al. 2009; Ferraye et al. 2010) published MRI slides accompanied by 3D reconstructions of microelectrode trajectories and contacts positions that the authors identified in the PPTg as well as in the subcuneiform nuclei. However, a careful examination of the MRI sagittal slides revealed that the electrode was located in the lower mesencephalic region with the distal tip at the level of the junction with the pons. In other views (axial projections) the lead appeared to be in a position which was more mesial and anterior with respect to the location of the PPTg indicated in Paxinos and Huang's atlas while the lead artifact could be appreciated in a midbrain slice. Thus, it is conceivable that the MRIs were taken parallel to Ca–Cp line rather than to the pontomesencephalic junction, and this could have modified the aspect of the spatial position of the lead. It should be kept in mind that the axial slides reported in the Schaltembrand and Wharen's atlas were obtained from a cut angle different to the inclination of the Ca–Cp line; hence, making any correlation between the anatomy of the pontomesencephalic site of stimulation and the MRI representations of the lead, as reported in the above-mentioned papers, may be difficult. The oscillopsia reported in two patients could be related to the diffusion of current to the nucleus of the III cranial nerve, which is located more mesial and ventral with respect to the mesencephalic tegmentum while the PPTg is located at the level of the nucleus of the IV cranial nerve, extending caudally within the first 5 mm of the pons as represented in Paxinos and Huang's atlas. In the patients implanted up to date by our group ($N = 23$) no side effects appeared except paresthesias in the contralateral hemisoma, which decreased as adaptation to the electrical stimulation took place. Lim et al. (2007) and Stone et al. (2009) presented one axial MRI, whereas Moro et al. (2010) reported five magnified details on the MRIs taken from six patients. The analysis of MRIs in the paper of Moro et al. (2010) reveals that the position of the distal contact of the lead could be identified at the intercollicular level in some cases, whereas in others appeared to overcome the inferior colliculus to reach the central part of the PPTg. The leads appeared to be correctly positioned in the sagittal projection but with a certain variation of the distance with respect to the midbrain–pontine tegmentum,

related to the trajectory slope. In the axial projections the contacts artifacts of the 3387® lead could be observed in different positions inside the mesencephalic region, but only one appeared to be in the pontine slide (patient no. 5). Nevertheless, in the coronal slides the comparison of the distance between the distal tip of the lead and the horizontal line connecting the two cerebellar peduncles demonstrated stochastic differences (Moro et al. 2010). It is well known that stochastic changes in stereotactic surgery are unavoidable, thus explaining different clinical and instrumental results, as also described by the Toronto group in different reports (Lim et al. 2007; Strafella et al. 2008; Stone et al. 2009; Yeh et al. 2010). Moreover, it is worth mentioning that the same groups have employed the 3387® Medtronic lead (Weinberger et al. 2008; Moro et al. 2010; Thevathasan et al. 2010), while other groups including us have utilized the more selective 3389® lead (Mazzone et al. 2008b, 2009, 2011). In this review, as well as in previous papers (Mazzone et al. 2008a, 2008b, 2009, 2011), we present CT scans and MRIs referring to several patients, that clearly document both the position and trajectory of the lead in the sagittal projection and the lead contacts being well positioned within the pontomesencephalic border. Thus, a precise measurement of the distance of the lead from the pontine junction is feasible by comparing the trajectory and the contacts position. The coronal view that we present has the same plane and angle of the lateral trajectory and directly demonstrates both the lead position in the brainstem and the position of the distal contact beyond the upper portion of the pons (Fig. 4a–c, slides 1–4). On the contrary, Thevathasan et al. (2010) did not present postoperative MRIs showing the lead position, whereas Ostrem et al. (2010) and Shimamoto et al. (2010) only showed a few images of implanted patients, thus, unfortunately a comparison of trajectory and final position is problematic.

Another criticism is the dimension of MRIs presented, which were frequently limited to a detail on the slides: it is not easy in many papers to verify the inlet point and trajectory outside the annex drawings (Piallat et al. 2009; Moro et al. 2010; Shimamoto et al. 2010).

In a recent neurological report (Stefani et al. 2010), the authors speculate about the lead position on the X-ray plain; however, the image was not acquired under stereotactic conditions and, as a consequence, artifacts appeared such as duplication of the anterior wall of the cranial fossa and rotation of the head. Thus, it is useless to attempt taking CT scans under nonstereotactic conditions.

The changing role and type of neurophysiology

The application in functional neurosurgery of IOMERs (Benazzouz et al. 2002) has introduced impressive changes to the traditional methods of identifying a target (Sterio et al. 2002). This has also led to the development of sophisticated mechanical and robotic devices for driving microelectrode in the brain, included the Maranello Stereotactic System® (Mazzone 2001) that was specifically developed to permit the positioning of multiple electrode in targeted structures (Fig. 3b). The methodology based on multiple targets allows simultaneous recordings from different nuclei and permits the evaluation of changes in neuronal activity occurring during macro- or microstimulation, as well as during pharmacological manipulations (Mazzone 2003; Peppe et al. 2004; Mazzone et al. 2005a, b; Stefani et al. 2007). The application of microdialysis during DBS represented a further innovation in neurosurgery (Fedele et al. 2001; Stefani et al. 2005; Sacchettoni et al. 2010). However, not all the neurosurgeons are unanimous in accepting these techniques since risky or unsatisfactory criteria were used to verify the target (Hariz and Fodstad 1999; Honey et al. 2001; Binder et al. 2003; Hariz et al. 2004; Binder et al. 2005). Moreover, IOMERs may require the patient to be awake and the withdrawal of drugs, which, in turn, may influence neuronal activity.

