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ORIGINAL ARTICLE

Targeting the brain: considerations in 332 consecutive patients treated by deep brain stimulation (DBS) for severe neurological diseases

Angelo Franzini · Roberto Cordella · Giuseppe Messina · Carlo Efisio Marras · Luigi Michele Romito · Alberto Albanese · Michele Rizzi · Nardo Nardocci · Giovanna Zorzi · Edvin Zekaj · Flavio Villani · Massimo Leone · Orsola Gambini · Giovanni Broggi

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Abstract Deep brain stimulation (DBS) extends the treatment of some severe neurological diseases beyond pharmacological and conservative therapy. Our experience extends the field of DBS beyond the treatment of Parkinson disease and dystonia, including several other diseases such as cluster headache and disruptive behavior. Since 1993, at the Istituto Nazionale Neurologico "Carlo Besta" in Milan, 580 deep brain electrodes were implanted in 332 patients. The DBS targets include Stn, GPi, Voa, Vop, Vim, CM–pf, pHyp, cZi, Nacc, IC, PPN, and Brodmann areas 24 and 25. Three hundred patients are still available for follow-up and therapeutic considerations. DBS gave a new therapeutic chance to these patients affected by severe neurological diseases and in some cases controlled life-threatening pathological conditions, which would otherwise result in the death of the patient such as in status dystonicus, status epilepticus and post-stroke hemiballismus. The balance of DBS in severe neurological disease is strongly positive even if further investigations and studies are needed to search for new applications and refine the selection criteria for the actual indications.

A. Franzini · R. Cordella (✉) · G. Messina · C. E. Marras · L. M. Romito · A. Albanese · M. Rizzi · N. Nardocci · G. Zorzi · E. Zekaj · F. Villani · M. Leone · G. Broggi
Fondazione IRCCS Istituto Neurologico "C. Besta", Via Celoria 11, 20133 Milan, Italy
e-mail: rcordella@istituto-besta.it

L. M. Romito · A. Albanese
Università Cattolica di Milano, Largo Gemelli 1, 20100 Milan, Italy

O. Gambini
Università degli Studi-AO San Paolo, Via A. di Rudinì 8, 20100 Milan, Italy

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Introduction

Deep brain stimulation (DBS) extends the conventional neurological treatment beyond the limits of drug and conservative therapies. This statement has been proved true in the treatment of advanced Parkinson disease and primary dystonia, but many preliminary studies and data suggest that other severe neurological diseases may benefit from DBS if the proper indication and the appropriate targets are known or properly investigated. In other words, DBS allows to interact with the nervous system networks alleged to be altered in specific neurological diseases, such as cluster headache, behavior disorders and other pathological conditions described in this paper. We report the experience of the National Neurological Institute "C. Besta" in 332 consecutive patients operated on between 1993 and 2010 (Fig. 1). Our results and considerations are reported "target by target" to underline the concept that single "anatomical" target may be functionally involved in the physiopathology of different neurological diseases, i.e., the zona incerta has been successfully targeted for Parkinson disease, essential tremor and refractory partial motor epilepsy. Finally, we focused this review to the targets that are less extensively described in the DBS literature.

Surgical methodology

Surgery is performed either in awake patients under local anesthesia, or in anesthetized patients when poor cooperation is expected (as in children). DBS procedures are always

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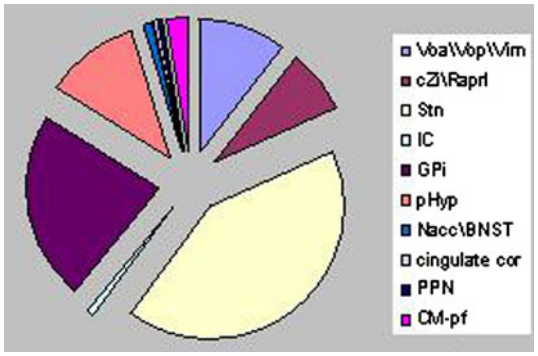

Fig. 1 Graphic representation of the whole series of deep brain electrodes implanted since 1993 at the neurological institute ''C. Besta'', in Milan [*Stn* subthalamic nucleus ($n = 138$), *GPi* globus pallidus pars interna ($n = 76$), *Voa–Vop–Vim* ventral thalamus ($n = 35$), *CM–pf* centromedian parafascicular complex ($n = 8$), *cZi\Raprl* caudal zona incerta\prelemniscal radiation ($n = 26$), *IC* internal capsule ($n = 3$), *pHyp* posterior hypothalamus ($n = 38$), *Nacc\BNST* nucleus accumbens\bed nucleus of the stria terminalis ($n = 4$), *PPN* peduncolopontine nucleus ($n = 2$)]

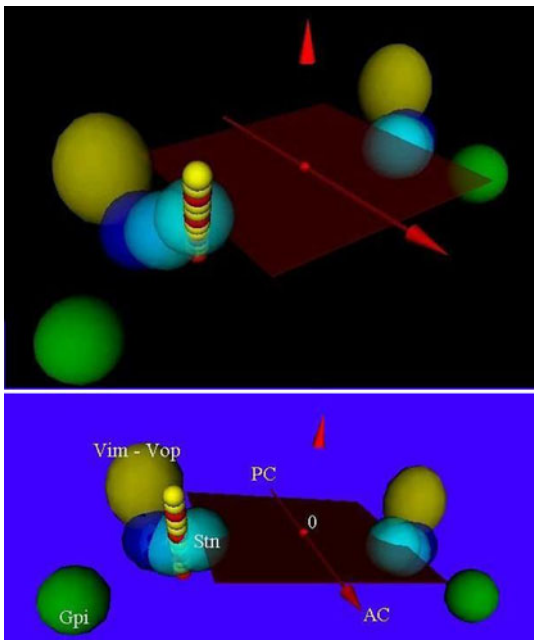

Fig. 2 3D computerized reconstruction of the probabilistic stereotactic digitalized atlas representing the commissural plane and the targeted volumes: *yellow*, Voa/Vop/Vim; *cyan*, Stn; *blue*, cZi/Raprl; *green*, GPi. In this plate, the electrode is placed within the anterior portion of Stn (contacts are represented in *red*)

performed in stereotactic conditions with the Leksell (Elekta Inc., Atlanta GA, USA), CRW (Radionics, Burlington, MA, USA) and Micromar (Micromar Inc., Sao Paolo, Brazil) frames. Computerized tomography (CT) is our examination of choice to recognize the anterior and posterior commissures in the stereotactic space, after positioning of the headframe. A probabilistic stereotactic digitalized atlas registered to the anterior commissure (AC)–posterior commissure (PC) line is utilized for the preliminary determination of the target coordinates (Fig. 2). The stereotactic CT images are then merged with the preoperative magnetic resonance images (MR; T1 and fast spin echo inversion recovery sequences with double dose of contrast agent) and a second calculation of the target coordinates is performed with the neuronavigation system (Stealth Station Treon Sofamor Danek, Medtronic Inc. Minneapolis, MN, USA) analyzing the merged images registered to the midcommissural point. Finally, the two set of data are matched, and the definitive coordinates, along with the planned trajectory, are adapted to the individual patient anatomy. A rigid cannula is then inserted through a small hand-drilled burr hole (5-mm diameter) and through the opened dura mater; the cannula is then indwelled till 15 mm above the estimated target. A high impedance microelectrode (250-μm tip, and impedance 1–1.5 MΩ; FHC Inc., Bowdoinham ME, USA) is then introduced within the cannula and advanced progressively to the target. Microrecording tracks are performed with 0.5-mm steps, and 1 mm beyond the target along the single planned trajectory. If microrecording fulfills the localizing criteria, the definitive electrode (Medtronic Inc. Minneapolis, MN, USA; St. Jude Inc., St. Paul MN, USA) is placed at the target through the same rigid cannula after the microelectrode withdrawal. Macrostimulation is then performed in bipolar configuration between the two proximal contacts and between the two distal contacts. At this stage of the procedure, clinical testing of the awake patient and electromyographic (EMG) recording in the anesthetized patient allow to search for favorable clinical response and/or for the appearance of side effects. If microrecordings and macrostimulation through the definitive electrode suggest its accurate placement at the right target, the electrode is secured to the burr hole with biological glue (Cryolife Inc., Kennesaw GA, USA), and a titanium microplate. The free distal plug of the electrode is then left beneath the galea ready for the connection to the extension lead and internal pulse generation (IPG). Otherwise if microrecordings and/or clinical and EMG monitoring suggest a suboptimal electrode placement, a new trajectory is planned trough the same burr hole. About 70% of our DBS procedures required one trajectory per side, 20% required two trajectories and only 10% required three or more trajectories.

