The Role of Functional Neurosurgery in Parkinson's Disease

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Parkinson's disease is the most common parkinsonian syndrome among a group of primary degenerative brain disorders that manifest parkinsonian signs and symptoms. First described by Sir James Parkinson almost 200 years ago [1], it is believed to affect 0.5–1% of the population above the age of 60. The cardinal motor phenomena include rest tremor, increased muscle tone (rigidity), bradykinesia and hypokinesia, as well as abnormal postural reflexes and locomotion.

Over the last decade, increased attention was focused on the non-motor manifestations of PD, such as cognitive changes, affective disorders (particularly depression), autonomic dysfunction (e.g., constipation, orthostatic hypotension), sleep problems, and sensory disturbances. In general, PD is still diagnosed clinically, but a definite diagnosis can be established only at autopsy with demonstration of eosinophilic cytoplasmatic inclusion bodies (Lewy bodies) in the substantia nigra. The differential diagnosis of PD is shared mainly with multisystem atrophy and vascular parkinsonism, as well as with a long list of other rare parkinsonian syndromes. On clinical grounds, it is sometimes extremely difficult to make the diagnosis, and 10–20% of patients are misdiagnosed even by movement disorders specialists.

Pathologically, PD is a degenerative disease of brainstem nuclei, mainly of the pars compacta in the substantia nigra where the dopaminergic cell bodies are located. As a result, the nigrostriatal dopaminergic pathway also degenerates progressively causing hypoactive dopaminergic transmission in the basal ganglia. The cause of the rather selective nigral dopaminergic cell loss in PD is unknown. Certainly, loss of dopamine in the caudate and putamen nuclei of the basal ganglia causes perturbations in other neurotransmitter systems within these nuclei and beyond.

Extensive neurophysiological and anatomical research over the last 15 years has indicated that the basal ganglia are only one component of large complex circuits that also involve parts of the cortex and thalamus [2]. Consequently, it is currently believed that due to the hypodopaminergic state at the level of the putamen there is an over-activation of the internal globus palladium, which, in turn, inhibits the thalamus through a gabaergic pathway that decreases the thalamocortical activation pathway. This hyperactivity is the result of decreased inhibition of the direct pathway from the putamen to the Gpi, and hyperstimulation of the Gpi by the subthalamic nucleus through the indirect pathway [Figure 1]. It is now widely accepted that the motor signs and symptoms in PD are largely due to hyperactivation of the Gpi [3].

Progress in understanding the basic pathophysiology of PD at the level of the basal ganglia was the basis for the development of modern functional surgical approaches to treatment of PD. It was first shown in monkeys rendered parkinsonian by treatment with methylpetrahydropyri-

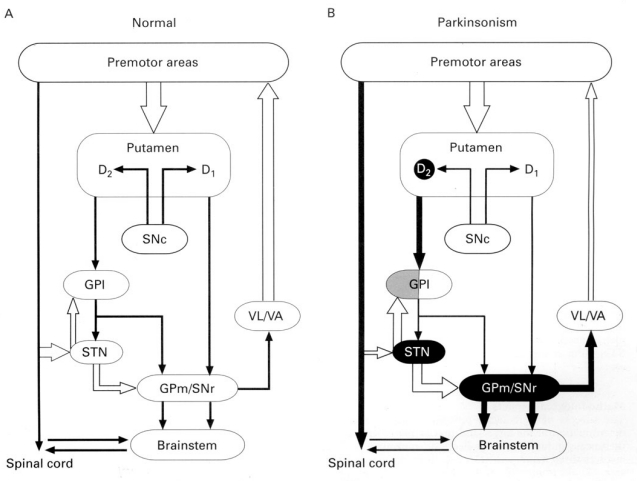

Figure 1. [A] Normal internuclei interaction in healthy persons ⇒ excitatory pathway, inhibitory pathway. [B] The situation in a parkinsonian patient. In black are the nuclei that are over-activated as a result of decreased dopaminergic stimulation at the nigro-striatal pathway.