Intraoperative microrecordings have been considered by some authors (Piallat et al. 2009) as an essential support in identifying a nucleus or its subterritories and they have been used to delineate the anatomical boundaries of the PPTg prior to the implantation of DBS leads (Shimamoto et al. 2010). On the contrary, other authors have denied the utility of this approach (Weinberger et al. 2008). The spontaneous electrical activity was also explored in some of our patients in an attempt to better delineate the target before the implantation of DBS leads (Mazzone et al. 2005b). Being aware of the risk inherent to multiple penetrations in a deep structure such as the PPTg, we limited the investigation to a single track in each patient. The strategy of a single track was also adopted by Shimamoto et al. (2010), whereas Weinberger et al. (2008) utilized two independently driven microelectrodes. Given the loss of PPTg neurons in PD, a single track does not assure the recording of a consistent population of neurons or the delineation of the boundaries of the spatial configuration of the PPTg. Hence, our conclusion that IOMERs are inappropriate and useless for identification of PPTg is in line with other authors (Weinberger et al. 2008) who did not find distinctive discharge patterns in the PPTg or clear nuclear boundaries using IOMERs, contrary to when dealing with the STN or the GPi which still have neurons present in PD. The only report that seems to validate IOMERs was published by Piallat et al. (2009) but the doubt arising from the loss of the cellular population in the PPTg (Braak et al. 2004; Hawkes et al. 2010) remains and represents a major source of uncertainty in this domain. Intraoperative bleeding has not been reported following

PPTg recordings, but several authors emphasized the increased risks inherent with the penetration of microelectrodes in such a deep structure as the PPTg compared to recordings that could be done in other basal ganglia nuclei.

Given the above limitations for the utilization of IOMERs, a real alternative may be represented by the study of SEPs which can be recorded intraoperatively using the stimulating lead under general anesthesia. We have already illustrated and discussed in two reports (Mazzone et al. 2007a, b, 2009) the SEPs recorded in the PPTg and their origin as waves traveling in the medial lemniscus (Insola et al. 2010). In a recent paper, Yeh et al. (2010) gave a different interpretation of the origin of SEPs recorded in the PPTg which was targeted under different surgical conditions than our methodology. They suggested that the SEPs recorded from the PPTg lead may represent near-field responses generated within the PPTg itself. Whatever may be their origin, SEPs may permit a correlation between the recorded waves and the distance of the lead contacts from the reference points utilized for planning, such as the obex (Insola et al. 2010; Mazzone et al. 2009). The anatomical relationships between LM, PPTg and lead contacts may be easily established, as previously described (Mazzone et al. 2007a, b) (Fig. 6a, b), and may be useful for verifying the accuracy of the PPTg planning (Mazzone et al. 2009, 2011). Overall, it seems that in the neurosurgery of the PPTg the intraoperative recording of SEPs may be a primary tool for verifying the correspondence of the target with the surgical planning. The intraoperative SEPs recordings may be done under general anesthesia, thus favoring the optimal management of patients and also reducing the duration of surgery compared to the time required by IOMERs acquisitions. Postoperatively, SEPs recordings allow to evaluate the relationship between the structure and the electric field generated by the lead contacts (Hemm et al. 2005; Mazzone and Scarnati 2009; Mazzone et al. 2011).

Another physiological parameter that can be utilized to validate the correct position of the stimulating lead in the PPTg is the blink reflex. Indeed this reflex is integrated in the pons and the PPTg is directly involved in the circuitry responsible of this reflex (Reese et al. 1995; Mazzone et al. 2009). The blink reflex is disrupted in PD and its prepulse inhibition has been reported to be abnormally reduced (Nakashima et al. 1994). However, it may be normalized by the mere presence of the lead in the PPTg and by the application of single electrical stimuli through the lead contacts. From the available literature it is known that the PPTg, the nucleus reticularis pontis caudalis and the substantia nigra pars reticulata (SNr) are all involved in the circuit responsible for prepulse inhibition (Kretschmer and Koch 1998; Fendt et al. 2001; Swerdlow et al. 2001). The basal ganglia are likely to exert their control over the prepulse circuit through the PPTg, which is reciprocally connected with several nuclei, including the STN, GPi and the SNr (Garcia-Rill 1991; Inglis and Winn 1995; Scarnati and Florio 1997). We found that single stimuli delivered through the PPTg DBS lead induced a significant prepulse inhibition of the blink reflex in PD patients who had abnormally reduced auditory and somatosensory prepulse inhibitions (Mazzone et al. 2009). Given the neuronal network involved in the prepulse inhibition, the effectiveness of electrical stimulation in restoring the blink reflex could be explained by the stimulating lead reaching a proper position. In some cases the R2 component of the blink reflex may be restored by the mechanical insertion of the lead as well as by a single stimulus delivered trough the contacts of the 3389® lead. The analysis of the blink reflex allows to assess postoperatively the contacts inside the nucleus and to optimize the choice of contacts for clinical purpose.

Sleep studies were also carried out during PPTg DBS (Mazzone et al. 2009; Lim et al. 2009; Arnulf et al. 2010). The variation in electroencephalographic patterns during non-rapid eye movements (NREM) and rapid eye movements (REM) phases of sleep was investigated in our initial patients who underwent multiple implantations (6 bilateral PPTg + STN or GPi and 2 unilateral PPTg). The PPTg DBS induced a clear arousal pattern in simultaneous recordings taken from the scalp as well as in the STN and/or the inner segment of the GPi during the NREM state, whereas no modifications were found in the REM state.