DBS targets

Subthalamic nucleus (Stn)

In the past three decades, the introduction of chronic high-frequency DBS of different targets [1, 2], mainly the ventro-intermediate nucleus of thalamus (Vim) [3], the globus pallidus internum (GPi) [4] and the subthalamic

nucleus (Stn) [5], has injected a great deal of excitement into the scientific community with regard to the treatment of severe Parkinson's disease (PD), obtaining major results and potential new insights into pathophysiological mechanisms of the disease. Currently, high-frequency Stn-DBS is considered the preferred surgical method to treat PD patient, as it has effectively provided significant improvement of the motor conditions of patients with motor fluctuations and dyskinesias and has allowed reducing antiparkinsonian medication [6, 7]. Several papers have been published about the 3–4 years postoperative follow-up of the implant of this target [8–13], while there is still a paucity of data at longer term, in particular at 5 [14–18] and 8 years [19] after Stn implant.

Operated series and results (1999–2010)

In our institute since 1999, 138 patients (73 males and 45 females) with PD underwent bilateral stereotactically guided Stn implants and received continuous stimulation for the consecutive years. Long-term follow-up is available in 118 patients, who had a diagnosis of PD according to the UK Parkinson's Disease Brain Bank Criteria [20] and fulfilled the recommendations of the CAPSIT-PD panel [21]. The patients had a mean (±SD) age at PD onset of 44.3 (±8.0) years, an age at implant of 56.5 (±7.5) years with disease duration of 12.6 (±7.2) years and a mean levodopa response of 60.1%. Main outcome measures of this study were the (a) motor efficacy of Stn stimulation, defined as the UPDRS-motor score variation between the preoperative condition without medication and the condition with stimulation on, but without medication and the (b) combined motor efficacy of stimulation and medication, defined by the variation of the UPDRS-motor score between the preoperative score without medication and the postoperative score with stimulation turned on and with medication. UPDRS dyskinesia score, duration of motor fluctuations and levodopa equivalent daily dosage (LEDD) (measured in mg) were computed for each patient. At the last follow-up (FU) (mean 41.4 ± 33.1 months), the motor efficacy of Stn stimulation was 56.4% (the UPDRS-motor score was preoperatively 47.9 ± 15.7; the UPDRS-motor score was at last FU 20.9 ± 10.4; the difference was $p < 0.001$) and the combined motor efficacy of stimulation and medication was 65.3% (the UPDRS-motor score was preoperatively 47.9 ± 15.7; the UPDRS-motor score was at last FU 16.6 ± 9.0; the difference was $p < 0.001$). The motor efficacy of Stn stimulation was not evenly distributed: rest tremor had the most remarkable changes, followed by rigidity, gait, lower limb akinesia, upper limb akinesia, gait and postural dysfunctions; speech item was not improved. Dyskinesias were improved in all the patients after implant. The duration and severity of motor fluctuation, and the severity of off-period dystonia were markedly reduced in all the patients during the period of observation.

The mean preoperative LEDD (961.3 ± 519.2) was greatly reduced during the first 6 months after implant and stabilized at values around 62% ($p < 0.001$) of the pre-implant dose at the last follow-up. In particular, at the time of implant, the patients were taking the following anti-parkinsonian medications: levodopa (135 patients), dopamine agonists (93 patients, among them 8 patients were on pergolide, 54 patients on ropinirole, 27 patients on pramipexole, 4 patients on subcutaneous infusion of apomorphine). Thirty-three patients were also on clozapine (most of them for the treatment of impulse control disorders). After implant, 10 patients were without dopaminergic medication, 14 took only dopamine agonists and 3 were only on controlled release levodopa preparations. After the implant, at last FU, no patient received apomorphine while three patients continued to take clozapine.

Surgical adverse events were reported in a minority of the patients: two patients had a brain hematoma with hemiplegia; a patient presented an unexplained fracture of the extracranic portion of the lead and underwent successful re-implant; two patients had monolateral stimulation system removal due to infection. The stimulation side effects were present in 29% of patients: hypophonia occurred in 17 patients; dysarthria was present in 11 patients. All the patients gained weight after surgery. Overall, these data indicate that chronic Stn-DBS is efficacious in controlling levodopa-responsive parkinsonian symptoms and allows maintaining a long-lasting reduction of dopaminergic treatment. The safety profile is positive.

Globus pallidus pars interna (GPi)

In the 1930s Russel Meyers performed, via craniotomy, selected basal ganglia lesions for the treatment of movement disorders, including globus pallidus [22]. After these experiences, burdened by high-mortality rate, in the 1950s, Spiegel and Wycis [23] used a stereotactic system to perform selective pallidal lesions for the treatment of PD. In the next few decades, attention moved from the pallidum to the thalamic targets, whose lesioning permitted a better tremor control, but side effects such as dysarthria and ataxia were frequent, particularly when lesions were bilateral. In the early 1990s, Laitinen, recovering the studies of his mentor Leksell [24], showed encouraging results through the lesioning of the posteroventrolateral part of the globus pallidus internus (GPi) for the treatment of PD [25]. In that year, the group of Grenoble gave a huge contribution to the worldwide diffusion of DBS by defining the target and parameters of stimulation for the treatment of PD [26]. In the following year, Sigfried et al. [4] treated a parkinsonian

patient with GPi bilateral stimulation, using the target defined by Leksell and Laitinen that showed satisfactory long-term results [27]. Only in the late 1990s, different groups started to stimulate GPi for the treatment of dystonia [28]. Krauss et al. [29] reported the first series of patients, followed by Coubes et al. [30]. In the 2000, our group suggested that also dystonic storm could be successfully treated by GPi-DBS, with resolution of the life-threatening situation [31]. In the past decade, GPi has been assessed as the best therapeutical stimulation target for severe forms of dystonia in both adults [32] and in pediatric population, as also underlined by our group [33]. Globus pallidus internus plays a relevant role in the motor output from basal ganglia to the cortex in the context of the basal ganglia-thalamo-cortical loops; intraoperative recordings, in patients affected by dystonia, permitted to disclose a particular high-frequency and bursting pattern of discharge that is one of the prominent features of the disease. The GPi portion where sensorimotor neurons are located, and from which ansa lenticularis emerges to reach the motor thalamus, is the ventroposterolateral portion. Although there is a little variety in the stereotactic coordinates, most frequently the tip of the electrodes, as suggested by Laitinen et al. [25], is located 3–6 mm under the intercommissurale plane, 2–3 mm anteriorly to the midcommissural point and 20–22 mm lateral to midline. To avoid side effects related to the proximity of the internal capsule, many authors prefer to set the coordinates more laterally, while optic tract involvement is prevented by a more dorsal positioning. Intraoperative microrecording and macrostimulation permit verifying the best functional electrodes location in relation to the possible side effects.

Operated patients and results (1999–2010)

