CHAPTER

# 48

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# Deep Brain Stimulation of the Medial Thalamus for Movement Disorders: The Role of the Centromedian–Parafascicular Complex

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OUTLINE



s0010

## INTRODUCTION

p0010

Parkinson's disease (PD) is a neurodegenerative disorder, clinically characterized by tremor, bradykinesia, and rigidity, that is progressive in nature. Dopaminergic therapy is effective, but, over years, becomes complicated by motor fluctuations ("on" and "off" states) and drug-induced involuntary movements, including chorea and dystonia. These motor complications, which can seriously impair quality of life (QOL) for patients and cause disability, are more common in patients with early onset of the disease, patients with longer disease duration, patients with more severe disease, and patients who take higher levodopa (L-DOPA) doses.

p0020

In the past decade, deep brain stimulation (DBS) has become an established therapy for PD patients whose response to drug therapy is poor or unsatisfactory. Chronic DBS has the advantage of being adjustable according to the patient's needs and is reversible. Conventionally, the first target of choice for DBS for PD is the subthalamic nucleus (STN). The practice parameters of the American Academy of Neurology (AAN)




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(Oahwa *et al.*, 2006) state that "DBS of the STN may be considered as a treatment option in PD patients to improve motor function and to reduce motor fluctuations, dyskinesia, and medication usage."

p0030 Recently, some authors have stressed the importance of adapting DBS to the specific symptoms of each patient by using alternative targets (Mazzone, 2003; Mazzone *et al.*, 1999, 2004, 2005a, 2005b, 2006, 2007a) to the STN. In this context, we have rediscovered previously forgotten targets for PD such as the medial thalamus, and have introduced a potential new target, the pedunculopontine nucleus (PPTg) (Mazzone, Lozano *et al.*, 2005; Mazzone, Stanzione *et al.*, 2005; Stefani *et al.*, 2007). Among the "forgotten" (Krauss *et al.*, 2001, 2002) sites of stimulation, of particular relevance is the centromedian–parafascicular (CM–Pf) complex. These thalamic nuclei are a classic target for the stereotactic treatment of chronic refractory neuropathic pain (Krauss *et al.*, 2001; Andy, 1980), however, CM–Pf complex DBS has also been used for epilepsy (Velasco *et al.*, 1995, 2007a, 2007b, 2007c) and for some vegetative states (Tsubokawa *et al.*, 1990; Yamamoto *et al.*, 2003, 2005). Another relevant issue for future development of DBS for PD and other movement disorders that we will discuss in this chapter is the use of multiple implants. The fact that lesions of the thalamic centromedian nucleus (CM) are usually associated with lesions of other targets is the "lesional analogy" to the use of multiple target sites of DBS for PD and other movement disorders (Adams and Rutkin, 1965; Mazzone, 2003; Mazzone *et al.*, 2004, 2005b, 2007a). We have recently implanted DBS electrodes into the CM–Pf complex of patients with PD who were also implanted in other targets such as the STN or the globus pallidus internus (GPi).

p0040 In this chapter, we will review the anatomic connectivity of the CM–Pf complex, its role in the pathophysiology of movement disorders, and describe the relationship between anatomic stereotactic planning, and surgical and clinical outcome. A stereotactic 3D reconstruction of the entire thalamus, obtained for surgical planning purposes, is shown in Figure 48.1.

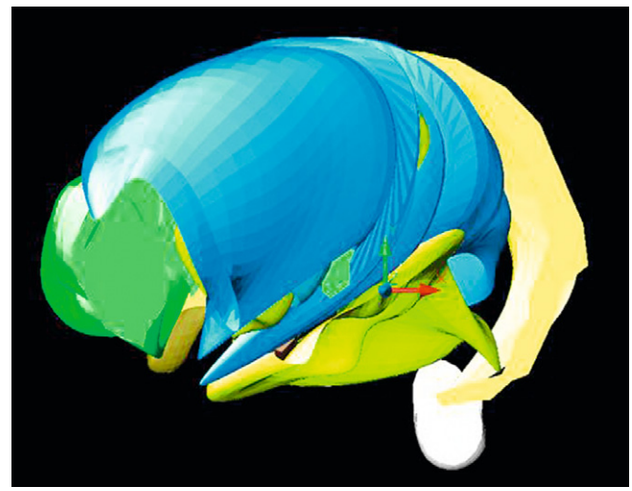


FIGURE 48.1 3D representation of the thalamus, based on sagittal slides of the Schaltenbrand and Wahren atlas. The reconstruction was done by means of the 3P-Maranello 3D stereotactic planning system (Mazzone, 2001, 2006; Mazzone *et al.*, 2007b) f0010

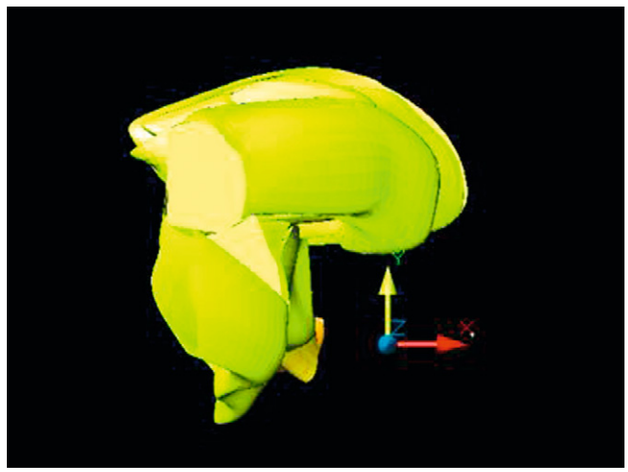
## s0020 ANATOMY OF THE CM–PF COMPLEX

p0050 Burdach, in 1912, defined the medial region of the thalamus as the "thalamus internus" (Hassler, 1959). Macroscopically, the dorso-medial thalamus is surrounded by the lamella medialis on its anterior, lateral, and inferior boundaries (Le Gros Clark, 1932; Jones, 1985). Its length is 18–20 mm according to the distance between the anterior third of the massa intermedia and the habenular commissural plane. The thalamic central gray represents its medial boundary. The medial thalamus constitutes the wall of the IIIrd ventricle, and it extends superiorly above the plane of the stria medullaris thalami. Because of its extension and size, the medial thalamus is commonly defined as the "nuclear medial region," or "medial territorium" (Le Gros Clark, 1932; Hassler, 1959; Jones, 1985) and its main efferent projections are directed to prefrontal cortex (Glees and Wall, 1946). The medial thalamus can be divided on the basis of its histological structure into a medial region ("the pars magnocellularis") and a lateral region ("the pars parvicellularis"). It can be further subdivided into the following nuclei: the nucleus medialis fibrosus, the nucleus medialis fasciculosus, the nucleus medialis fasciculosus superior, and the nucleus medialis caudalis (internal, external, paralamellaris). A stereotactic 3D reconstruction of the medial thalamus is shown in Figure 48.2.

p0060 Three thalamic regions are generally considered to be "independent" from the specific thalamocortical connections (Simma, 1951; Starzl *et al.*, 1951), namely:

- the thalamic central gray, or midline nuclei (immediately below the ependyma, surrounding the massa intermedia) u0010
- the habenular ganglion, which is considered as a part of the thalamus by Schaltenbrand but often not included in the thalamus by other authors u0020
- the nuclei surrounding the medial thalamus, commonly (but inappropriately) termed intralaminar nuclei (IL) or lamella medialis. u0030

p0100 The IL nuclei are the interlaminaris, the centromedian, the parafascicularis, the limitans, the cucullaris, the commissuralis, the fasciculosus (at the entrance of



f0020 **FIGURE 48.2** 3D representation of dorso-median nuclei, surrounded by the nuclei of lamella medialis. The reconstruction was done by means of the 3P-Maranello 3D stereotactic planning system (Mazzone, 2001, 2006; Mazzone *et al.*, 2007b)

the inferior thalamic peduncle), and the parataenialis (below the stria medullaris).

p0110 On the basis of anatomical and functional data, the midline and the IL nuclei seem to be involved in a variety of limbic motor, cognitive and sensorimotor processes (Van der Werf *et al.*, 2002). The main focus of this chapter will be on the centromedian and parafascicular nuclei.