In the last two unilaterally implanted patients, affected also by REM behavior disorder (Arnulf 2006), this symptomatology was reduced in one patient and disappeared in the other. Ponto-geniculo-occipital waves were not found in our recordings, contrary to the report by Lim et al. (2007) on a study solely carried out in one patient. This discrepancy could be due to the different selection criteria for patients, the different leads employed or the different sites of stimulation as can be argued from the MRIs reported in the Lim et al.'s paper.

Electrophysiological recordings from muscles innervated by V, VII, XI and XII cranial nerves are also being performed by our group to better define the physiology of the brainstem and to strengthen the rationale for preferring the unilateral implantation of PPTg in selected patients as a first choice target before considering other structures. The data that we have collected up to now show that electrical stimulation from the contacts of the unilaterally implanted lead may induce bilateral compound muscle action potentials that can be recorded from the orbicularis oculi and oris, masseter, sternocleidomastoideus and genioglossus muscles. These potentials were due to the spread of the electrical field to nuclei, root

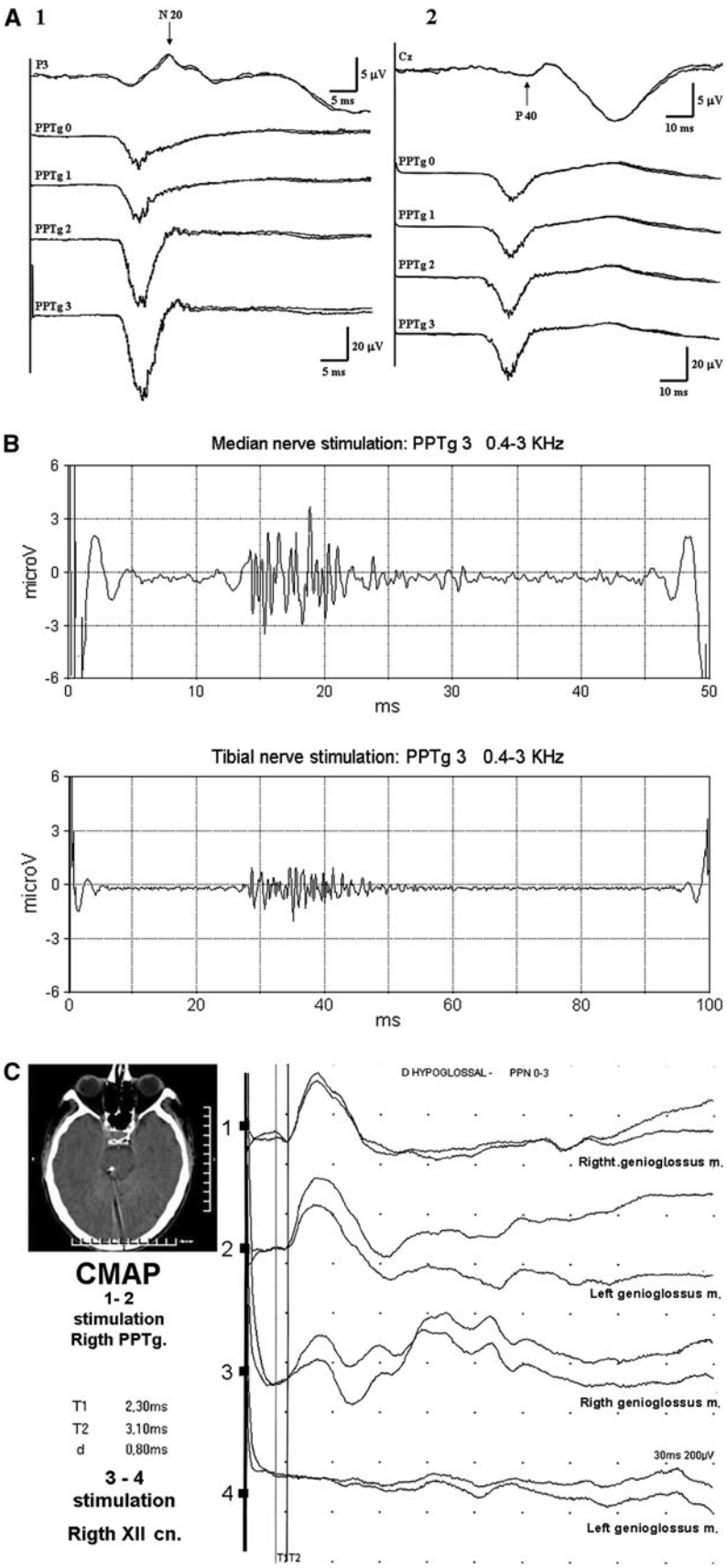

Fig. 6 A representative example of relationships between SEPs and lead contacts. **a** SEPS were recorded from the surface and from lead contacts following median (*left column*) and tibial (*right column*) nerve stimulation in the same patient. Two superimposed averages recorded from the scalp (parietal and central regions) and from the four contacts of the lead implanted in the PPTg contralateral to the stimulated side. Note the progressive amplitude increase of the biphasical PPTg potential from caudal to rostral contacts. The maximal amplitude was recorded at contact 3. Several high-frequency wavelets characterized the low-frequency SEP component. **b** SEPs recorded from contact 3 of the PPTg lead following median (*upper trace*) and tibial (*lower trace*) nerve stimulation. Recordings were filtered off-line by a 400–3,000 Hz (12 dB roll-off) bandpass. Note the different shape between the median and tibial high-frequency oscillation bursts. The bursts evoked by the median nerve stimulation had the largest amplitude, whereas the bursts evoked by the tibial nerve stimulation showed the longest duration. **c** Traces *1* and *2* show compound muscle action potentials recorded from the genioglossus muscle following a single stimulus delivered through contacts 0^{-} and 3^{+} of the lead implanted in the right PPTg. The unilateral stimulation produced bilateral responses in the genioglossus muscle and caused tongue contraction. Traces *3* and *4* show compound muscle action potentials recorded following stimulation of the XII cranial nerve at neck level. Responses could be solely recorded in the ipsilateral side. The CT scan shows the location of the lead tip