Out of 62 dystonic patients submitted to GPi-DBS, a total of 47 patients were available for follow-up (26 adults and 21 with age lower than 18 years old) with different types of dystonia, diagnosed according to the Fahn's criteria [34]. They underwent bilateral GPi electrode implantation. Neurologists followed adult patients belonging to Group 1, while pediatric neurologists treated the pediatric–adolescent group (Group 2). Preoperative clinical evaluation included in all patients assessment of dystonia with videotape recordings and the administration of the Burke, Fahn and Marsden Dystonia Rating severity score (BFMDRS). After surgery, all the patients were evaluated monthly and the clinical status was assessed with videotape recordings and the BMFDRS. The overall mean follow-up was 50 months. In Group 1, the mean age of dystonia onset was 12.9 years (range 0.5–63 years), and the mean age at the time of surgery was 33.7 years (range 18–68 years); the higher age at onset of dystonia (a case of Meige syndrome) was 68 years. Fifteen patients were affected by a primary form of dystonia (10 generalized and 5 segmental), while 11 patients were affected by generalized secondary dystonia. In Group 2, the mean age of disease onset was 4.9 years (range 0.5–15 years), and the mean age at time of surgery was 12.2 years (range 4–24 years). All the patients showed a generalized dystonia: 17 patients suffered from a primary form, while 4 from a secondary one. Five patients during the course of the disease developed a status dystonicus. Four of them had a primary dystonia and the remaining had a secondary one. All but two patients affected by neuroleptics-induced dystonia (tardive dystonia) did not improve immediately after surgery; the response was delayed and appeared after a time ranging between 1 week and 6 months. Clinical improvement was observed in the first month in 70% of cases, and in whole responder patients (childhood and adult onset patients) it was observed within the first year. According to the BFMDRS evaluation, in Group 1 the mean improvement was 40.2% (ranging between 7.7 and 94%; preop BFMDRS 51.2 ± 25.3; BFMDRS at last FU 30.6 ± 19.1), with a better outcome for patients with primary dystonia (45.2 vs. 33.3% in the patient affected by the secondary form); the two cases with the neuroleptic-induced form showed an amelioration of 42 and 80%. Our experience in these patients showed a short time lapse (72 h) between the delivery of electrical current to GPi and the maximal therapeutic effect [35]. The patient affected by Meige's syndrome gained a benefit of 94%, after 36 months of follow-up. In the childhood-onset dystonia group, the reduction of the postoperative BMFDRS score resulted in a mean improvement of 42.1% (ranging between 0 and 92.9%; preop BFMDRS 67.4 ± 22.5; BFMDRS at last FU 39.0 ± 24.1): in the primary form, we noticed a better amelioration (43.1 vs. 37.5% in the secondary dystonia). The patients (three in Group 1 and two in Group 2) affected by a primary form, with the genetic mutation DYT1+, showed a mean improvement of 63.8% (range 43.1–92%). We also observed that patients with mobile forms showed a better response to high-frequency stimulation of the GPi; axial dystonic postures and movement responded to a greater extent compared to oromandibular dystonia, fixed dystonic postures or task-specific dystonia such as writing dystonia. Moreover, a better outcome could be reached in cases with short disease duration. For this reason, we strongly recommend an early surgery to avoid muscle retraction and skeletal deformities. On the other hand, in 20% of patients of Group 2, we reported a long-term efficacy reduction, despite an optimal regulation of the stimulation parameters. Furthermore, in one pediatric patient suffering from a severe form of secondary dystonia, who was successfully treated by GPi-DBS 2 years previously, the stimulation device on the right side became infected because of the skin erosion of the head along the path of the connector. Considering the risk of relapse of

erosion, because of the thinness of the patient, a right pallidotomy was then performed by the DBS electrode, before its subsequent, definitive removal. A long-lasting stable control of dystonia was observed, and 9 months after the lesioning procedure, with the left DBS electrode still active, the BFMDRS was the same as that recorded with bilateral stimulation [36]. We observed a higher incidence of complications in dystonic patients versus PD patients: hardware-related migration of the electrode in four cases; breaking of the electrodes in two cases; one patient had dislodgement of the left electrode to a position close to the left amygdala and developed behavioral changes consisting of depression, psychotic symptoms and heightened pain perception [37] related to the surgical procedure; infection in five cases; intracranial hemorrhage in one case. In one case dysarthria and dysphagia were related to the bilateral stimulation and recovered activating only one electrode. All the complications, other than hemorrhage, were successfully managed. Our series showed that GPi-DBS is a safe and effective therapeutical option in the treatment of severe, and also life-threatening, forms of dystonia. The large variability in results suggests a major role of careful preoperative selection of the patients. Finally, it has to be remarked that worst results have been obtained in 11 patients affected by dystonia due to cerebral palsy. One more patient (a female aged 28 years at implant) with a drug refractory Tourette's syndrome underwent bilateral GPi implant: the postoperative improvement of the Yale Global Tic Severity Scale (YGTSS) was 75% (preop YGTSS score: 75; postop YGTSS score: 19), and this result was maintained stable up to the last follow-up at 5 years. Bilateral GPi-DBS has been also utilized in 13 PD patients in which levodopa-induced dyskinesias were the prominent symptoms. In all cases, DBS produced disappearance or marked reduction of dyskinesias. The reduction of drug dosage ranged between 20 and 40%, maintaining satisfying control of the disease. None of these patients presented speech problems, but two patients after 4 years of chronic stimulation developed severe akinesia resistant to levodopa therapy.

Thalamic ventral nuclear complex (Voa\Vop\Vim)

Hassler first targeted the ventrolateral thalamus for PD symptoms in 1952, and Cooper did the same for multiple sclerosis (MS) tremor in 1967. Autopsies of their lesioned patients suggested that the ventralis oralis posterior (Vop) and ventralis intermedius (Vim) nuclei were involved in the origin of tremor [38]. Also in the 1960 during thalamotomies, Hassler and co-workers found that high-frequency stimulation of the Vim nucleus of the thalamus dramatically reduced tremor [39]. The first series of Vim nucleus as a target for DBS in patients with parkinsonian tremor have been reported in the late 1990s [40]. In the following years, the number of reports dealing with the efficacy of chronic high-frequency Vim-DBS increased consistently and included also posttraumatic tremor [41–44]. The Vim nucleus has also been reported as a successful target for DBS in tremor associated with phenylketonuria, mercury poisoning and genetic syndromes [45–49]. Bilateral stimulation of Vim has been more effective than unilateral stimulation in the treatment of head, voice and midline tremor [50, 51]. In spite of the efficacy of bilateral Vim stimulation, it should be used cautiously due to potential adverse effects related to stimulation, such as dysarthria, gait and postural impairment. Despite Vim nucleus being an optimal target in essential tremor (ET), in parkinsonian tremor it should not be used as primary target because of poor benefit on bradykinesia and rigidity [52]. Even if most authors have targeted the Vim to treat tremor in MS patients, some others have preferred the Vop suggesting better control of the ataxic component of tremor [53]. Bittar and co-workers have used Vop only in patients with distal tremor [54]. Foote achieved improvement of tremor in a post-traumatic tremor patient stimulating simultaneously Vim and ventralis oralis anterior (Voa)/Vop trought a double electrodes implant aimed to interact with the pallido- and cerebello-thalamic circuits (Deuschl et al. [55]; Foote et al. [56]). Broggi et al. [57] reported optimal results in 12 patients following Voa–Vop–zona incerta high-frequency stimulation. Four patients were affected by multiple sclerosis, three by posttraumatic tremor, and five by parkinsonian tremor [57]. The Vim nucleus is bordered by the internal capsule laterally, and posteriorly by the ventralis caudalis (Vc) nucleus. The electrode is typically placed at the anterior border of Vim to ensure that stimulation does not extend caudally to Vc, evoking intolerable paresthesias. Several authors have reported the optimal coordinates of targeting the Vim nucleus, [50, 58]. The AC–PC plane is the optimal axial plane for the electrode tip ($Z = 0$ in the commissural coordinates system). The most used X and Y coordinates for Vim targeting are 5 mm posterior ($Y = -5$) and 13 mm lateral to the midcommissural point ($X = 13$ mm) (Table 1). The optimal lateral coordinate may vary with the degree of brain atrophy and third ventricle dimensions. Somatotopic representation of body segments within the Vim nucleus consists in a more lateral localization of the upper limb and hand ($X = 12$–14 from the midline), while the inferior limb and the foot are more medially represented ($X = 10$–12). Intraoperative microrecordings and macrostimulation should be performed to identify the upper limb somatotopy in the thalamus to guide the laterality of lead placement. Following the targeting, it is critically important to test the implanted lead with intraoperative stimulation through a temporarily

Table 1 Overall scheme of our series regarding number of patients, specific diseases, intracerebral target chosen, and coordinates of the related targets

Target	Total patients	Indications	Coordinates related to the AC–PC midpoint
Stn	138	Parkinson's disease	$X = \pm 12$; $Y = -4$; $Z = -4$;
GPi	76	62 Dystonias	$X = \pm 19$; $Y = 2$; $Z = -6$
		1 Tourette's syndrome	
		13 PD	
Vim\Voa\Vop	35	18 Essential tremor	$X = \pm 14$; $Y = -1\backslash -5$; $Z = 0$
		7 MS tremor	
		9 post-traumatic tremor	
		1 hemiballismus	
CZi/RARPL	26	23 PD	$X = \pm 12$; $Y = -7$; $Z = -4$
		3 Epilepsy	$X = \pm 10$; $Y = -5$; $Z = -3$
IC	3	2 Post-stroke pain	$X = \pm 17$; $Y = -7$; $Z = +2$
		1 post-stroke fixed dystonia	
CM–pf	8	2 Parkinson's disease	$X = \pm 8/10$; $Y = -12/14$; $Z = 0$
		4 Lennox–Gastault	
		2 Pain	
pHyp	38	22 CCH, 1 SUNCT, 5 MS, 4 Atyp pain, 6 aggressive behavior	$X = \pm 2$; $Y = -3$; $Z = -5$
NACC\BNST	3\1	Obsessive compulsive disorder	$X = \pm 3$; $Y = +16$; $Z = -2$
Cingulate cortex 24/25	2	1 Somatoform chronic pain	$X = \pm 8$; $Y = 23$; $Z = 29$
		1 Major Depression	$X = \pm 7$; $Y = 29$; $Z = -3$
PPN	2	Parkinson's disease	$X = +5$; $Y = -18$; $Z = -15$
Total	332		

connected external pulse generator. This method allows the confirmation of successful tremor suppression with high-frequency stimulation, and the thresholds for stimulation-induced side effects can be measured. Parameters of chronic definitive electrical stimulation are: 130–180 Hz; 60–90 μs; 0.5–3 V. The most commonly reported stimulation-related adverse events are paresthesias, dysarthria, gait disorders and disequilibrium, although they are frequently viewed as mild and tolerable or amenable to reprogramming [44, 50, 52].