## s0030 The Centromedian Nucleus (CM)

p0120 This nucleus is indicated in the literature with different terminologies, such as nucleus centralis thalami, center median of Luys, nucleus centrum medianum, and centre médian. It coincides with the nucleus initially defined as "mb" by Vogt and Vogt (1941) and appears to be particularly developed in humans and anthropomorphic primates. Le Gros Clark (1932) proposed that it should be consider apart from the other components of the intralaminar system. In humans, this nucleus represents the largest neuronal aggregate within the medial lamella system. The CM can be further subdivided into a ventral–caudal subregion, represented by the pars parvocellularis (Ce.pc), and a dorso-rostral portion, represented by the pars magnocellularis (Ce.mc). These two subregions give different projections to the basal ganglia, the former to the putamen and the latter to the caudate nucleus.

p0130 Histologically, the pars parvocellularis is a dense network of thick fibers, interspersed with small, dark-staining bundles. The lamella medialis accessoria, in the dorsal pars of the nucleus, is an aggregate of these fibers, which run in a dorsolateral direction. The neurons with light nuclei are of medium size and contain a moderate amount of Nissl substance. In the pars parvocellularis there is a higher concentration of glial cells in comparison to nerve cells. The interneurons, which are not richly branched, contain diffusely dark nuclear inclusions which are delimitated by thin membranes, interspersed within the nucleus. The nerve cells are grossly triangular, whereas in the pars magnocellularis they are pear- or cube-shaped with an abundant content of Nissl substance. The fiber network in the pars magnocellularis is dense, with single thick fibers running in a dorsolateral direction. The cellular bodies are arranged in a dorsolateral direction, that is, parallel to fibers. The pars parvocellularis is lighter and contains an even lighter region, which, however, shares the same cytoarchitecture with the rest of the nucleus, and therefore it cannot be considered as an individual nucleus.

### *Afferent Connection Fibers of the CM* s0040

p0140 The medial lemniscus divides, in the rostral part of mesencephalon, into a lateral and a medial component. The medial component enters the thalamus through the ventral pars of the CM. Therefore, the medial lemniscus forms a sort of capsule which covers the ventral and caudal parts of the CM. Degeneration studies and thalamic potentials evoked by cutaneous stimulation demonstrate that these fibers run through the CM and terminate into the nucleus ventralis, which is part of the thalamic trigeminal representation. The CM, according to results of animal studies (Albe-Fessard and Kruger, 1962), plays a major role in the perception of pain, as also clinically confirmed by the fact that pain relief is obtained following its coagulation (Sugita *et al.*, 1972; Sano, 1977).

p0150 Many authors (McLardy, 1948; Jones and Leavitt, 1974; Matsumoto *et al.*, 2001) have stated that fibers running in the brachium conjunctivum reach the CM. In humans, these fibers originate in the nucleus emboliformis of the cerebellum. Other afferent fibers arise from the reticular formation. Moreover, fibers from the Forel's tegmental fascicle (FFO) reach the CM caudally and ventrally, and, in part, run through its ventral region. These FFO fibers represent the rostral pars of the dorsolateral tegmental fasciculum, which runs in the midbrain dorsally with respect to the tegmental fasciculum. This structure represents the secondary dorsal trigeminal tegmental pathway of Wallemberg, which is considered to be the only ipsilateral trigeminal pathway. Many fibers innervating the CM nucleus arise from the ipsilateral vestibular nuclei. In the cat, stimulation of these pathways induces horizontal ipsilateral head turning, which is in agreement with their vestibular nature. The fibers forming these pathways run through the

CM, and terminate into the internal pars of the nucleus ventralis intermediaris (Vim). This particular pathway was considered to form the ascending pars of the ipsilateral brachium conjunctivum by Carrea and Mettler (1954). Fibers that directly end into the to CM originate from the anterior midbrain reticular formation (reticulothalamic pathway); these fibers are involved in the long-delayed electrophysiological responses which can be recorded in the CM following stimulation of peripheral sense organs. These responses are very similar to those recorded following stimulation of midbrain or pontine reticular formation.

s0050 ***Efferent Connection Fibers of the CM***

p0160 Efferent fibers form dark bundles that emerge from the lateral portion of the CM nucleus (Monakow, 1895; Le Gros Clark, 1932; Starzl *et al.*, 1951; Jones and Leavitt, 1974). Afferents from the pars parvicellularis run caudally and ventrally in respect to those originating from the pars magnocellularis, which leave the nucleus in the dorso-rostral tip and cross the Vim, and the ventralis oralis posterior (Vop), until reaching the internal capsule. Once reaching the internal capsule, they cannot be followed any further. It is known that they do not reach the cortex. In fact, CM neurons do not degenerate after decortication or hemispheric deafferentation. Vogt and Vogt (1941) demonstrated that the majority (two-thirds) of output fibers from the CM reach the striatum. In cats, electron microscopic examination after coagulation of the pars parvicellularis of CM has shown synaptic degeneration in the putamen. Likely these projections are cholinergic, because the acetylcholinesterase activity in the striatum decreased after coagulation of the CM. The pars magnocellularis projects to the caudate nucleus whereas the pars parvicellularis sends fibers to the putamen. According to the studies of Percheron and coworkers in macaques, neurons located in the CM project to the sensorimotor territories of the striatum (Fenelon *et al.*, 1991). Moreover, through the thalamic circuitry the putamen and the caudate receive indirect projections from the cerebellum and the reticular formation.

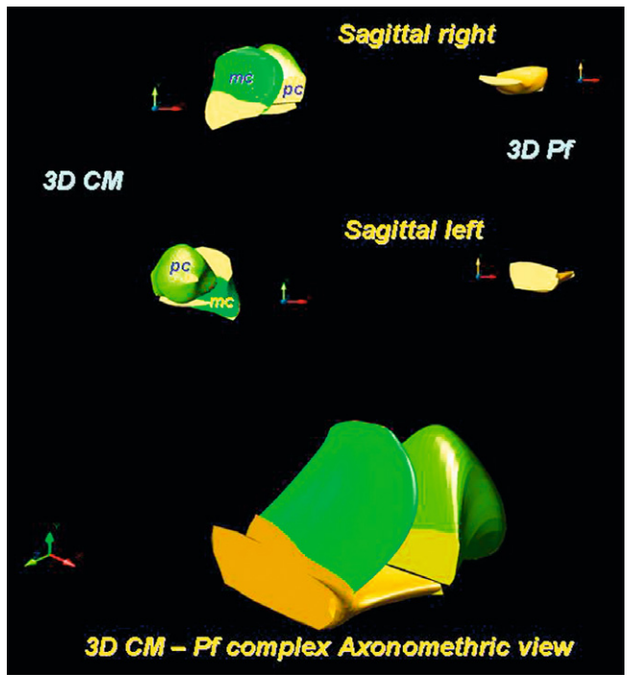
## s0060 The Parafascicular Nucleus (Pf)

p0170 The term parafascicular nucleus (Pf) was originally proposed by D'Hollander (1922) because of its relationship to the Meynert's retroflexus fascicle. The Pf is the medial projection of the CM and no clear separation of their neurons and fibers exists in mammals. The difference is even more difficult to observe when examining the thalamus of lower mammals. Consequently, it has been suggested that a certain separation of the two structures is specific only in humans. The shape of the Pf is trapezoid, with a large ventral base. Its anatomic boundaries are as follows: rostrally, the intralaminar nucleus; ventrally, the zona incerta; caudally, the pretectal region, the arcuate nucleus, and the nucleus limitans; medially, the nucleus endimalis. Histologically, the Pf is distinguishable from the CM because it contains a lower number of fibers. The density of fibers increases in the rostral portion towards the lamella medialis. Medially, it is hardly distinguishable from the medial central gray. The Pf neurons are similar to the neurons of the pars magnocellularis of the CM, though they are darker and a tear-drop shape. Nissl substance is present in coarse particles, which are distributed in the dendrites. The nuclear membrane and the nucleolus are dark and the nucleolus is vacuolized. The Pf contains many interneurons, with an indistinct nucleus.