PD = Parkinson's disease

Gpi = globus palladium

Table 1. Neurosurgical intervention in Parkinson's disease

Type of operation	Site of intervention	Best candidate	Effect on drug therapy	Effect on parkinsonian symptoms			Disadvantages
				Tremor	"off" symptoms	Dyskinesia	
Lesioning procedures	Thalamus Vim (unilateral)	Unilateral Tremor-predominant PD	Can replace drug therapy for tremor	++	-----	+	Speech disturbances when done bilaterally
	Pallidum Gpi/GPe (unilateral)	Advanced PD with unilateral dyskinesias	Minor changes of medications	++	++ (30%)	+++	Cognitive changes when done bilaterally
Deep brain stimulation	Thalamus Vim	Tremor-predominant PD	Decrease anti-tremor treatment	+++	---	---	Improves only tremor
	Pallidum Gpi bilateral	Advanced PD with dyskinesia	Minor changes	+	++	+++	Mild effect on tremor
	Subthalamic nucleus (bilateral)	Advanced PD on/off and dyskinesia with good response to levodopa	60–80% decrease in total levodopa dose/day	+++	+++	---	Needs fine tuning. Dyskinesia as side effect

Vim = ventral intermediate nucleus, Gpi = internal globus pallidum, Gpe = external globus pallidum, PD = Parkinson's disease

dine, and later in PD patients that ablation of the GPi or the subthalamic nucleus can alleviate parkinsonian symptoms [4]. In spite of extensive research and our increased basic understanding of the pathophysiology of parkinsonism, the exact mechanism whereby lesions or stimulation of the Gpi or subthalamic nucleus (see below) ameliorate parkinsonism is still not known.

The pharmacological treatment of PD underwent a real revolution during the past three decades. The introduction of levodopa provided clinicians for the first time with a replacement drug that could replenish the insufficient endogenous dopamine in brains of PD patients. Due to the dramatic effect of oral levodopa in ameliorating parkinsonian symptoms in a short time, most physicians were prescribing levodopa liberally and in relatively high dosages (oral levodopa was usually taken with a peripheral dopa decarbosylase inhibitor to facilitate its entry into the central nervous system). Only a few years later, in the early seventies, did it become clear that the improvement induced by levodopa may be rather short, lasting months to several years.

After an initial "honeymoon" period, many patients develop a complex syndrome linked to the long-term exposure to high doses of exogenous levodopa. The syndrome is manifested by motor response fluctuations that reflect strong physical and mental dependency on levodopa, with abstinence-like symptoms if the next levodopa dose has not been taken on time. This is also associated with increased sensitivity to the drug and the development of troublesome involuntary movements (dyskinesias and dystonias) as well as psychosis. Many neurologists now believe that the liberal use of levodopa during the seventies, eighties and early nineties is responsible for the large population of PD patients who live longer but are facing very complex and difficult to manage complications associated with long-term levodopa treatment.

These patients suffer from marked disability and a poor quality of life. Unfortunately, there is currently no effective pharmacological solution to their severe motor and mental disturbances. The failure of pharmacology and the misery of these patients were the driving force that led to re-exploration of the possible efficacy of neurosurgical interventions in PD.

History of Neurosurgical Interventions for PD

For many years, neurosurgeons and neurologists have searched for a neurosurgical procedure that will ameliorate resistant parkinsonian symptoms or replace failing pharmacological treatment. Two major stages may be distinguished historically: open functional neurosurgery, and closed (stereotactic) functional surgical intervention.

The first attempt at neurosurgery for relief of parkinsonism was in 1912 in France, when Leriche performed bilateral posterior cervical spinal rhizotomy at C5, C6 and C8 levels for suppression of tremor [5]. Later, others conducted various operations such as cervical chordotomy, sympathetic ramicotomy and ganglionectomy, as well as cerebellar dentatectomy for the treatment of parkinsonian tremor and rigidity. None of these procedures yielded satisfactory results and all were rapidly abandoned. James Parkinson himself reported a parkinsonian patient who had temporary relief of tremor follow-

ing cortical infarction [1]. One hundred years later, Bucy and Case [6] were the first to extirpate the Brodmann areas 4 and 6, in a patient with post-traumatic rest and action tremor. The successful suppression of tremor in this case paved the way for over 10 years of cortical ablations, incisions, and undercutting for the treatment of parkinsonian tremor and other hyperkinesias. Around 1950, cortectomy was abandoned despite some tremor suppression, because of the increasing disappointment with the actual functional improvement, technical difficulties with identification of the cortical somatotopy, and intolerable complications. In parallel, during those years, several groups performed transection of the corticospinal tract at different levels, as well as other descending tracts, without satisfactory and long-lasting symptomatic improvement.