Operated patients and results (1993–2010)

A total of 34 patients (age 19–78 years) underwent ventral thalamus DBS (Voa, Vop, Vim) to treat drug-refractory non-parkinsonian tremor (Table 1). The youngest patient was affected by post-traumatic tremor of the right upper limb, and the older one was affected by essential tremor of the left side of the body. The etiology of tremor was post-lesional in nine cases (trauma, ischemia, surgical sequelae), essential tremor (ET) in 18 patients, and was associated with MS in 7. Thirteen patients required bilateral DBS implants for bilateral tremor. The best results in spite of the age and duration of the disease have been obtained in patients affected by essential tremor prevailing on one side (6 right side, 5 left side): this group includes 11 patients who had considerable tremor reduction or complete tremor disappearance. This is usually quantified through the visual quantification of the reduction of amplitude in drawing the Jankovic's spirals and lines. All returned to normal life without side effects related to the chronic thalamic stimulation. At the time of exhaustion of the batteries (3–5 years after surgery), tremor was still controlled by stimulation in all cases. Contralateral tremor on the untreated side appeared or worsened in all cases, but no contralateral implant was performed. Similar results were obtained in the control of tremor in patients affected by bilateral essential tremor (6 cases), but all these patients complained of mild to severe speech impairment due to dysarthria related to stimulation. One of these patients developed postural imbalance, which disappeared on turning off bilaterally the stimulation. Also in post-lesion tremor, the best results were obtained with unilateral implants (6 cases), while speech impairment was noticed after bilateral thalamic implants (3 patients). DBS in MS patients allowed the control of tremor, but not the control of the associated ataxia which limited consistently the execution of finalistic movements. Dramatic improvement was obtained in extremely severe syndromes (4 cases) characterized by high-amplitude distressing tremor of bilateral limbs and

head in completely invalidated patients, who had disappearance of tremor but not the restoration of finalistic movements. Also in these cases, bilateral surgery was associated with speech impairment: all these patients regained calm and relaxed postures. Finally in one of these patients, surgery was followed by a relapse of the demyelinating disease. Thalamic DBS best results are expected in unilateral ET in spite of the age and duration of the disease. Patients should be warned that bilateral surgery may be associated with speech impairment. Alternative targets for the treatment of tremor, such as the centrum medianum nucleus (CM) of the thalamus and the caudal zona incerta (cZi), have been investigated to reduce speech side effects and to improve the control of the ataxic component of some invalidating tremor syndromes. Anyway in patients with medication-resistant invalidating tremor, DBS of the ventral nuclear complex of the thalamus (Voa, Vop, Vim) should be considered [59]. Vim-DBS has been also performed to stop continuous abnormal movements in one patient who developed hemiballismus after a small mesencephalic stroke. Vim-DBS allowed the withdrawal of the patient from the intensive care unit and his return to normal life.

Caudal zona incerta (cZi) and prelemniscal radiations (Raprl)

Zona incerta (Zi), also described by Forel as the "region of which nothing certain can be said" [60], is a thalamus derived region [61] lying medially and laterally along the posterior portion of the subthalamic nucleus (Stn). In the last few decades, several studies confirmed the structural, physiological and functional complexity of this deep brain structure, where a great variety of connections to different sides of the central nervous system have been reported [62–65]. The heterogeneity of Zi suggests its role in different neurological functions including visceral activity [66], arousal [67], attention [68] and both posture and locomotion [69]. According to the results reported by previous reports [70–72] that showed interesting data after stereotactic lesions of Zi for Parkinson disease (PD), in recent years Zi-DBS has been proposed as symptomatic treatment for both bilateral and unilateral PD [73–76]. Plaha et al. [74] reported that stimulation of neighboring dorsal and dorsomedial zones [pallidofugal fibers and rostral Zi (rZi)] allowed a significant therapeutic benefit of parkinsonian symptoms. Consequently, the Bristol group started to treat patients affected by advanced PD with DBS targeting three different, but contiguous, areas: Stn, rZi/pallidofugal fibers and caudal Zi (cZi). Outcomes emphasized that high-frequency stimulation of cZi resulted in greater improvement in contralateral motor performance including tremor, rigidity and bradykinesia. Moreover, different authors suggested that Stn stimulation for PD may harbor a certain amount of side effects, including speech impairment, cognitive decline and behavior disturbance [6, 77, 78]. Plaha et al. suggested [75] that stimulation of cZi permitted a lower incidence of speech deterioration, and supposed a better neuropsychological outcome. Also, Velasco et al. [76] suggested an alternative target to Stn to treat advanced PD. These authors implanted DBS electrodes in the prelemniscal radiations (Raprl) medially to the Stn and very close to the Zi. The surgical methodology to target cZi or Raprl is the same for Stn implants with intraoperative microrecordings and macrostimulation at the target. The definitive electrode implant is posterior to the subthalamic boundaries localized with microrecordings (cZi) and medially to Stn for the Raprl (Fig. 3). The target coordinates of cZi related to the midcommissural point are $X = 12$, $Y = -7$ and $Z = -4$, while those for the Raprl are $X = 10$, $Y = -5$ and $Z = -3$ (Table 1).

Operated patients and results (2003–2010)

Nineteen patients affected by advanced PD, candidates to DBS (age 60–72 years), were selected for stimulation of the cZi and/or the Raprl due to the presence of mild

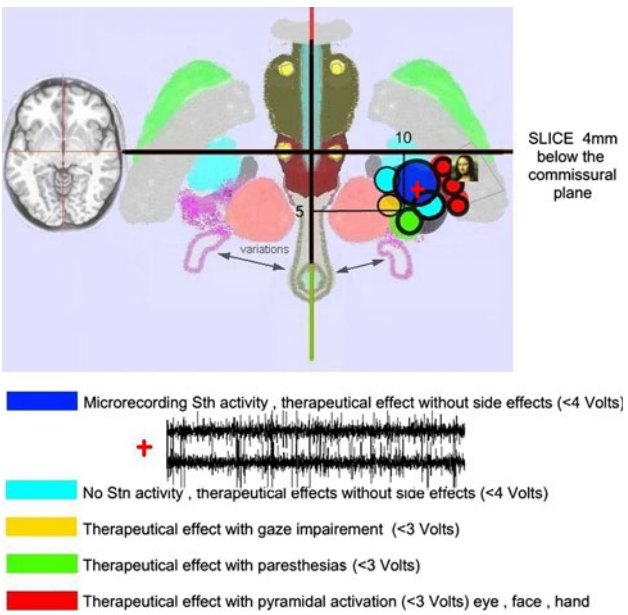

Fig. 3 Axial section (4 mm below the AC–PC line) of the digital atlas showing intraoperative responses to electrical stimulations within Stn and at its boundaries. *Each circle* is colored and referred to the color legend in the *bottom panel*. Note that the area where therapeutic results are achieved without side effects is larger than the Stn area itself, and extends posteriorly and medially to Stn