## Afferent and Efferent Connection of the Pf s0070

p0180 The Pf receives afferent projections from the midbrain reticular formation which originate from the vestibular nuclei, particularly from the secondary vestibular pathways (Glees and Wall, 1946; Simma, 1951). Efferent Pf fibers run rostrally within the lamella medialis and enter the inferior thalamic peduncle, through which they leave the thalamus. As the CM, the Pf does not degenerate after decortication. According to Vogt and Vogt (1941) the efferent fibers of the Pf run directly to the medial portion of the caudate and the putamen. Brockhouse considered these fibers to be involved in the "fundus striati." Experimental surgical coagulation of the Pf demonstrated degeneration of synapses within the nucleus accumbens septi and in the fundus striati. This latter structure, though containing the same neurotransmitters present in the caudate and in the putamen, contains more noradrenaline and GABA, and a reduced amount of dopamine (Castle *et al.*, 2005). In the macaque, neurons located in the PF nucleus appeared to selectively innervate the associative territories of the striatum (Fenelon *et al.*, 1991). These latter results, obtained with the use of selective neuronal tracing techniques, deserve greater attention than those obtained with electrocoagulative methods since the latter, in addition to destruction of nerve cells, also cause degeneration of fibers "en passage" within the coagulated nucleus, thus causing generalized degenerative processes in structures that otherwise would be presumed to be reached by specific fibers alone.

p0190 A 3D representation of the CM–Pf complex, created for surgical planning, is given in Figure 48.3.




f0030 FIGURE 48.3 3D representation of the CM and Pf nuclei, in right and left sagittal views, and in axonometric perspective. The reconstruction was done by means of the 3P-Maranello 3D stereotactic planning system (Mazzone, 2001, 2006; Mazzone *et al.*, 2007b). mc = pars magnocellularis; pc = pars parvocellularis

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## EXPERIENCE DERIVED FROM FUNCTIONAL NEUROSURGERY

p0200 The first report concerning the functional neurosurgery of thalamic nuclei was published by Hécaen *et al.* (1949), who performed a successful medial thalamotomy involving the CM–Pf complex for the treatment of intractable pain in humans two years after Spiegel and Wycis had introduced the functional stereotactic surgery technique. This early success was followed by a large number of medial thalamotomies aimed at alleviating intractable nociceptive and neuropathic pain. Because of the confusion present in some early reports regarding the nomenclature of thalamic nuclei (medial thalamus proper or intralaminar nuclei), and because there were relatively poor clinical definitions of the symptoms (neuropathic pain or nociceptive pain), the interpretation of these early results is questionable.

p0210 The first medial thalamic radiosurgical lesions were performed by Leksell and coworkers in 1972 (Leskell *et al.*, 1972) while Richardson in 1977 (Richardson, 1983, 1995) presented the first results of his treatment of pain by using DBS. It is important to remember that, in the pre CT and MRI era, electrode positioning could only be performed visually. The target chosen by Richardson was the periventricular gray, but post-mortem studies revealed that the medial Pf was the optimum target for pain relief. Recently, in a paper by Caparros Lefebvre, the improvement of L-DOPA-induced dyskinesias and/or tremor observed following thalamic DBS appeared to depend on a slight variation of the electrode placement which could differently influence stimulation of the CM-Pf complex (Caparros-Lefebvre *et al.*, 1999).

p0220 After the pioneering experience of Cooper *et al.* (1965), in 1978 DBS of the CM was applied with the aim of controlling epileptic seizures, in particular tonic–clonic seizures and atypical absences (Velasco *et al.*, 1995, 2007a, 2007b, 2007c). DBS of the CM was attempted on the basis of its spatial and topographical features, and also because the CM was considered to be a relay in the non-specific reticulo-thalamo-cortical pathway ("centroencephalic," Penfield and Boldrey, 1937) that is involved in the generalization of seizures. More recently, using *in vitro* and *in vivo* techniques, it has been shown that the nucleus reticularis plays a major role in the propagation of epileptic discharges. Although, at the time, there was no animal evidence, Arduini and Lairy-Bounes(1951) showed that stimulation of the midbrain reticular formation could inhibit strychnine-dependent thalamic spikes. Low-frequency stimulation of the CM was reported to induce EEG synchronization, while high-frequency stimulation had an opposite, desynchronizing, effect (Velasco *et al.*, 1995, 2007a, 2007b, 2007c).

### The CM–Pf Complex and Movement Disorders s0090

p0230 On the basis of experimental data (Benabid *et al.*, 1983; Duncan *et al.*, 1998), we have considered the CM–Pf complex as a candidate target for patients affected by movement disorders. Indeed, if, on the one hand, it is know that medial thalamotomy is effective in controlling movement disorders (Andy, 1980), on the other hand , there is evidence, derived from post-mortem studies and consequent re-evaluation of a series of Vim-implanted patients, that slight movement of the stimulating electrode towards the CM–Pf complex leads to improved efficacy. To explain these results, there are two alternative hypotheses: (1) the salient effect on dyskinesias and tremor might depend on the spreading of currents to the Vim and ventralis oralis (Vo) nuclei; and (2) the benefits observed might also be a consequence of a *direct* stimulation of the CM–Pf complex. Anatomic and physiologic data support the latter hypothesis since stimulation of the CM–Pf complex could in turn affect the GPi through the Nauta–Mehler circuit, the second

largest efferent/afferent pathway connecting the CM–Pf complex and the GPi , which is also known to be involved in levodopa dyskinesias as its inactivation suppresses the levodopa-induced abnormal movements. Moreover, stimulation of the CM–Pf complex only improves choreic dyskinesias whereas off-period dystonias are improved by thalamic stimulation. This result is quite different from what it is observed in simultaneous Vim + Vo lesions. This differential effect is a strong argument supporting the segregation of pallidal pathways involved in either choreic or dystonic dyskinesias inside the thalamus.

p0240 Electrophysiological studies in animals and humans do not allow to fully understand the pathogenesis of tremor. Some authors (McLardy, 1948; Albe-Fessard and Kruger, 1962) have described rhythmic activity in thalamic neurons, particularly in the Vim, that is synchronous with tremor. There is also evidence supporting a major role of the basal ganglia in the generation of tremor likely due to an abnormally synchronized oscillatory activity at multiple levels of the basal ganglia-thalamo-cortical loop (Deuschl *et al.*, 2000; Magnin *et al.*, 2000; Bergman and Deuschl, 2002; Hammond *et al.*, 2007). Moreover, suppression of tremor through stimulation of the Vim or by treatment with levodopa results in a reduction of regional cerebral blood flow, not only in the premotor and motor cortex but also in the striatum and in the cerebellar deep nuclei (Duncan *et al.*, 1998).

p0250 Recently, some authors have suggested that the cholinergic pathway that emerges from the pedunculopontine nucleus (PPTg) and projects to the parafascicular region of the CM–Pf complex might be involved in motor processes, and, in particular, in the genesis of tremor. Therefore, it might be hypothesized that anticholinergic drugs might act at this level, rather than at intrastriatal sites. Further data have shown that the CM–Pf exerts a powerful control on the basal ganglia through its glutamatergic excitatory projections to both the STN and the GPi (Féger, 1977; Féger *et al.*, 1977).

p0260 The CM–Pf complex also projects to the striatum and the cerebral cortex. Different studies suggest that the CM–Pf complex and the Vo are involved in motor functions, as several pallidal axons, ending in the ventrolateral region, have collateral branches that reach the CM–Pf (Féger *et al.*, 1977; Guillazo-Blanch *et al.*, 1999). From the experience with DBS, it is commonly agreed (however, not always demonstrated) that the position of the DBS electrode is strongly related to its therapeutic effects (and vice versa). Thus, it is believed that there is a strong spatial-functional relationship within brain structures, particularly within the basal ganglia and thalamus. Patients experiencing improvement in both tremor and levodopa-induced dyskinesias are supposed to be stimulated in the CM–Pf complex (or at least at the level of afferents reaching at the same time the CM–Pf complex afferents and the Vim afferents). As a result, we believe that there is enough evidence to consider the CM–Pf complex as a potential new target for DBS and this belief is strongly supported by clinical experience and observation.

## The CM–Pf DBS in the Treatment of Hyperkinetic Movements s0100

p0270 The CM–Pf complex may play a key role in alleviating L-DOPA-induced involuntary movements. In particular, peak dose dyskinesias that follow standardized, 200 mg therapy, L-DOPA are modulated by CM–Pf DBS. In a study by Krauss, 12 patients were implanted with a DBS electrode into the medial thalamus to optimize drug-insensitive control of pain. In 3 out of the 12 patients, manifesting co-morbidity with movement disorders, high-frequency stimulation dramatically affected coincident involuntary movements. In one woman choreoathetosic movements of her right foot ceased, whereas in a 72-year-old man a sustained reduction in his stump dyskinesias was observed.