fibers, corticobulbar bundle and finally, following a further current intensity increase, to the corticospinal tract. The activation of the latter tract induces motor responses in the contralateral thenar eminence; whereas the peripheral electrical stimulation of the above-mentioned cranial nerves evokes responses in the ipsilateral muscles (Fig. 6c).

The clinical analysis: changes in the assessment of the outcome and new related application possibilities

Deep brain stimulation tailored to the symptoms of PD arose from the need to improve clinical results. Simultaneous implantations of the GPi and the STN, or the GPi and the STN plus the Cm–Pf complex were performed in order to realize a tailored stimulation in the same patient, and to evaluate the differences between the two traditional targets (Mazzone 2003; Peppe et al. 2004; Mazzone et al. 2005a). This theoretical approach has always been controversial, at least until the appearance of recent papers in which the role of the GPi was reevaluated (Rodriguez-Oroz et al. 2005; Okun et al. 2009). The goal of our approach was a comparative assessment of the clinical effects obtained by stimulating a single target or both targets in the same patient. This approach was extended to take into account the mounting evidence of the involvement of the PPTg in basal ganglia disorders. When we began our research with PPTg DBS we selected patients who showed symptoms that were refractory to the stimulation of the STN, but in the light of recent results this limitation now seems to be out of date.

In 2005 the idea of applying the DBS to the PPTg was conceptually not dissimilar in many aspects to the principles that led to the STN DBS. Our first two papers (Mazzone et al. 2005b; Stefani et al. 2007) were devoted to this original approach and we perform simultaneous implantation of the STN and the PPTg. Following this experience it was expected that the clinical effects of the PPTg stimulation could have the same characteristics as those induced by STN stimulation, or that they could be synergistic with the action of the STN DBS, or enhance the effectiveness of the STN DBS. Hence, it was believed that PPTg DBS and STN DBS could share analogous outcomes. The work by Stefani et al. (2007) was inspired by these principles and directed towards comparing the results obtained through simultaneous implantations in different targets. However, given the results of our recent work, the original idea of considering PPTg stimulation ancillary with respect to STN stimulation appears to be outdated. In addition, there are many papers based on the anatomical and pathological interpretations of what happens in PD that contradict this axiom.

As the number of implanted patients increased (Mazzone et al. 2008b, 2009, 2011) it appeared to be clear that the peculiarities of the treated symptoms required new procedures of evaluation with respect to the canonical and subjective clinical assessments. Furthermore, the results of the traditional clinical evaluations could have suffered from the low number of patients enrolled, where usually there were no more than 6 except the 11 patients reported by Thevathasan et al. (2010) as results of the joint surgery of 3 centers.

In recent works (Ferraye et al. 2010; Moro et al. 2010; Thevathasan et al. 2010) a small effect of the stimulation of the PPTg on some motor signs, particularly on gait and reaction time, was reported for patients evaluated using the traditional Unified Parkinson Disease Rating Scale (UPDRS II and III, sub items 27–30). The evaluation was performed with great accuracy and precision and was unobjective but: (1) the site of stimulation appeared to differ between patients groups, (2) the lead position was illustrated by MRIs only in a few papers (Table 1) the neurosurgeons utilized different leads and different stimulation parameters. However, in spite of the discrepancy between an unsatisfactory evaluation of the PPTg effect on gait, freezing, posture, and reaction time and the positive effects on falls the authors recognized the PPTg as a promising target requiring further investigations. Wilcox et al. (2010) published a case report in which robust improvements were found on gait and posture in a patient affected by a primary progressive freezing of gait who was bilaterally implanted in the PPTg. Certainly complex symptoms such as freezing, unstable posture and difficulty in walking should undergo a more objective and instrumental analysis in a large number of patients to assess the effects of PPTg DBS and to eliminate variables linked to the subjectivity of the evaluators. This former criticism deserves particular attention since subjective evaluations may contribute significantly to the differences reported in the literature. An instrumental and objective analysis may in fact reveal more consistent data and subtle changes that cannot be appreciated by mere observational estimations such as those provided by the traditional evaluation methods.

Some reports (Stolze et al. 2001; Lubik et al. 2006; Tabbal et al. 2008) are examples of how quantitative evaluation can provide important data in the assessment of patients and faithful correlations between DBS effects and the target employed.