speech impairment and/or behavioral diseases, such as depression and apatheia. These patients were treated with bilateral DBS of the cZi (11 patients), bilateral implants within the Raprl (4 cases) and asymmetric implants (Raprl on one side and cZi on the contralateral side) in four cases. The long-term results at 2–7 years follow-up (mean 4 years) are closely similar to the long-term results obtained with Stn-DBS: the motor efficacy of cZi and/or the Raprl stimulation was 42.8% (the UPDRS-motor score was preoperatively 49.5 ± 12.8; the UPDRS-motor score was at last FU 28.6 ± 10.2; the difference was $p < 0.001$); the incidence of speech impairment was 36% and depression 18%. No difference between the Raprl and cZi chronic stimulation was found in our series. Also, the asymmetrical implants could not prevent speech impairment and behavioral side effects. Anyway, these data and results suggest that the volume of the target within the so-called subthalamic region actually exceeds the volume of the subthalamic nucleus itself, also including the cZi and the Raprl (Fig. 3), which enlarge the target posteriorly and medially in areas which are not characterized by typical multiunit neuronal activity of the Stn cells (Fig. 3). The cZi has been targeted also to treat refractory epilepsy originating in the central motor cortex in one patient affected by post-traumatic epilepsy, and in one patient affected by focal motor cortex dysplasia. DBS of cZI has also been used to treat status epilepticus with partial motor seizures in one patient affected by Rasmussen encephalitis. The well-documented connections between the ZI and the contralateral motor cortex supported the rationale for this original DBS application [79]. DBS induced up to 85% decrease of the number of seizures in the post-traumatic patient, and 50% seizure rate reduction in the patient affected by cortical dysplasia. In the third patient, cZi-DBS induced the disappearance of status epilepticus [79]. Finally, it has to be remarked that cZi may be stimulated with the same electrode targeting the caudal portion portion of Voa–Vop nuclei, if a proper stereotactic trajectory is planned (70° sagittal angle to the commissural plane and 20° coronal angle). Recently, four patients affected by PD with tremor prevailing on one side underwent this procedure with the 3,387 Medtronic electrode (4 stimulating contacts along 12 mm) connected to the Activa PC pulse generator. Complete tremor control was obtained with activation of the proximal thalamic contacts and with activation of the distal cZi contacts; the Activa PC pulse generator allowed to stimulate both regions with different current intensities and different electric fields and stimulating programs. In conclusion, we consider these targets as a valid alternative to Stn in the treatment of PD and tremor, and we strongly support cZi-DBS to treat motor partial epileptic seizure refractory to drugs and amenable to ablative surgery.

Posterior limb of the internal capsule (IC)

Adams et al. [80] were the first to describe pain relief after chronic stimulation of the posterior limb of the internal capsule (IC) in patients with central pain. In the following years, a few other reports have investigated the role of IC electrical stimulation in pain control [81–88]. IC stimulation has also been employed to improve movement disorders including spasticity due to trauma, tremor of the upper limb, cerebral palsy and dystonia [89, 90]. In a case described by Irving Cooper in 1980, pain and spasticity, caused by a car accident, were relieved by implanting DBS leads in the pulvinar and in the posterior limb of IC. Other authors reported that electrical stimulation of this latter region in chronic pain patients induced motor responses accompanied by pain relief [86]. The mechanisms of pain relief by IC stimulation are not clear. Unlike the stimulation of the periventricular gray matter (PVG) and periaqueductal gray (PAG), the IC-DBS is not correlated with an increase in the endorphin levels [91] and should involve a pain inhibiting pathway different from the opiate-mediated system. Experimental models have been employed to identify the neural systems involved in IC stimulation [92]. In animal models, these authors demonstrated that a train of electrical pulses delivered to IC elicited suppression of activity of nociceptive neurons in thalamic sensory nucleus. Furthermore, IC stimulation in cats has been demonstrated to have inhibitory effect on deafferentation hyperactivity in neurons of the spinal trigeminal nucleus [85].

Operated series and results (2001–2010)

We have implanted DBS leads to stimulate the motor fibers of the posterior limb of the internal capsule, adjacent to the sensory thalamus (Fig. 4) to treat central pain, spasticity

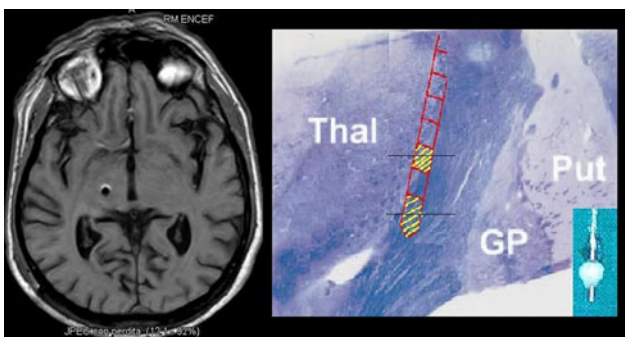

Fig. 4 Postop MRI (*left panel*) showing the electrode placement close to the IC and adjacent to the sensory thalamus in a patient with post-stroke pain referred in the lower limb. In the *right panel* graphic representation of the coronal section at the target showing the boundaries of the thalamus and the IC fibers. In the *lower right corner* of the image are represented the electrode and the estimated electric field, which in our case involved the thalamic sensory nucleus and IC fibers

and fixed dystonia of the lower limb. In our opinion, this target represents a valid option in the treatment of pain and spasticity of the lower limb as an alternative to motor cortex stimulation (MCS) recently proposed for post-stroke syndromes involving the upper limb and hand [93, 94]. In fact, IC chronic stimulation may interact with the same sensorimotor neural networks alleged to explain the mechanism of action of MCS, but works better when the inferior limb is involved due to the cortical representation of the lower limbs, which lies in the interhemispheric fissure and thus not an easy target for the placement of epidural electrodes. Stimulation of the posterior limb of the internal capsule (IC) has been employed to treat post-stroke neuropathic pain of the lower limb in two male patients, and in a 31-year-old female who had post-stroke fixed dystonia of the foot (inward rotation) [95, 96]. Both patients with post-stroke neuropathic pain reported improvements in the subjective perception of pain, as indicated by VAS, from the DBS at long-term follow-up (5 and 2 years, respectively). In one of these, the pain control was in parallel with an improvement in gait clumsiness and spasticity of the contralateral leg and foot [95]. The last one was affected by a post-stroke fixed dystonia of the foot and had a dramatic improvement of focal dystonia 2 days after the implant. At the 24-month follow-up, the clinical benefit of the procedure was continued to be maintained and the patient did not show any neurological signs associated with a stimulation-related side effect. The definitive stereotactic coordinates related to the commissural system midpoint were: 17 mm lateral (*X*), 7 mm posterior (*Y*) and 2 mm above the commissural plane (*Z*) (Table 1). The stimulation parameters ranged between 80 and 100 Hz, 60 ms, 1 V. In our opinion, IC-DBS seems to be a reliable DBS target to treat pain, spasticity and fixed postures of the inferior limb in post-stroke syndromes, and may be a valid alternative to MCS in selected cases.

Centromedian–parafascicular complex of the thalamus (CM–pf)

Two years after the introduction of the functional stereotactic technique by Spiegel and Wycis [23], Hécaen et al. [97] performed the first stereotactic lesion of the CM–pf complex for the treatment of intractable pain. Leksell and coworkers in 1972 [98] performed radiosurgical lesions within the CM–pf complex to treat chronic and neoplastic pain. More recently, a large number of CM thalamotomies aimed to alleviate intractable nociceptive and neuropathic pain have been reported by Weigel and Krauss [99]. In 1978, CM-DBS was proposed for the treatment of drug-refractory epileptic seizures not amenable to resective surgery; in particular, Velasco et al. [100–103] treated a certain number of patients affected by tonic-clonic seizures, atypical absences and Lennox–Gastaut syndromes. The rationale for this application was the hypotheses that CM may act as a relay in the non-specific reticulo-thalamo-cortical pathways involved in the generalization of seizures through the modulation of cortical excitability [104]. CM–pf DBS has been also utilized in the field of movement disorders in the treatment of tremor in PD patients as suggested in 1999 by Caparros-Lefebvre et al. [105] and recently by Mazzone et al. [106]. Finally, DBS of the CM–pf complex has been proposed for the treatment of patients affected by Gilles de La Tourette syndrome refractory to conservative therapy [107]. The published data suggest that CM–pf is the target of choice to treat this rare but invalidating disease [107, 108].