### *Data Interpretations* s0110

p0280 What is the mechanism that underlies this small but consistent effect of CM–Pf DBS? We primarily hypothesize that DBS, delivered into the CM–Pf, affects thalamostriatal pathway and, in turn, striatopallidal projections. Since the early 1990s, the CM output to the sensorimotor territories of the striatum and the widespread output of the Pf within the matrix compartment have been well described by utilizing anterograde axonal tracers. As emphasized by Kimura (2004), CM–Pf output fibers reaching the putamen belong to reverberant circuits (Pf–caudate–GPi–Pf and CM–putamen–GPi–CM), thus defining an intra-basal ganglia loop, parallel to the well-known corticostriatal–STN–GPi. Therefore, CM–Pf output fibers may affect, consistently with a function of selection gating, the execution (or the dysfunction) of movement controlled by the corticostriatal–nigral pathways. By establishing asymmetric synapses with dendrites of medium-sized spiny cells, ipsilateral fugal axons may re-shape the input/output ratio of corticostriatal projections over dendritic spines, where the interaction between dopamine and glutamate takes place and have a clinical relevance. In addition, neurons of the CM–Pf complex supply striatal neurons with information concerning behaviorally significant sensory events that, in turn, can activate conditional responses of striatal neurons in combination with dopamine-mediated nigrostriatal inputs. The CM–Pf

complex, indeed, may conveys sensory information to the striatum, thus influencing the responsiveness of striatal neurons to salient stimuli during the preparation and execution of rewarded sensorimotor or attentive tasks. Thus, the possibility to remodulate the glutamatergic outputs to the striatal targets according to exogenously administered L-DOPA may be of utmost importance for the functioning of the CM–Pf complex. In such a way not only the occurrence of dopamine-mediated dyskinesias may be reduced, but also their duration, quality and severity.

s0120 ***Patient Selection***

p0290 In our series, targeting the CM–Pf complex for DBS, patients were selected according to the following criteria:

u0040 • diagnosis of Parkinson's disease responding to L-DOPA
u0050 • age less than 65 years
u0060 • no regard to gender
u0070 • extremely painful symptoms at onset and during the course of the disease
u0080 • disease of duration less than 20 years
u0090 • absence of any psychiatric disorder
u0100 • presence of freezing of gait, dyskinesias, and tremor.

p0370 On the basis of these above criteria, 9 patients, 6 men and 3 women, with a mean age of 56.1 ± 8.3 years (range: 51–64), a disease duration of 12.5 ± 8.4 years (range: 8–17), and a mean L-DOPA daily intake of 890 ± 195 mg (range: 600–1200) were enrolled into the study. Seven patients received bilateral implantation into the CM–Pf complex plus bilateral implantation into the GPi (because of the prevalence of dyskinesias), whereas two patients were implanted into the CM–Pf complex plus bilateral STN (because of the prevalence of tremor).

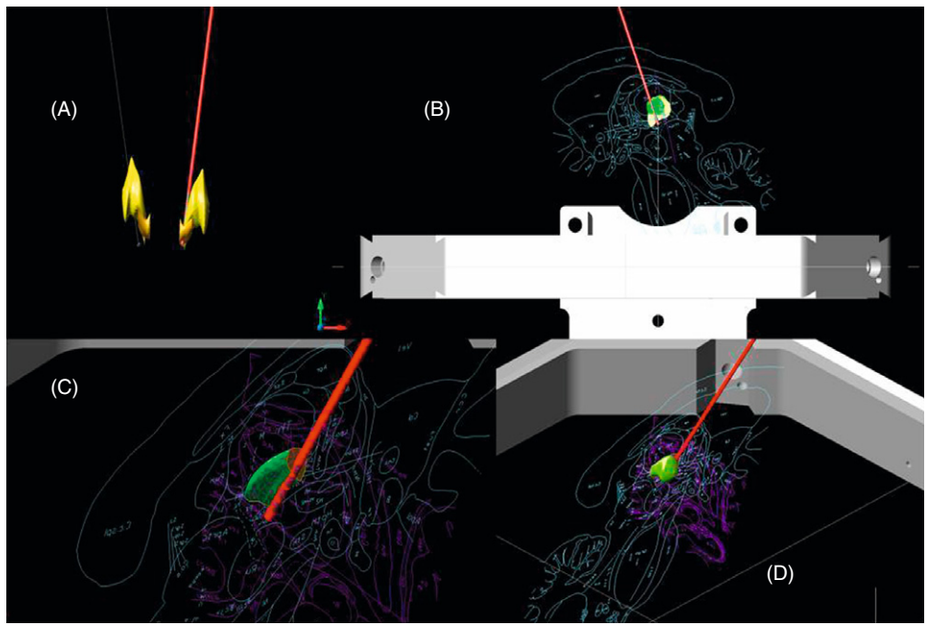
p0380 The first three patients implanted received their leads into the CM of one side (right hemisphere = 1 patient; left hemisphere = 2 patients) and leads into the Pf nucleus of the contralateral side (left hemisphere = 1 patient; right hemisphere = 2 patients). The main purpose of these early procedures was to identify, in each of the patients, the most effective target. After this preliminary experience, all patients were bilaterally implanted into the Pf nucleus.

s0130 ***Surgical Planning and 3D Stereotactic Anatomy***

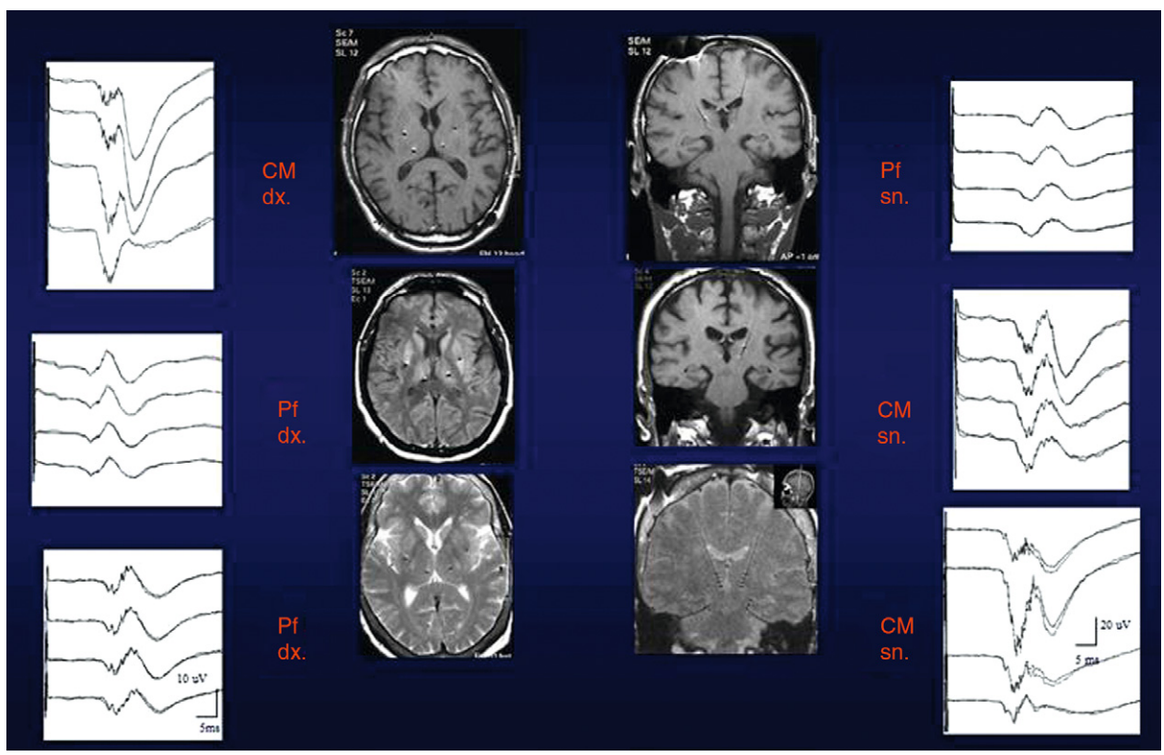
p0390 To reach targets within the thalamus, in particular the CM–Pf nuclei, it was necessary to adjust our initial classic planning procedure. This procedure, based on non-telemetric ventriculography with intraventricular contrast injection and overlapping of individualized 2D sections of the Schaltenbrand and Wahren atlas, was replaced by informatic ventriculography, performed through stereotactic angio-CT scans (axial planes) superimposed with individualized 2D atlas slides fitted on the basis of clearly detectable borders of the CA–CP plane. The 3D reconstruction of the thalamic nuclei, in particular the CM–Pf complex, was made utilizing the sagittal 2D slides provided by the atlas (Schaltenbrand and Wahren, 1977) (Medico Cad 2D and 3D Planning System, 3P Maranello sterotactic system, CLS–Srl, Forlì, Italy). This novel tridimensional modeling was included into the 3D planning system, enhancing the precision of the presurgical planning. This tool allowed us to produce a model of every single thalamic nucleus and to directly verify, within a 3D model, the spatial relationships between leads and targets. This model also could be fitted onto anatomical landmarks measurements made for each individual patient. The 3D planning also made it possible to overlap the 2D sections obtained from the atlas to the 3D reconstruction (Figure 48.4).