Tables 2 and 3 show the results of our 23 patients followed up in relation to different times of implantation from 2005 up to date. The first six patients were studied, operated on and evaluated according to traditional methodologies. Since they were subjected to multiple implantations, the presence of a lead in the STN could have confused the understanding of the real efficacy of PPTg DBS, at least

Table 3 Neurological evaluations: UPDRS III; items 27–30

Pts	UPDRS III OFF drugs/OFF DBS	UPDRS III ON drugs/OFF DBS	UPDRS III ON DBS/OFF drugs	Items 27–30 (pre ON drugs)	Item 27–30 (post ON DBS)	Follow-up (years)
0	*73*	*67*	*NE*	*12.6*	*NE*	–
1	*55*	*43*	*21*	*5.6*	*2.9*	*5*
2	*42*	*30*	*18*	*3.8*	*1.9*	*5*
3	*73*	*35*	*16*	*3.2*	*2.1*	*5*
4	*85*	*39*	*37*	*4.5*	*2.9*	*4*
5	*79*	*43*	*41*	*2.6*	*1.7*	*4*
6	*70*	*26*	*37*	*2.6*	*1.9*	*4*
7	73	42	NE	7.9	NE	–
8	84	54	45	6.2	3.9	3
9	87	73	57	5.4	3.1	3
10	88	38	42	4.7	2.8	3
11	87	43	20	5.2	3.5	3
12	60	15	18	6.3	3.2	2
13	87	43	33	5.9	3.4	2
14	68	27	29	4.6	2.3	2
15	88	38	36	3.5	1.9	2
16	60	15	12	2.6	1.8	2
17	48	13	18	5.7	3.2	2
18	97	48	43.5	12.9	3.5	1
19	78	38	40	6.2	3.7	1
20	53	18	16	5.6	2.7	1
21	87	22	25	4.5	2.5	1
22	68	27	30	3.9	2.7	1
23	84	54	42.5	4.9	3.8	1

Values in italics represent first group of patients implanted bilaterally in STN and PPTg. Non-italic entries represent patients implanted after 2007

due to the use of by the traditional UPDRS evaluation method (Stefani et al. 2007). In this context, it should be kept in mind that a continuous stimulation of the two structures may induce several effects in the brain, such as long-lasting neurotransmitters release, synaptic changes, and reorganization of connectivity (Lee et al. 2004; Benabid et al. 2005; Schweder et al. 2010a, b) which may confound the understanding of the stimulation of a single site in the same patient, irrespective of the evaluation method. These six patients were successively investigated for language (Zanini et al. 2009), memory tasks (Costa et al. 2010) and cerebral metabolism (Ceravolo et al. 2010), and they were finally reinvestigated for gait through an instrumental analysis (Peppe et al. 2010). However, as stated above, the application of DBS to two different targets in the six patients represents an objective limitation when interpreting the results, even if an improvement of language and gait occurred when stimulating the PPTg alone. Moreover, no postoperative neuroradiological control image was provided. Given the above criticisms, it is appropriate to consider the first 6 patients implanted in our hospital from 2005 to 2007 (Table 2 patients 0–6) in both the STN and PPTg separately from the remaining 16 patients (up to date) who were implanted in the PPTg alone after 2007 (Tables 2, 3). These latter patients were selected taking into account the possibility that they could be optimal for a unilateral implantation of the PPTg according to the clinical examinations carried out by neurologists and neurorehabilitators belonging to the Catholic and La Sapienza Universities and the San Giovanni Battista and San Raffaele Hospitals in Rome. In the selection particular attention was devoted to guarantee appropriate comparison of clinical differences with respect to age-matched healthy controls. Patients showing severe tremor as main symptom or whose rigidity was well controlled by L-dopa were not considered eligible for PPTg DBS as they could be treated with DBS of other targets (Mazzone et al. 2005a; Mazzone and Scarnati 2009). However, we took into account the effects of PPTg DBS on rigidity in patients selected for PPTg DBS in the global evaluation of UPDR III scores, and undoubtedly the reduction of rigidity may have contributed to movement improvements.

Table 4 Neurological evaluations

UPDRS III mean (±SD) score values					
	OFF drugs/OFF DBS	ON drugs/OFF DBS	OFF drugs/ON DBS	Subitems 27–30 (pre-op)	Subitems 27–30 (post-op)
Combined targets (9 Pts)	71.7 ± 13.4*,#	40.8 ± 11.9*	30.8 ± 1.7#	4.9 ± 1.7§	2.5 ± 0.9§
PPTg alone (13 Pts)	76.7 ± 15.9*,#	34.3 ± 13*	30.7 ± 13.6#	5.5 ± 1.4§	2.9 ± 0.6§

Mean ± SD, $P < 0.0001$ Anova followed by a Newman–Keuls test: §, *, # correlated to items with reciprocal statistical significance

The comparison of UPDRS III single scores between patients who received combined implantations and those who were unilaterally implanted in the PPTg did not reveal any statistically significant variation in OFF drugs/OFF DBS, ON drugs/OFF DBS and OFF drugs/ON DBS conditions, as well as in subitems 27–30. However, when considering the mean values of UPDRS in patients subjected to combined implantations there was a high statistically significant difference by comparing OFF drugs/OFF DBS condition to both ON drugs/OFF DBS and OFF drugs/ON DBS (Table 4). The same highly significant difference resulted also when comparing the above-mentioned conditions in unilaterally PPTg implanted patients (Table 4). The differences by comparing the mean values of UPDRS in ON drugs/OFF DBS and OFF drugs/ON DBS conditions did not reach levels of significance but a trend for a better response to the DBS rather to drugs was apparent, in particular in patients subjected to combined implantations. Moreover, the differences in the mean values of 27–30 subitems by comparing in these patients preoperative ON drug condition and postoperative ON DBS condition were also statistically significant (Table 4). Overall, these results show that PPTg DBS mimics the effects of dopaminergic drugs and that the implantation of