Operated patients (1993–2010)

Our experience with CM–pf DBS is limited regarding the number of treated patients, but includes all the classical indications of this target. Two patients underwent CM-DBS for chronic pain with only transitory benefits. Four patients underwent CM-DBS for Lennox–Gastaut syndromes; in these epileptic patients, the electrodes were implanted within the more lateral portion of the nucleus as suggested by Velasco et al. [102]. The authors have proposed that the best stereotactic coordinates for CM are 8–10 mm lateral from the commissural line, the *Y* close to the anterior border of the PC, and the *Z* at the plane of the AC–PC line (Table 1). The stimulation parameters were set at 130 Hz, 300–450 μs and 2 V [102, 109]. Only one of these patients obtained significant reduction of the number of seizures (>50%) during the first 6 months of follow-up. Better results were achieved in two patients affected by PD, in which CM–pf DBS allowed obtaining control of tremor and improvement of associated bradykinesia and rigidity. In one more case, CM–pf DBS was performed contralateral to a right Vop-cZi implant in a parkinsonian patient highly invalidated by severe limbs and head's tremor, who was also affected by a severe speech impairment. The implant resulted in excellent control of tremor on both sides and head, but the goal of preserving speech through a thalamic asymmetrical implant could not be achieved (when both the electrodes were activated, the patient complained of severe dysarthria, which disappeared when the stimulation was delivered only to one side either when Vim-cZi or CM–pf was turned off). In our opinion CM–pf is a good target for unilateral tremor when associated with bradykinesia and rigidity in parkinsonian patient, but cannot prevent speech impairment with bilateral implant.

Posteromedial hypothalamus (pHyp)

The posteromedial hypothalamus (pHyp) is part of the limbic system, and classically it has been linked to the control of behavioral states [110, 111]. Stereotactic lesions of the posterior hypothalamus (posterior hypothalamotomy) have been performed to treat aggressive behavior and facial cancer pain [112–114]. The Japanese neurosurgeon reported that after posterior hypothalamotomy, patients affected by untreatable disruptive behavior and sub-average intelligent quotient (IQ) showed decreased aggressiveness with improvement of IQ in almost 50% of the treated cases, because the patients were more cooperative after hypothalamotomy [114]. pHyp is located above the mammillary bodies at the level of the third ventricle. The pHyp contains homogeneous population of small to medium sized cells, with occasional large neurons scattered throughout the rostrocaudal extent of the nucleus. Cell packing density is low relative to neighboring hypothalamic structures; fiber tracks course through and around the pHyp along its rostrocaudal extent [115]. Major fiber tracks and cell morphology, and packing density differences of adjacent structures demarcate the boundaries of the area dorsally (thalamus, fasciculus retroflexus, periaqueductal gray), ventrally (dorsal premammillary nucleus, dorsomedial tuberomammillary nucleus, supramammillary decussation), caudally (periaqueductal gray and mesencephalic reticular formation) and laterally (lateral hypothalamic area, zona incerta, fornix, mammillothalamic tracks). The periventricular hypothalamic nucleus and fiber systems separate the pHyp from the ependyma of the third ventricle. The rostral border of pHyp appears to extend as a uniform structure rostrally to the level of the dorsal hypothalamic nucleus. The pHyp receives afferents from cortical, subcortical and brainstem structures involved in autonomic regulation. These include the insular cortex, septal nuclei, amygdala, subiculum, bed nucleus of stria terminalis, central gray, parabrachial nucleus, nucleus of the solitary tract and brainstem reticular nuclei, and also receives inputs from structures such as the cingulate, frontal, parietal and insular cortices [115, 116].

In the last decade, there has been resurgence of attention to the pHyp as the target for the placement of DBS leads in the treatment of disorders such as chronic cluster headache (CCH) [117–119]. Neuroimaging techniques have shown the activation of the ipsilateral posterior hypothalamus during CCH bouts [120, 121]. This activation may be specific in these patients, since it is not reported in other painful conditions such as migraine. Moreover, the pHyp is activated in nitroglycerin-evoked cluster headache pain bouts, and is not activated when the subjects are pain free [120]. The stereotactic coordinates to targeting this area are 2 mm lateral to the AC–PC line, 3 mm behind the midcommissural point, and 5 mm below the commissural line (Table 1). The parameters used for chronic electrical stimulation were as follows: frequency 185 Hz, pulse width 60–90 ms, amplitude 1–3 V in unipolar configuration (case as anode).

Operated patients and results (2001–2010)

DBS of the pHyp has been performed in 38 patients. As many as 22 patients were affected by CCH [118, 122], 1 by short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) [122], 5 patients by refractory recurrent trigeminal neuralgia (TN) involving the first trigeminal branch and associated with multiple sclerosis [123], 4 patients by atypical facial pain [124] and 6 patients by aggressive behavior (2 patients also had co-morbid refractory and generalized multifocal epilepsy; [122, 125]).

Following the DBS implants, the intensity and duration of pain bouts was significantly reduced in CCH patients, and 71% of the postoperative days were pain free. The mean time to pain freedom or reduction was 42 days (range 1–86 days). The overall drug dosages were also decreased to less than 20% of the preoperative regimen. The mean amplitude of stimulation used was 2.4 V (0.6–3.3 V). In the last 2 years of follow-up, three patients no longer benefited from stimulation despite several changes in the parameters. In these three patients, the disease changed from the chronic form to the episodic form (that is, periods of complete remission lasting several months, alternating with periods of attacks). At long-term follow-up (8 years), 63% of CCH patients were classified as DBS responders. Complete pain control was achieved in the patient suffering from SUNCT. This 66-year-old woman was suffering from a 14-year history of SUNCT localized in the left orbital region and upper corner of the mouth. The frequency of pain bouts ranged from 70 to 300 per day, and this condition was resistant to multiple drug treatments, including carbamazepine, gabapentin, sodium valproate, lamotrigine, indomethacin, topiramate, steroids and tramadol. Initial stimulation parameters were set at the bipolar mode with a frequency of 30 Hz, and a pulse width of 60 ms. These settings did not lead to any clinical improvement, so we tried unipolar stimulation with 180 Hz from the first postoperative day. This stimulating parameters along with the adjunct treatment of lamotrigine (100 mg/day) led to the complete and definitive remission of symptoms, which was confirmed at the last clinical examination at the 5-year follow-up [122, 125].

All the five patients who had pHyp-DBS to treat MS-related trigeminal neuralgia described a reduction of paroxysmal pain attacks within the first trigeminal branch. In three of them, the pain control was achieved 24 h after the

stimulation was turned on. All but one reported complete control of paroxysmal pain with the aid of low-dose carbamazepine (200–400 mg/day). The last patient did not need medications to control paroxysmal pain after surgery. However, DBS efficacy seemed to be limited to the trigeminal ophthalmic branch. In fact, none reported recurrence of paroxysmal pain in the first branch, but three of them reported recurrence of pain in the II and III trigeminal branches [123]. The patients with atypical facial pain reported no beneficial effects after pHyp-DBS. The stimulation target's coordinates as well as the stimulation parameters were the same as for trigeminal autonomic cephalalgias (TACs; 180 Hz, 60 ms, and 1.3 V mean voltage). After 4 months of stimulation, the continuous pain was the same as preoperatively, and repeated changes in the stimulation parameters did not modify the clinical picture.

Since 2002, we have treated six patients affected by refractory disruptive behavior with pHyp-DBS. All of the patients needed major restraint measures and two were chronically hospitalized. The etiology of the disease was post-traumatic in one case with bilateral damage of the temporomesial structures, congenital (unknown origin) in three cases (normal MRI), heart arrest in one case (MRI demonstrated only diffuse damage of frontal cortex) and perinatal toxoplasmosis in the last case [126]. The target coordinates were the same as in CCH patients. The stimulation parameters were as follows: frequency 185 Hz, pulse width 60–90 ms, and stimulation amplitude in monopolar mode with case positive 1–3 V. The aggressive behavior disappeared in two patients, and in the other two there was a marked reduction in duration and frequency of rage attacks and aggressiveness (>50% compared to pre-neurostimulation). pHyp-DBS induced a reduction of the epileptic seizures in the two patients with co-morbidity of epileptic seizures (around 50%).

Ventral striatum (nucleus accumbens and bed nucleus of the stria terminalis)

Heath [127] described the effects of electrical stimulation of subcortical structures in behavior disorders including the septal area very close to the nucleus accumbens (Nacc). In the late 1970s, Laitinen [128] described the emotional responses to electrical stimulation of the anterior limb of the internal capsule near the Nacc in psychiatric patients. However in these reports, electrical stimulation was still used as a physiological evaluation of the brain target to study and predict the clinical effects of lesioning [129]. The first case of chronically implanted stimulating electrodes in the septal area was a patient with post-plexus avulsion pain in the late 1960s, operated on by Delgado [130].