p0400 We added a Multi Planar Reconstruction (MPR) of the CT scan to this procedure. In such a way it was possible to choose the single axial CT slide on which the computation of the x, y, and z coordinates should be performed (Fast TC, 3P Maranello sterotactic system, CLS–Srl, Forlì, Italy). The values for the x, y, and z coordinates were then systematically compared with those obtained from informatic ventriculography, in order to verify any correspondence or difference in coordinates. For the CM: y was at 3–5 mm (2/12) anterior to the posterior commissure (PC), x was at 8–10 mm lateral to the commissural line, and z was at AC–PC. For the Pf, y was at 3–5 mm (2/12) anterior to the PC, x was at 6–6.5 mm lateral to the commissural line, and z was at −2/−3 mm with respect to the AC–PC line. The trajectory from the outside to inside was angled of about 20 degrees, and the trajectory from forwards to backwards was about 12/15 degrees, extraventricularly. The macro-electrode that we used for the IL thalamic complex was the Medtronic, 3389 electrode array with four platinum–iridium cylindrical electrodes (1.27 mm diameter and 1.5 mm length) and a center-to-center separation of 2 mm (Medtronic Inc., Minneapolis, MN). Micro-recordings with tungsten microelectrodes were occasionally performed since most patients were under general anesthesia. In all implanted patients somatosensory evoked potentials (SSEPs) were recorded (Figure 48.5).

p0410 Fifteen to 30 days following surgery, we implanted a double Kinetra pulse generator (Medtronic, Inc., Minneapolis, MN) into the infraclavicular region.



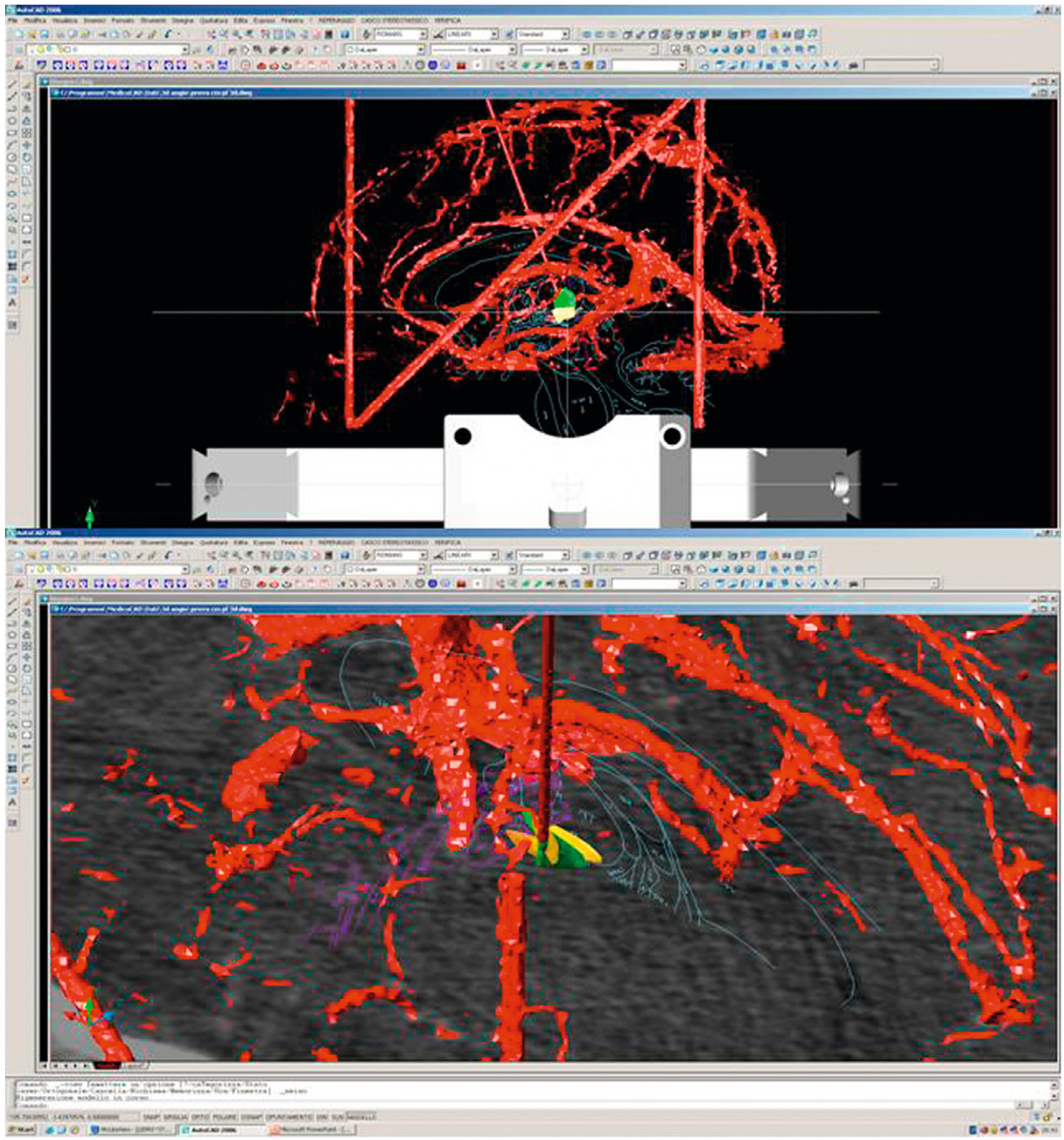

f0040 **FIGURE 48.4** 3D planning. (A) 3D reconstruction of the bilateral CM–Pf complex, with representation of the leads trajectories, respectively reaching the CM (on the right side) and the Pf (on the left side). (B) targeting of the Pf nucleus, with overlapped 2D sagittal slide taken from the Schaltembrand atlas (sl 6.5). (C) Targeting of the Pf nucleus, with superimposed 2D slide from the Schaltembrand atlas in sagittal and coronal projection (in blue). The electrode (in red) and the CM (pars parvicellularis, in green) are visible. (D) Targeting of the Pf nucleus; the electrode (in red) and the axonometric view of the 3D CM–Pf complex are visible, together with the 2D slide from the Schaltembrand atlas in sagittal and coronal (in blue) projections




f0050 **FIGURE 48.5** Median somatosensory evoked potentials obtained from the lead contact inserted in the CM and in the Pf. MRI in post-surgical controls was performed in order to compare lead position and recording sites. On left and right sides of the MR imaging (middle), SSEP traces are shown

p0420 A relevant matter in the technological evolution of the targeting procedure was the implementation of 3D cerebral angiography, reconstructed from the stereotactic angio-CT scan and included into the 3D planning system. The angiogram is not influenced by screw artifacts (carbon tips) and allows evaluation of the risk of conflict between leads and vessels (Figure 48.6).

p0430 Also, after our initial experience with this procedure, we modified the instrumentation used. In our early implantations, we used the classical 3P Maranello stereotactic apparatus, which has an autocarrying hemiarch and a robotic microdrive with multiple independent tracks, placed on the arch system and controlled via an infra-red remote control device. In later implantations,



f0060 **FIGURE 48.6** Pre-surgical planning: the 3D angiography (lateral view; in red) allowed evaluation of the risk of conflict between the leads and the brain vessels. The lower panel shows an enlargement of the angiographic planning: 3D representation of the target, the lead and, in background, the axial CT scan slide on which the targeting was performed