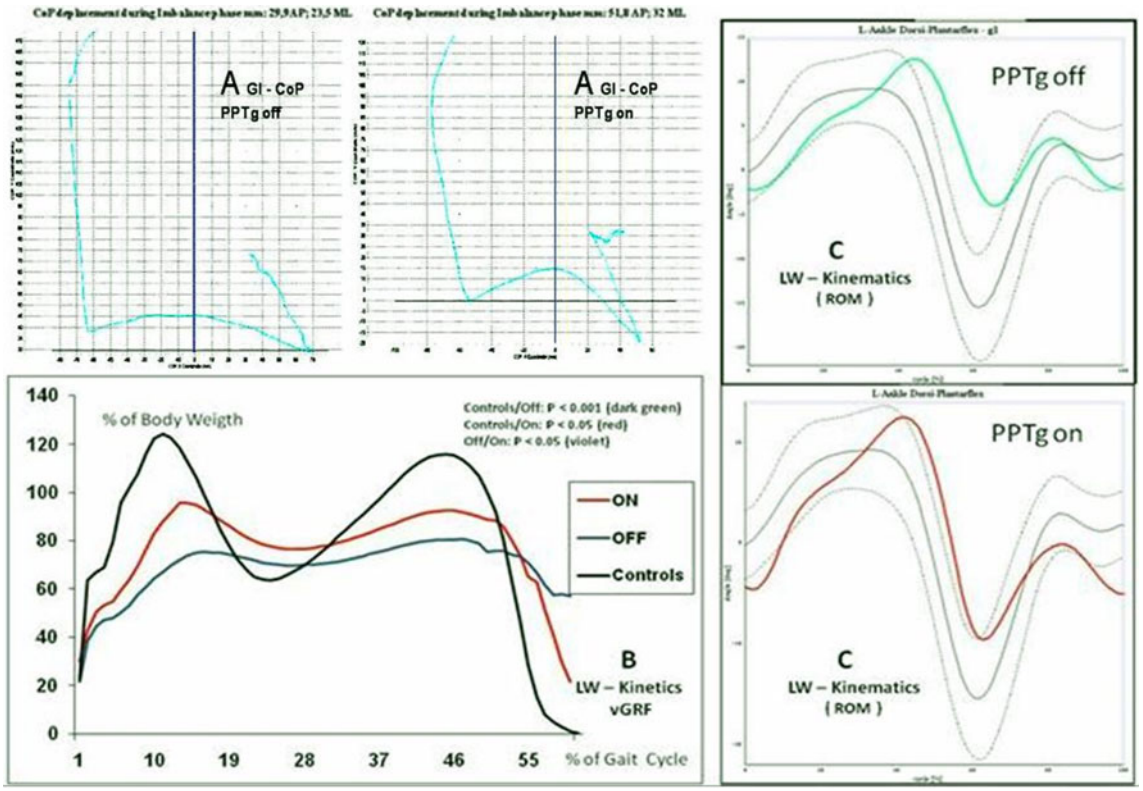

Fig. 7 A representative example of gait analysis in patients subjected to PPTg DBS. **a** Gait initiation (*GI*), expressed as the displacement of the center of pressure (*CoP*) during the imbalance phase has a shorter duration during PPTg ON (*right*) compared to PPTg OFF (*left*). In this patient the percentages of improvement under the PPTg ON condition were 43.6% in the anteroposterior plane and 26.6% in the mediolateral plane compared to the PPTg OFF condition. **b** Level of walking (*LW*) as kinetic evaluation of vertical ground reaction force (*VGRF*) under PPTg ON condition improves significantly compared to OFF conditions and to controls. **c** Level of walking (*LW*) as kinematically evaluated through range of movement (*ROM*) under the PPTg ON condition (*red trace*) is closer to the normal range (*grey traces*) compared to the PPTg OFF condition (*green trace*). The kinematic evaluation considered the left ankle dorso-plantar flexion (up-down). Courtesy of Dr. M. Paoloni, University of Roma "La Sapienza"