The first description of clinical improvement of obsessive–compulsive disorder (OCD) through DBS within the ventral striatum was by Nuttin [131]. The authors described the effects of bilateral stimulation of the anterior limb of the internal capsula in four patients suffering from severe OCD. In three of them, some beneficial effects were noticed. The stimulation parameters were 100 Hz, 210 μs and 4.7 V. Following this report, the anterior capsule has been targeted along its rostrocaudal dimension to study the effects of stimulation not only in its ventral portion, but also to include the adjacent ventral striatum which comprises the Nacc. The observation that the most often used contacts are those more ventral has suggested that that the ventral striatum might be the optimal location for chronic stimulation. This is in accordance with neuroimaging and animal studies, which have proposed that the most ventral portion of the internal capsule along with the ventral striatum might hold therapeutic potentials. Subsequently, DBS of the nucleus accumbens was introduced by Sturm [132]. The nucleus is located immediately underneath the anterior limb of the internal capsule, and covers a large area of the basal forebrain rostral to the anterior commissure. Laterally to the Nacc are the claustrum and the piriform cortex, while medially the vertical part of the diagonal band of broca is located. Close to the dorsal part of the nucleus are the rostral extensions of the globus pallidus and the anterior limb of the internal capsule. Dorsolaterally, the nucleus extends into the ventral putamen, while dorsomedially into the ventral caudate. The human Nacc has afferents from the basolateral amygdala via the ventral amygdalofugal pathway, and most probably also from the central and medial amygdaloid nuclei via the sublenticular and supracapsular parts of the extended amygdala [133, 134]. It sends afferents to various structures comprising the pallidum, striatum, mediodorsal thalamus, prefrontal, including cingulate cortex and, as mentioned above, to mesolimbic dopaminergic areas [132]. The nucleus accumbens is divided into two principal parts: a central core and a peripheral shell. The former is associated with the extrapyramidal motor system, and the latter with the limbic system. Since dopamine is a major transmitter in the nucleus accumbens, a modulating function on amygdaloid–basal ganglia–prefrontal cortex circuitry can be assumed [135–137]. In the first reported cases, the DBS implant was bilateral, although the most significant improvements were achieved on stimulating the right accumbens. Indeed, the authors have decided to target only the right accumbens. The clinically effective stimulating parameters were 90 μs impulse duration, 130 Hz and amplitudes between 2 and 6.5 V. The outcomes were favorable in three out of four patients without any adverse effects. Nevertheless, only one out of ten patients had beneficial effects of monolateral stimulation and indeed the actual trend is the bilateral Nacc

stimulation [138]. The most worrisome adverse effects were transient hypomania and suicidal tendencies [139].

Operated patients and results (2006–2010)

Conservative treatments of OCD consist of selective serotonin reuptake inhibitors and cognitive behavioral therapy [139]. Nevertheless, some patients have persistent symptoms leading to chronic functional impairments. In these cases, the proposed surgical treatments have included anterior capsulotomy and cingulotomy [139]. Chronic stimulation of the nucleus accumbens ($n = 3$) and the bed nucleus of the stria terminalis (BNST) have been introduced in the treatment of obsessive–compulsive disorder (OCD) as an alternative to lesional surgery. The target coordinates were ±3 mm lateral to the intercommissural point, 16 mm anterior to the midcommissural point and 2 mm inferior to the AC–PC line (Table 1). All the three patients who underwent bilateral placement of DBS electrode in the Nacc presented a slow, but evident, clinical improvement of OCD symptoms, as documented by Y-BOCS scores which dropped, respectively, by 40 and 30% (2 patients). Also, clinical improvement was achieved in depressive symptoms [140]. This result is still noticeable at the 3-year follow-up. The last OCD patient of our series had bilateral stimulation of the ventral striatum close to the BNST, and he also obtained significant reduction in OCD symptoms at the 1-year follow-up when the premature exhaustion of the IPG resulted in the recurrence of disease. One of our cases had a rechargeable IPG implanted due to the short duration of the IPG life. In conclusion, our experience confirm the literature data about the ventral striatum DBS for OCD, and in our opinion good results may be expected if the selection of patients to DBS would be better defined.

Cingulate cortex Brodmann's areas (BA) 25 and 24

Functional neuroimaging has been gaining wider acceptance as an important tool to understand some aspects of several neurological and neuropsychiatric conditions [141]; correlating phenomenology to dysfunction, it is not surprising that it has recently played such a role for major depression. In fact, Mayberg [142] and Seminowicz [143] pointed out the modulating role of subgenual cortex with regard to negative affective states and its relation to the efficacy of the different treatment modalities; metabolic activity of this region correlates with responsiveness to serotoninergic, ECT, ablative surgery and transcranial magnetic stimulation therapies [144–146].

Moreover, subgenual cingulate cortex (Brodmann's area 25) has reciprocal connections with many cerebral regions (hypothalamus, amygdala, orbitofrontal cortex, medial prefrontal cortex, anterior and posterior cingulated cortices) known to be involved in the different aspects of depressive disorder.

The first study to report the results of DBS of BA 25 was the one of Mayberg [147] in six patients. Selection criteria for surgery were the clinical history of major depressive disorder (MDD) of at least 1-year duration as diagnosed according to the DSM- IV, a minimum score of 20 on the 17-item Hamilton Depression Rating Scale (HDRS) and failure to a minimum of four treatment modalities (comprising medications, psychotherapy and ECT). Exclusion criteria were: co-morbid Axis I disorders, cluster B Axis II disorders, suicidal behavior within the past year and concomitant medical condition potentially interfering with surgery.

Three years later, the same group reported the results of BA 25 DBS in 14 additional patients, thus resulting in a 20-patient series. At 12 months' follow-up, 55% of the patients were responders and 35% were remitters; the maximal improvement of mood was achieved within 3 months, whereas improvement in the other aspects of depressive disorder (such as anxiety and somatic symptoms) required longer times. Interestingly, at PET scan performed in eight patients who benefitted from stimulation, an increase in metabolism was observed in the white matter adjacent to the electrodes, whereas significant changes in metabolism were observed in brain areas known to be functionally related to BA 25 (for instance, decrease in orbitofrontal cortex and medial prefrontal cortex and increase in the lateral prefrontal cortex and in the anterior and posterior cingulated gyrus).

Also, the anterior cingulated cortex has been proposed for chronic stimulation by bilaterally implanted electrodes (Fig. 5). The volume and the stereotactic coordinates of the

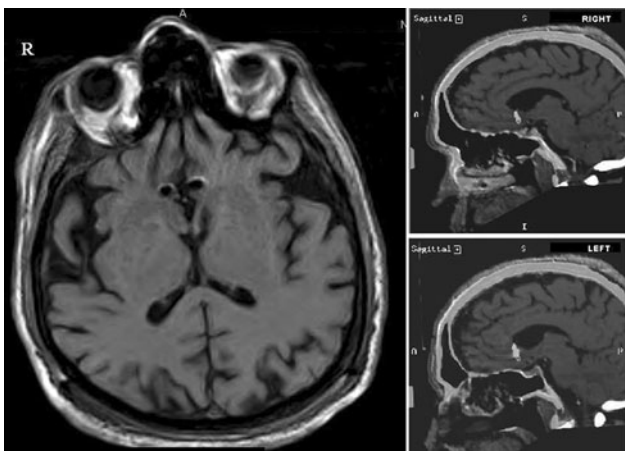

Fig. 5 Postoperative MRI showing the axial section with bilaterally implanted DBS leads in the Brodmann's area 25 (subgenual cingulate cortex) in a patient affected by major depression. The *right panel* displays the sagittal view of both sides

stimulated tissue corresponds to the target of stereotactic cingulotomy, and to the Brodmann's area 24. This target has been proposed in the past to treat obsessive–compulsive disorders or chronic pain by radiofrequency lesion [148]. The same target has been proposed by Spooner et al. [149] for neurostimulation to treat chronic neuropathic pain. Finally, Hutchison et al., in the same area, recorded pain-neuronal activity in awake humans. This demonstrates the role of the Brodmann's area 24 in processing pain experiences [150].

Operated patients and results (2007–2010)

Chronic stimulation of BA 25 (Fig. 5) was performed in one patient affected by major depression, who had previously undergone uneventful vagal nerve stimulation (VNS). The patient, a 46-year-old male, suffered from the disease since 20 years before the first admission to our institute. Antidepressant medications of several classes, ECT and psychotherapy were ineffective. VNS was effective only for a limited period (4 months), after which he progressively worsened and was unable to perform his daily activities, including going out for a walk or gardening.