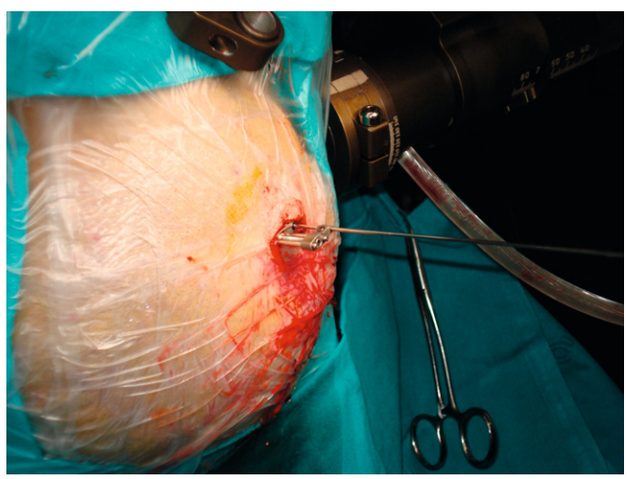
we utilized a skull-applied low profile, multiple microdrive system without a hemiarch (Velasco *et al.*, 2007b) or, in very recent procedures, without any frame at all (Mazzone, 2001, 2006; Mazzone *et al.*, 2007b) (Figure 48.7).

s0140 ***Neurophysiological Investigations***

p0440 The utilization of deep anesthesia in 14 out of 18 surgery sessions did permit consistent investigations of the firing pattern of extracellularly recorded CM–Pf neurons. Moreover, the neuronal activity recorded did not prove useful to define the target boundaries. However, previous investigations did describe a mixed population composed of tonic and bursting units in the CM–Pf complex (the latter less frequent than in classical thalamic motor nuclei). Magnin and coauthors (2000), in a pioneering work , showed the coexistence, within the human IL complex of (1) rhythmic classical bursts, sustained by low-threshold calcium spikes, but not synchronous with rest tremor, and (2) tremor-locked units detectable in the center of the IL complex, "precisely in phase with EMG-recorded tremor."

p0450 Thus, we can postulate that the powerful effects of DBS on tremor, as described in this chapter, might depend upon a direct modulation of these pacemaker thalamic tremor units.

p0460 However, the effectiveness of CM–Pf DBS on the contralateral tremor may also be due to other mechanisms. At first, axons branch and send axon collaterals to specific cortical regions that might provide functional modulation of cortico-fugal excitatory outputs that affect tremor. Alternatively, both the CM and Pf nuclei might modulate extensive projections directed to discrete areas of the lenticular nuclei. In this regard it is noteworthy that Pf neurons innervate cholinergic interneurons, the dendritic shafts of putamen projection cells and, intriguingly, the head of the caudate. These pathways underlie the hypothesized "associative"' role of IL in PD patients. Within this context, the Pf-mediated control of tremor could, at least partially, depend upon a peculiar effect on the endogenous chronic integration of sensory and limbic circuits impinging on the motor effectors. This hypothesis is corroborated by the observation that intraoperative switch ON of CM–Pf DBS (when anecdotally tested in one out of four surgery session and in one implanted patient) provided small or negligible impact on tremor, at odds with the consistent effect that is detectable with chronic DBS.



f0070 **FIGURE 48.7** Intraoperative picture showing the multiple-microdrive, archless, skull-applied system

p0470 Finally, we should also consider the possibility that the CM–Pf DBS affects other thalamic nuclei (such as the ventralis oralis anterior (Voa) and the Vim), whose roles in influencing tremor have been unequivocally established (see Benabid *et al.*, 1983; Caparros-Lefebre *et al.*, 1999). Yet we believe that our careful surgical targeting – and, in particular, our specific coordinates (see discussion of planning above) – minimize the spreading of the electrical field.

***Patient Evaluation*** s0150

p0480 After surgery and post-surgical neuroradiological (MRI) imaging for appropriate electrode positioning, DBS was activated (switched on) for 24 h/day into one single target – into the GPi, the STN, or the CM–Pf. Sometimes the DBS was switched on simultaneously for both implantations. At the same time, PD medication therapy was progressively reduced until optimal stimulation parameters were achieved. The main side effects of stimulation that we have seen included paresthesiae, facial contractions or dystonia, and, in order to avoid these unwanted side effects, the intensity of the stimulus was individually adjusted.

p0490 The stimulation parameters for the CM or the Pf that we used were as follows:

- unipolar cathodal stimulation using the "0" contact as negative and the case as positive; in every patient, this configuration of stimulation was subject to change according to clinical improvement u0110
- frequency: 185 Hz rate u0120
- pulse width: 90 μsec u0130
- amplitude: 1.5–2.5 V amplitude u0140

p0540 In a tremor study in two patients, we used bipolar stimulation with 2 and 3 V amplitudes respectively (Peppe *et al.*, 2001, 2004). To matrix the clinical response to our procedure, we used the Unified Parkinson's Disease Rating Scale Section III (UPDRS-III) and the Abnormal Involuntary Movements (AIM) Scale. To make these evaluations comparable, these scales should

be administered in the morning, at least one month after tapering the dopaminergic therapy to the minimal efficacious level, and following an overnight drug suspension.

p0550 Evaluation in the condition of DBS-OFF was always performed. The stimulator was switched off in the evening (21:00h) and kept off during the entire night. In the following morning, a drug-response test was performed as follows: L-DOPA at a dose of 200 mg was administered followed by clinical scoring (including the evaluation of freezing). Thereafter an evaluation was repeated every 60 minutes. After this DBS-OFF test was performed, a DBS-ON test was done. One hour after the end of the DBS-OFF test, the stimulus was switched on in the GPi (or the STN), or in the CM–Pf, or in both targets, until the following morning. Again, clinical measurements were performed before and after a single L-DOPA dose of 200 mg. In order to identify the optimal stimulation and effect of L-DOPA on each stimulus modality (DBS-ON/drug ON), the procedures were repeated, in a random order.

p0560 UPDRS mean values, before and after surgery, were measured in the following conditions: worst OFF and best ON (under L-DOPA), before and after bilateral implantation; best ON under IL–STIM (no drug); best ON under GPi–STIM (no drug); best ON stimulation of both targets; the latter plus L-DOPA.

p0570 As for any surgical procedure, all patients involved in our study were clearly informed by neurologists and neurosurgeons of the risks and benefits associated with the intended procedures. We received approval by our Local Ethics Committee and a written, informed consent was obtained from each patient who participated the study.

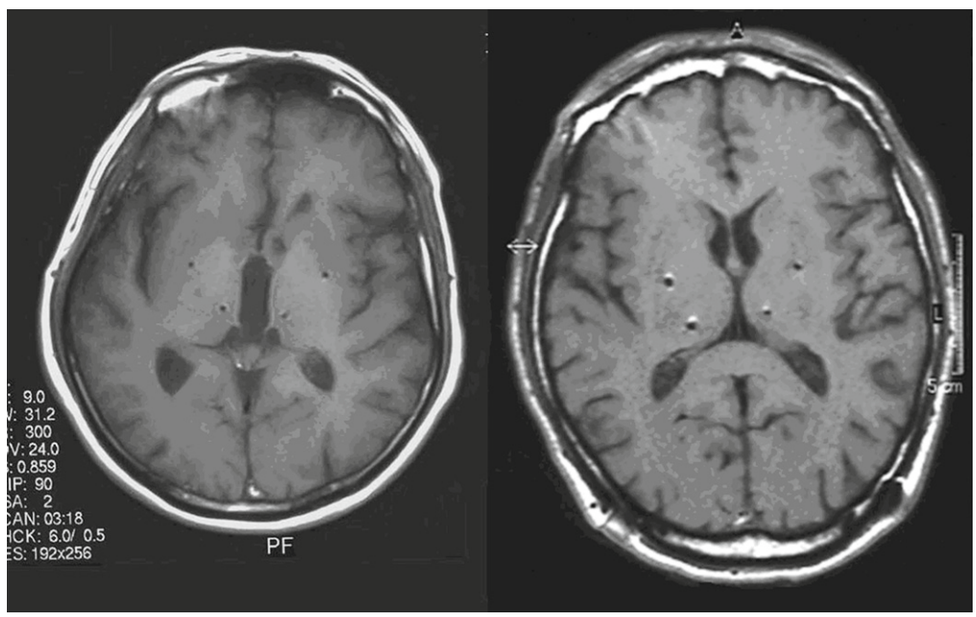
### *Data Analysis* s0160

p0580 The effect of different DBS modalities on UPDRS was separately studied by means of nonparametric, one-way Friedman ANOVA test in the drug-OFF condition (STIM-OFF, GPi-ON, CM–Pf-ON, and GPI + CM–Pf-ON). The effect of L-DOPA-ON was separately studied with a one-way Freidman ANOVA test and compared to the baseline condition for each DBS situation (STIM-OFF, GPI-ON, CM–Pf-ON, and GPI + CM–Pf-ON). The effect of each different DBS combination (STIM-OFF, GPI-ON, CM–Pf-ON, and GPI + CM–Pf-ON) on AIMs was studied using a one-way Friedman ANOVA test. When statistically significant effects were found, comparisons were made by means of the Wilcoxon matched-pairs test. The accepted significance level was $p < 0.05$.