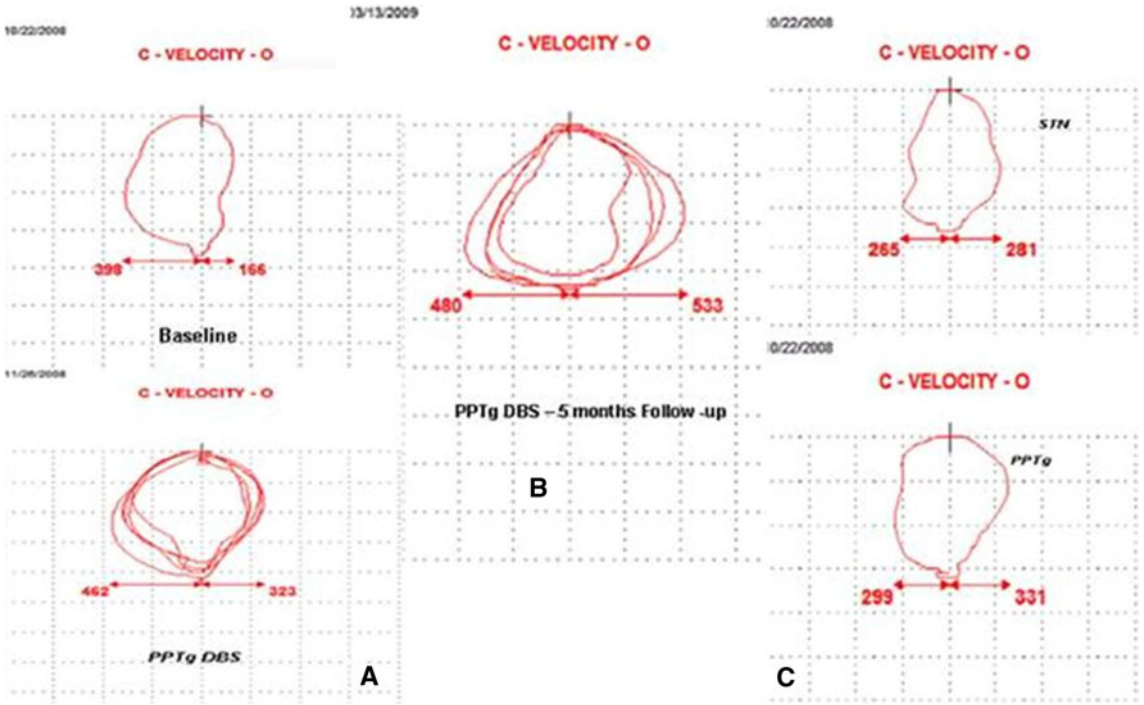

Fig. 8 A representative example of improvement of jaw opening–closing cycle induced by unilateral PPTg DBS in parkinsonian patients. **a** Electrognatographic recordings (10 mm × 10 mm × div; speed = 250 mm/s × div). Jaw opening: *right side* of the cycle; jaw closing: *left side* of the cycle. The *upper record* was obtained in baseline condition PPTg OFF/drugs OFF (Capit) while the *lower record* was obtained during PPTg DBS ON/drugs OFF (Capit). **b** After 5 months of chronic PPTg DBS ON/drugs OFF (Capit), opening speed reached values which were in the range of age-matched normal subjects. This beneficial effect was also observed during jaw closing movements, although at a lesser extent. **c** Patient with bilateral STN (*upper record*) and PPTg (*lower record*). Note the higher values in opening and closing speeds when DBS was applied to the PPTg in comparison to the STN. Courtesy of Dr. G. Falise, University of Rome "La Sapienza"

the PPTg alone may be sufficient to improve motor disabilities and drugs requirements, as also illustrated in Fig. 9.

The gait analysis has been completed within 1 year after neurosurgery up to date in 6 out of the 16 unilaterally implanted patients and it has been accompanied by surface electromyographic recordings from hind limb muscles, as reported by Caliandro et al. in this issue. These patients were studied according to different ON and OFF conditions related to drugs and PPTg DBS and also compared to age-matched healthy subjects. Figure 7 illustrates the main results obtained during PPTg DBS on:

- The gait initiation (GI), i.e. the displacement of the center of pressure in the imbalance phase (CoP/ip) (Fig. 7a);
- The level of walking (LW) as evaluated through kinetic (ground reaction force) (Fig. 7b) and kinematic (range of movements) analyses (Fig. 7c).

According to the data collected from these patients, the unilateral PPTg DBS may influence the GI process in patients affected by PD. Indeed, patients showed a significantly decreased duration of the first phase of the GI during the ON condition, i.e. the phase in which the CoP shifts posteriorly and laterally on the leading foot. All patients but one displayed an increased displacement during the imbalance phase of the GI, probably reflecting the ability to perform a wider range of movements during the PPTg DBS. Moveover, all of the patients in the ON condition walked significantly faster and with an increased stride length, whereas the cadence did not significantly differ between the ON and OFF conditions or with respect to the controls. We may therefore hypothesize that the increased walking velocity obtained in the ON condition was through an increase in stride length. It is worth noting that the kinematic feature associated with spatio-temporal changes, i.e. an increased pelvic tilt, was achieved by patients in the ON condition throughout the whole gait cycle, which probably played an important role in increasing stride length. As no other significant change was observed for the kinematics of gait during the PPTg DBS, it is conceivable that the main effect of PPTg DBS on gait may be linked to spatial–temporal parameters rather than to the scalarity of joint motion.

Since motor disabilities in PD also affect voluntary and rhythmic jaw movements (Robertson and Hammerstad 1996; Robertson et al. 2001), whose control is subserved by different neuronal circuits, and since L-dopa treatment