Surgery was performed under local anesthesia; the stereotactic coordinates related to the AC–PC midpoint were: $X = \pm 7$; $Y = 29$; $Z = -3$ (Table 1). Intraoperative stimulation was tested with a combination of several parameters and did not lead to any acute affective, cognitive or behavioral changes. After 6 months of chronic stimulation (180 Hz, 90 μs, 3 V), the patient gradually started to improve, although the search for stimulation parameters considered to be optimal for the clinical result was found only after 5 months of trial and error attempts. At the 2.5-year follow-up, the HDRS decreased from 32 to 12, and thus the patient can be considered a responder according to the previously mentioned criteria.

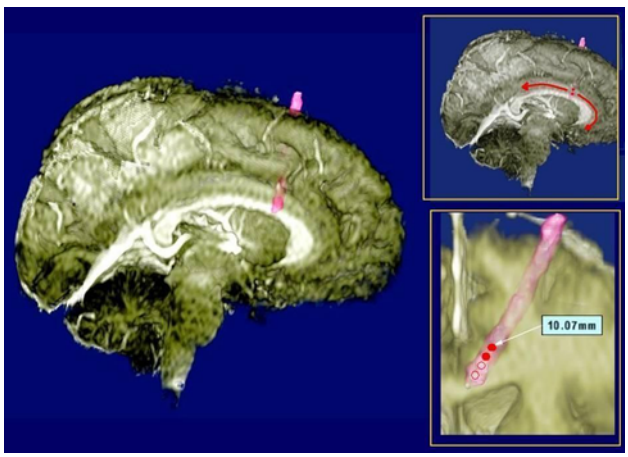

Fig. 6 Postoperative 3D reconstruction illustrating the placement of the DBS lead in the cingulated cortex (Brodmann's area 24) in a patients affected by pain disorder

Functionality in the different spheres of his life gradually improved, and the patient now spends much more time in working and goes often out for a walk.

The second patient treated by chronic stimulation of the cingulate cortex was implanted in the Brodmann's area 24 (Fig. 6) for chronic pain of somatoform origin, without organic substrate of the disease (pain disorder, according to DSM–IV TR). The chronic pain syndrome involved the face, head and sometimes the upper limbs, and lasted for 10 years without remission. The patient attempted suicide six times for concomitant depressive symptoms. The painful syndrome was refractory to conservative therapy comprising drugs, psychotherapy and rehabilitation. The stereotactic coordinates related to the AC–PC midpoint were: $X = \pm 8$; $Y = 23$; $Z = 29$ (Table 1). We considered DBS of the Brodmann's area 24 as the most appropriate therapeutic option due to the co-existence of behavioral symptoms and pain. After 6 months of continuous stimulation (180 Hz, 90 μs, 3 V), pain disappeared and for the first time since 10 years the patient attained remission of the pain and returned to a normal life. Eight months later, pain recurred with the same characteristics as prior the implant. However, it only lasted 2 months and then disappeared again. Thereby, in this patient a chronic condition changed into an episodic form characterized by alternating periods of remission and relapse of pain.

Pedunculopontine nucleus (PPN)

The role of the pedunculopontine nucleus (PPN) in the control of gait and voluntary movements has been demonstrated in experimental models of primates suggesting its therapeutic application since 1998 (Aziz et al. [151]).

PPN chronic stimulation in man was patented in the USA in 2002 by Lozano and Rise, but the first implants in human beings was published by Mazzone et al. [152] and Plaha and Gill [153] who reported their work in the same issue of "Neuroreport" in 2005. Nevertheless, the clinical research on PPN is still in a preliminary stage and the available published series suggest applications aimed at improving gait and axial symptoms in advanced Parkinson disease(PD) (Ferraye et al. [154], Peppe et al. [155]) and in neurodegenerative extrapyramidal disorders such as supranuclear cerebral palsy. PPN stimulation has been used in patients affected by PD with previous subthalamic (Stn) implants or as a stand alone application in PD patients whose gait and posture impairment were the prevailing symptoms (Moro et al. [156], Stefani et al. [157]).

Operated patients and results (2010)

Right PPN has been targeted utilizing the neuronavigator and the standard calculation referred to the commissural

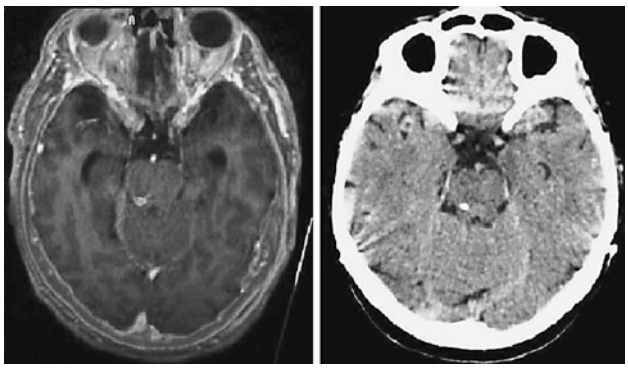

Fig. 7 Postoperative MRI (*left panel*) and CT (*right panel*) axial section showing the tip of DBS leads within the right PPN nucleus in the two reported patients

system [158]. In both cases, the coordinates referred to the midcommissural point were: $X = 5$, $Y = -18$, $Z = -15$ (Table 1). The coronal angle of the trajectory was 10° and the sagittal one was 75°. The entry point was very close to the midline and immediately anterior to the motor cortex. In both patients, the trajectory crossed the lateral ventricle. We choose such trajectory due to the cylindrical oblongated shape of the PPN in the rostral pons. Macrostimulation at the target elicited paraesthesias referred to the contralateral face, when the stimulation exceeded the amplitude of 3 V with a frequency of 25 Hz and pulse width of 90 μs. Microrecordings showed neuronal activity at the target (Fig. 7).

Current parameters for definitive chronic stimulation of the right PPN were: 25 Hz, 90 μs and 2 V amplitude. The clinical result was excellent in a patient who had previous Stn implant, but still complained of daily falls and gait impairment. UPDRS score after PPN-DBS decreased from 29 to 15. The second case was a patient affected by severe akinesia due to neuroleptic abuse, in whom stand alone right PPN-DBS was performed. The chronic low-frequency stimulation allowed an immediate improvement of gait and finalistic movements.

Complications

The incidence of complications is related to 580 electrodes implants in 332 consecutive patients operated on between 1993 and 2010. Massive brain hemorrhage with fatal outcome occurred in two cases of Stn implant (0.3%); permanent neurological deficits due to deep hemorrhage occurred in six patients of whom one was a Vim implant and the other Stn implant (1%). Transient neurological deficits due to deep hemorrhage occurred in eight patients (1.4%), postoperative seizures in seven patients (1.2%), hardware removal due to infection in 32 cases (5.5%), 6 of whom had cerebral abscess at the origin of the stereotactic trajectory (0.9%), hardware failure in 30 patients (5%), and late electrode migration in 20 patients (3.4%) of whom 8 were under 14 years old. The reported risk rates are reported for single electrode implant surgery, and patients who need more than one electrode implant may expect a higher risk rate.

Conclusions

DBS gave a new therapeutic chance to a significant number of patients affected by severe neurological diseases and in some cases controlled life-threatening pathological conditions, which could result in death such as in status dystonicus, status epilepticus and post-stroke hemiballismus. In the overall series, the benefited item in patient responders to DBS was the quality of life. Many young patients could return to work and to social activities as in patients affected by primary dystonia, tardive dystonia, CCH, obsessive compulsive disorders and advanced Parkinson's disease.

Some DBS applications need more investigations and careful evaluation of long-term follow-up as in the treatment of major depression and complex behavioral diseases. DBS in many cases had a synergic action with conservative therapies including drugs, rehabilitatory and psychotherapeutic treatments. On the other hand, some problems still limit a wider application of DBS and these include mainly the incidence of complications, which in few cases may be extremely invalidating or even fatal. Also, hardware complications may contribute to reducing the benefits of DBS in terms of quality of life. In our opinion, the future challenge of DBS deals with the selection of patients; in fact, each therapeutical application is affected by a certain number of nonresponder patients who may be exposed to the surgical risks in vain. This consideration is particularly true for pain and behavioral syndromes; also, a certain number of patients affected by movement disorders may undergo a not-useful procedure due to the loss of improvement or to the appearance of stimulation-related side effects such as speech impairment in PD. Some patients may also require multiple-target DBS to achieve a satisfying control of the disease as may happen in PD patients requiring PPN-DBS to treat gait impairment poorly benefited by a previous Stn-DBS. In conclusion, we think that DBS should be considered a valid therapeutic option in severe neurological disease; nonetheless, further investigations and studies should be encouraged to search for new applications and refine the selection criteria for the actual indications.

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