### *Results* s0170

p0590 The usual trajectory for implantation of the electrode array into either the CM or the Pf is shown in Figure 48.4. For an example of a postoperative MRi with bilateral GPi and CM–PF DBS, see Figure 48.8 (Mazzone *et al.*, 2005b).

p0600 Intriguingly, OFF scores were significantly improved in the postsurgical period (UPDRS-III 62.3 vs. 71.4).




f0080 **FIGURE 48.8** Post-surgical, T1-weighted MRI scans, showing the electrode tips implanted in the CM–Pf complex and in the GPi. On the right: CM implantation in the right thalamus, Pf lead in the left. On the left: bilateral Pf implantation

Stimulation-ON produced a statistically significant reduction of UPDRS when compared to the OFF condition in all modalities (Friedman ANOVA, main effect "Modality": $p < 0.005$). The Wilcoxon matched-pairs test showed a statistically significant UPDRS reduction during CM–Pf ($p < 0.01$) and GPi ($p < 0.01$) stimulation. In particular, GPi DBS produced a mean reduction of 41.5%, CM–Pf DBS, a mean reduction of 35.4%, but with a relatively modest impact on rigidity (data not shown). Most importantly, however, the combined stimulation of both nuclei reduced UPDRS by 49.9% (statistically significant when compared to CM–Pf or GPi alone). The Wilcoxon matched-pairs test showed a statistically significant mean reduction during CM–Pf (or the combined STIM) ($p < 0.001$) compared to GPi DBS alone (no effect) (Figure 48.9).

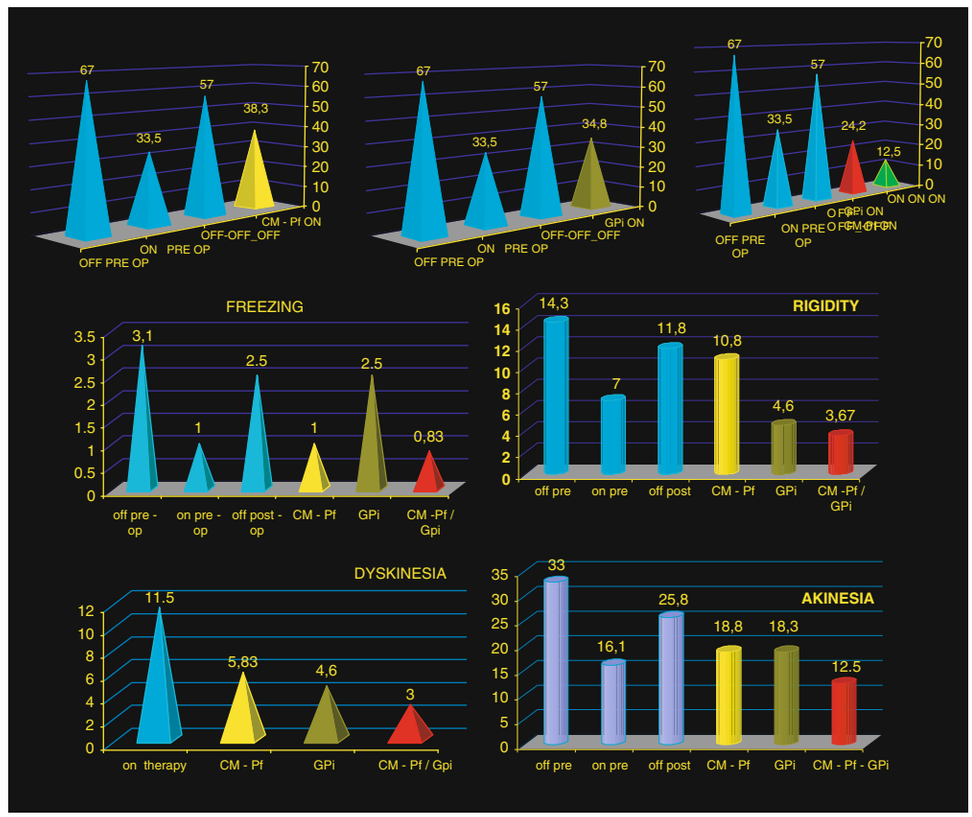
p0610 Finally, a significant change in the L-DOPA-induced AIMs was observed during GPi DBS, when compared to the STIM-OFF condition. The GPi-related impact on AIMs was particularly prominent (Friedman ANOVA, main effect: $p < 0.0002$).

p0620 There were no severe adverse events (i.e., hemorrhage) during the surgical procedures. In one patient the macro-electrodes in the left hemisphere had to be removed as a result of infection. One year later, the patient was reimplanted into the same targets with a full replication of the favorable former response to DBS.

## DISCUSSION

s0180

p0630 After 3 years of follow-up, our data reveal that the combination of CM–Pf DBS and GPi DBS still provides a slightly better effect than GPi DBS alone on involuntary movements. Aside from the specific impact on AIMs, IL DBS produced a significant reduction of UPDRS-III when compared to the OFF condition in all modalities (Friedman ANOVA: main effect "Modality": $p < 0.005$). The Wilcoxon matched-pairs test showed a significant UPDRS-III reduction during CM–Pf DBS ($p < 0.01$); however, in the immediate post-surgery




f0090 **FIGURE 48.9** *Upper row:* (left) mean value of UPDRS-III in preoperative and postoperative time: OFF and ON therapy and during CM–Pf DBS; (middle) mean value of UPDRS-III in preoperative and postoperative time: OFF and ON therapy and during GPi DBS; (right) mean value of UPDRS-III in preoperative and postoperative time: OFF and ON therapy and during GPi/CM–Pf DBS. *Lower row:* mean value of UPDRS-III subscore for rigidity, freezing, bradykinesia, and dyskinesias in preoperative and postoperative time: OFF and ON therapy and during DBS with a single and both targets activated



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phase, the mean reduction of UPDRS-III was 35.4%, and the impact on rigidity modest. Of utmost importance is the fact that the combined stimulation of both nuclei reduced UPDRS-III by 49.9% (statistically significant when compared to CM–Pf DBS or GPi DBS alone) (Figure 48.9). At 3-year follow-up, the effectiveness of CM–Pf DBS (and its association with GPi DBS) declines slightly.

p0640 In our patient population, we were able to observe the effects of CM–Pf DBS on tremor in two women with a 7- and 12-year disease history, respectively, affected by idiopathic PD. Both women were selected for dual bilateral implantation within the STN and the CM–PF, in consideration of rather disabling and drug-resistant tremor (and a persistent prominence of sensory symptoms in OFF). The main post-surgery results in these women can be summarized as follows:

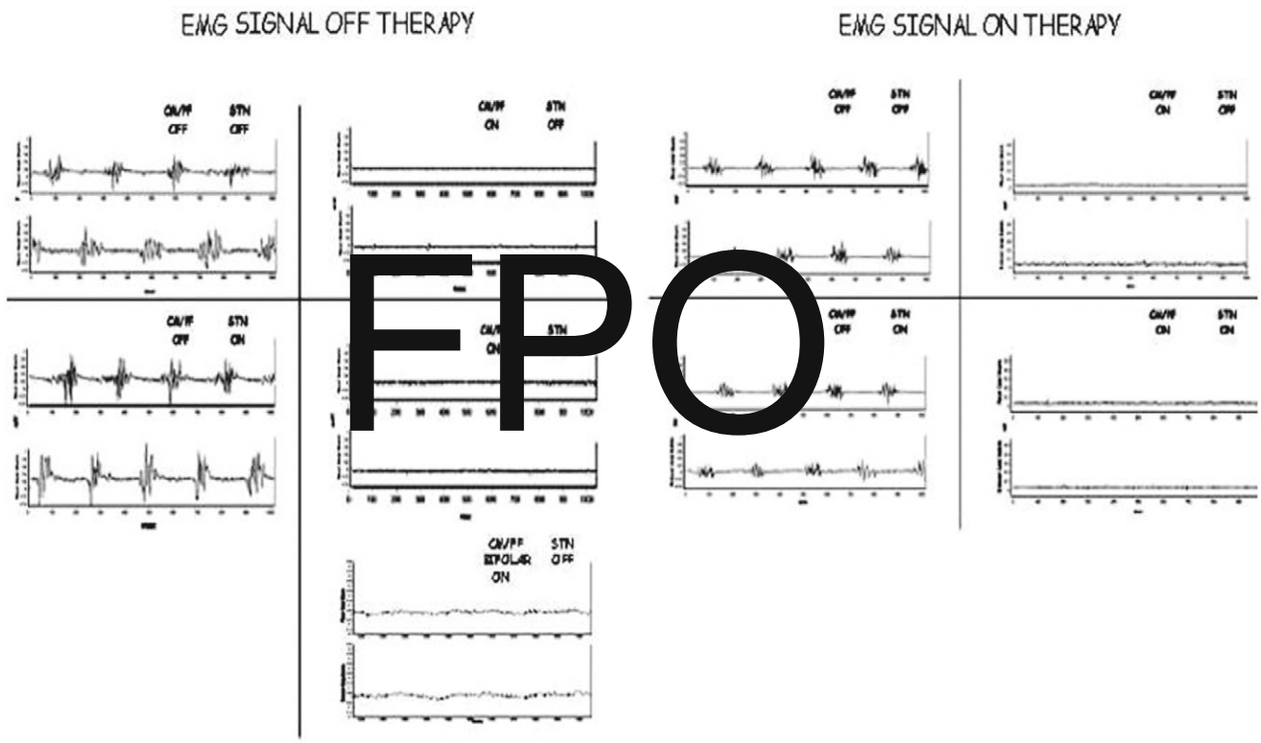
u0150 • STN DBS induced an improvement of extrapyramidal symptoms as CM–Pf DBS, as determined by the UPDRS-III (Tab. II).

u0160 • In UPDRS-III item 20, focusing on resting tremor, there was maximal reduction when CM–Pf DBS was switched ON (Figure 48.10).

p0670 Electrophysiological assessments corroborated this clinical data (Figure 48.10). In fact, although the mean and maximal acceleration of the contralateral hand tremor was strongly reduced by the differing DBS conditions during CM–Pf DBS, it was diminished more than when STN DBS was turned ON. It should be noted that stimulation of both targets together did not induce a further reduction of acceleration values when compared to stimulation of CM–Pf alone. Moreover, CM–Pf DBS seemed to be particularly effective on muscle burst frequency, as shown by the EMG power spectrum data. In fact, the abnormal muscle activity, synchronized at 4.5 Hz, which represents the standard PD tremor frequency, was not strongly changed by STN DBS. In contrast, during CM–PF DBS, all patients did not show tremor-related muscle activity.

## A New Look Towards the PPTg/CM–Pf Projection and Extrapyramidal Disorders s0190

p0680 All of our patients were subjected to routine neuropsychological testing and psychological counselling. Among others, all patients were tested with the Beck Depression Inventory (BDI) for measuring mood levels, the State–Trait Anxiety Inventory for assessing anxiety, and all underwent a Structured Clinical Interview (DSM-IV-R Axis II Disorders – SCID-II) to investigate personality traits. It is important to note that, to this date, our CM–PF implanted PD patients




f0100 FIGURE 48.10 Accelerometric tracings of tremor in patients before and during DBS of the CM–Pf nuclei, or STN (Peppe *et al.*, 2001, 2004)

(n = 9, with prolonged clinical follow-up >3 years in 8 patients) manifested no prominent psychic, depressive, or cognitive sequelae of their procedure. There was, however, an actual documented improvement in mood in 3 patients.

p0690 In recent years, we have also performed the innovative implantation of the (PPTg, usually associated with stimulation of either the STN or the GPi. Actually, aside from the different degree of gait amelioration provided by low-frequency PPTg DBS, it is worth considering the profile of non-motor effects driven by PPTg DBS at low frequency(25 Hz). First, none of the PD patients implanted in the brain stem have shown any cognitive or psychiatric deficits as a result of implantation and stimulation. Secondly, these patients have manifested a clear increase in their quality of life and a peculiar amelioration of disordered sleep structure. Of great interest, the neuropsychological tests administered (mostly designed to investigate attention and frontal executive functions) suggest (1) a transient but consistent feeling of "well-being" and (2) significant amelioration in gait analysis and verbal fluency. These observations fit well with extensive increase of metabolic activity in associative regions of the frontal cortex observed via FDG-PET scans. It is clear that our multitarget strategy involving structures such as the CM–PF and the PPTg, and designed for patients with severe PD, has a great potential for success without causing cognitive or psychic side effects. Of course, our results in this small cohort of patients require further corroboration by implanting and collecting appropriate date in a much larger number of patients. We are also studying whether FDG-PET consumption augments in frontal regions during clinically efficacious CM–PF DBS. In this regard it is important to take into account that: (1) both the CM–Pf and PPTg degenerate at a given extent in PD (in particular, Henderson *et al.* (2000) showed a 30–40% apoptotic-like loss of neuronal elements in Parkinsonian patients, irrespective of disease stage); (2) a robust projection from the PPTg in animals and in humans is directed towards the CM–Pf complex which, in turn provides a powerful excitatory drive to the putamen trough PF fibers. By combining the above findings it is reasonable to hypothesize that a deranged "PPTg–CM–PF pathway" may be correlated with clinical aspects of "late" PD such as emotional fragility, alterations of sleep and deficit in working memory. Conversely, by targeting the PPTg–CM–PF pathways, we might ensure a re-modulation of thalamic outputs towards cortical and basal ganglia associative regions, with potential benefits for patients. Resurgent hypotheses indicate that the efficacy of DBS is not simply a consequence of a "jamming" or of a "shunting" device effect but, instead, relies on a likely "activating" role in rescuing high-frequency oscillations shared by the whole circuit.

## SUMMARY AND PERSPECTIVES s0200

p0700 According to Jones' thought, the intralaminar thalamic nuclei represent the "forgotten components of the great loop of connections joining the cerebral cortex through the basal ganglia to the thalamus" (Davis *et al.*, 1998; Tasker, 2001). In human anatomy, these nuclei are involved in the sensorimotor basal ganglia circuitry. They receive strong inputs from the striatum, the brain stem, and the cerebellum. The CM receives relevant afferents from the GPi. Notably, among the brain stem nuclei the PPTg nucleus projects to the Pf through cholinergic neurons and the electrical stimulation of this pontine nucleus is known to modulate the discharge pattern of Pf neurons (Capozzo *et al.*, 2003). For this reason, in our personal experience, the surgery of the Pf and the clinical results obtained from the DBS of this nucleus, have provided the rationale for developing the targeting and implantation procedures of the PPTg.

p0710 The glutamatergic efferent projections of the CM–Pf complex are essentially directed towards the striatum and the cortex (Matsumoto *et al.*, 2001). As mentioned above, it has been suggested that even the activity of the STN is regulated by afferents from the Pf (Féger, 1977). Overall, these observations support a crucial role of the DBS of the CM–Pf complex for the treatment of movement disorders. Nevertheless, the following limitations of the available data must be considered.

u0170 The effects of stereotactic lesions of the CM–Pf complex on movement disorders in earlier studies are difficult to assess, because in most cases additional lesions occurred in neighboring nuclei; on the other hand, medial thalamotomy for the treatment of movement disorders is now rarely performed.

u0180 Spread of the electrical field and current to adjacent structures of the thalamus, in particular, to the centro-lateral nucleus (another forgotten target) (Krauss *et al.*, 2001, 2002, cannot be excluded.

u0190 The effect of the DBS of the CM–Pf complex, as well as the effect of selective lesions, might depend on its impact on different neuronal substrates within the CM–Pf complex. The neuronal degeneration in the CM–Pf complex, which commonly occurs in PD patients, may affect preferentially some neuronal subpopulations, and this might modify the effects of the DBS.

u0200 No study reported in the literature directly refers to patients specifically implanted in the CM–Pf



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complex for the treatment of movement disorders with the exception of that reported by Mazzone *et al.* (2006). Some reports (Caparros-Lefebvre *et al.*, 1999) described the serendipitous effect of CM–Pf stimulation in patients implanted in Vim; whereas other reports, focused on patients implanted for pain treatment, in whom modifications of motor performance were observed as well.

u0210 Results reported in the literature often refer to short-term follow-up methodologies, which were not completed by long-term observations (Krauss *et al.*, 2001, 2002).

u0220 A larger series of patient is therefore necessary to fully evaluate the safety and efficacy of CM–PF DBS in the treatment of motor disorders.

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