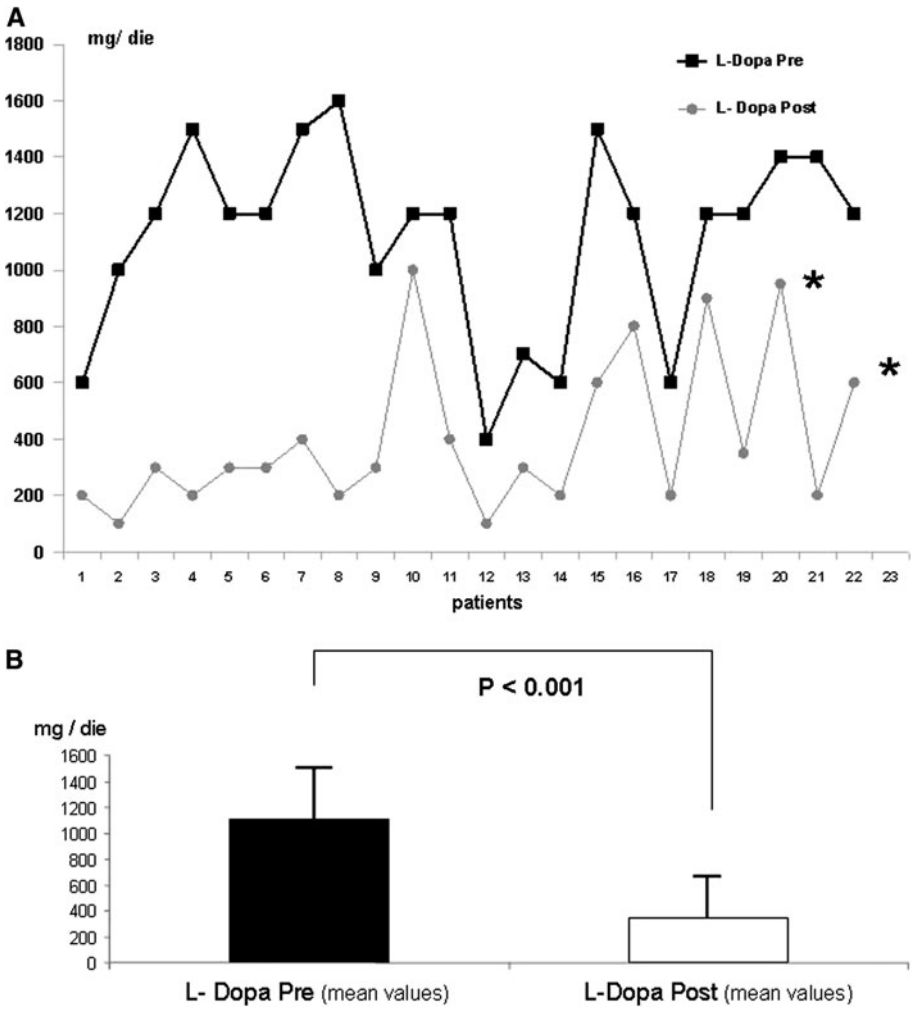

Fig. 9 **a** Daily L-dopa dose before (*black line*) and following 4–5 months of continuous PPTg DBS (*gray line*) in 22 patients subjected to PPTg DBS. The *asterisk* indicates that in two patients (Nr.21 and Nr.22) subcutaneous lisuride or apomorphine infusion was no longer required following PPTg DBS. **b** Mean (±SD) daily L-dopa dose (*black bar*) before and following DBS (*white bar*). The reduced requirements of L-dopa was statistically significant ($P < 0.001$, ANOVA followed by a Newman–Keul test)

improves specific aspects of these motor symptoms we are currently investigating the possibility that PPTg DBS may influence oromandibular movements besides limb movements. The PD patients who underwent unilateral PPTg DBS preoperatively showed a serious disruption of jaw motor performance compared to age-matched normal subjects (Barciela et al. 2002). The instrumental gnatographic evaluation carried out on 16 patients according to different ON and OFF conditions related to drugs and PPTg DBS showed more consistent improvements in jaw movements (Fig. 8) than those provided by the classic UPDRS evaluation, thus providing further support for the efficacy of PPTg DBS with respect to the traditional targets. The two experimental conditions, i.e. drugs OFF (capit)—PPTg DBS OFF and drugs OFF (capit)—PPTg DBS OFF were chosen in order to compare the PPTg DBS outcome to the effects of dopaminergic drugs withdrawn.

From the body of clinical evidences discussed, it can be argued that most patients appeared to be controlled by the DBS of a single target, i.e. the PPTg, in all parkinsonian symptoms and not just in gait and postural disturbances. Patients with unilateral PPTg DBS required reduced L-dopa and L-dopa agonists, as reported in Fig. 9. The reduction of drug dosages, the abolition of subcutaneous apomorphine or lisuride (two cases; Fig. 9a), and the improvement in jaw movements following PPTg BDS, add further support to the hypothesis of a specific role of the PPTg not only in the progression of disease but also in the actual stage of the disease, in agreement with authors who provided evidence in favor of the staging of PD (Braak et al. 2004).

Conclusions

Stimulation of the PPTg represents a new tool for understanding some of the functions of the brainstem as well as the role of PPTg in the control of different symptoms in PD and in other neurodegenerative disorders. The introduction of PPTg DBS has contributed to change neurosurgical axioms and methodological concepts that seemed immutable. There is still a lack of univocal interpretations about the sites of stimulation and type of leads employed, and the

results so far have been characterized by different interpretative and evaluation criteria. According to our experience, the PPTg must be considered as a reference point in a region of imbricated nuclei crossed by ascending and descending connections. Among these structures are nuclear formations which can be affected to varying degrees in the different stages of PD and other degenerative disorders and which cannot be unambiguously considered as being responsible for the effect of PPTg DBS. The differences in the results obtained by different groups can be explicated by differences in the stimulated site, in the individual characteristics of patients, in the type of leads employed and, finally in the type of stimulation applied. However, it is undeniable that the PPTg may play an effective role as a target for treating the symptoms of PD.

The PPTg may be considered as a neurosurgical reference point in the brainstem, that, when stimulated, may induce clinical effects, most likely due to its position and anatomical connections. In light of the above considerations, a concern arises: it may be hazardous to ascribe to the PPTg with the same role assigned to the STN by clinical and theoretical interpretations. In any case, the relevance of our PPTg experience also arises from a reinterpretation of the mechanism of action of DBS in PD and in other pathologies, as also demonstrated recently by the applications of DBS in psychiatric disorders. In conclusion, the neurophysiological and clinical observations obtained in implanted patients suggest new directions and open up new horizons for the treatment of neurological and psychiatric disorders other than PD.

Acknowledgments The authors wish to thank Dr. Marco Paoloni, University of Rome La Sapienza, for carrying out gait analysis; Dr. Gianni Falise, University of Rome La Sapienza, for evaluating oromandibular movements and Dr. Guido Vagliasindi, University of Catania, for evaluating the lead electrical field. E.S. was supported by grants from MIUR (Cofin 2008) and University of L'Aquila. Paolo Mazzone wishes to dedicate this paper to the voice of the Japanese soprano Akiko Taniguchi.

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