It was Meyers who first intentionally performed a transventricular ablation in the basal ganglia for the treatment of parkinsonism. After 12 years of experience and 38 operated cases, he published his favorable results and concluded that section of the pallidofugal fibers was the most successful technique, having relieved tremor and rigidity in 60% of his patients [7]. However, a high mortality rate with the transventricular approach to the basal ganglia later forced neurosurgeons to abandon this approach as well. From the early 1950s, functional neurosurgery for parkinsonism focused on lesioning of the globus pallidum and the ansa lenticularis. Lesions were made either directly through the substantia perforata anterior by cutting through the temporal lobe, or by ligation of the anterior choroidal artery. Despite symptomatic relief of most parkinsonian symptoms with these techniques, they were also discarded because of frequent complications and a high mortality rate of around 13%.

Thus, because of the high mortality and morbidity rates associated with open functional neurosurgery for parkinsonism, there was an obvious need for safer techniques. It was Spiegel and his colleagues who gained scientific recognition for the stereotactic approach to access deep brain structures [8]. To plan and target the stereotactic intervention, they combined a modified Clarke-Horsley stereotactic frame, first developed in 1906, with visualization by plain X-rays or ventriculography of cerebral midline structures, such as the third ventricle or the calcified pineal glands. The development of a stereotactic atlas by the same group 5 years later won even further recognition for the stereotactic intervention in parkinsonism. Initially, the inner segment of the globus pallidum and the ansa lenticularis were chosen as the targets for discrete lesioning in parkinsonian tremor and rigidity. However, the results of (ansa) pallidotomy for tremor were often disappointing, and a modification of the targeting suggested by Leksell's group from Sweden (1960) gained wide acceptance. They placed the lesion in a more ventroposterior position in the globus pallidum [9]. At the same time, other groups advocated the placement of the lesion in the thalamus instead of the pallidum. Hassler and Riechert [10] introduced the ventrolateral thalamic nuclei (Voa and Vop) as preferred targets for control of tremor and rigidity with fewer complications [10]. Cooper and Bravo [11] stressed the beneficial role of thalamotomies in parkinsonism. They published their experience with 700 patients who underwent anterior choroidal artery occlusion, and this approach slowly replaced pallidotomies [11]. Spiegel and coworkers [12] as well as others also aimed for the Forel's field H, as well as for subthalamic regions without major side effects. However, all groups avoided the subthalamic nucleus itself because of fear of major complications, particularly hemibalism.

Until 1969, at the time when levodopa was first introduced, more than 37,000 reported stereotactic neurosurgical operations had been conducted, mostly for the treatment of parkinsonism [13]. The rate of morbidity dropped to less than 10% and the mortality decreased to less than 1%, making this approach more attractive. However, the stereotactic intervention to relieve parkinsonian symptoms was used in only a selected group of 12–15% of the parkinsonian population. Suppression of tremor and rigidity could be expected in 80–90% of the operated cases with no effect on bradykinesia. Bilateral operations were rarely performed due to a high rate of dysarthria and a higher risk for cognitive decline. The ideal case was an asymmetric, tremor-predominant patient. Meta-analysis showed that symptomatic improvement did not always lead to functional benefit for the patient, and in addition, surgery did not influence the progression of the disease.

Functional neurosurgery for PD since the introduction of levodopa

The introduction of levodopa to replace dopamine for the treatment of PD gave the neurological community hope that this may finally be the ultimate and definitive anti-PD therapy. The initial phenomenal success of levodopa led to a sharp decline in the need for stereotactic interventions for PD and they became quite rare. It took more than 10 years of treatment and cumulative information to realize that despite its dramatic symptomatic effect, levodopa was still not the final solution for PD. We now know that levodopa has only a modest effect on tremor and on axial symptoms, such as dysarthria, dysphagia, postural instability and freezing of gait. Furthermore, there are many short-term and particularly long-term side effects, including motor response fluctuations ("wearing off," "on-off," "delayed on" and "no-on" phenomena), dyskinesias ("peak dose," "beginning and end of dose," "all or none") and "off"-period dystonia. In addition, psychotic symptoms, other behavioral disturbances, sleep disorders and autonomic failure rendered the new form of advanced PD frequently intolerable. All these resulted in the re-introduction of stereotactic thalamotomies in the early eighties [14]. In addition, thalamotomy was proposed as a possible treatment for levodopa-induced dyskinesia.

Modern Surgical Approaches

Lesional surgery — pallidotomy

It can be stated that the modern era of functional neurosurgery for PD was rekindled by Laitinen et al. [15], who reported on 38 patients with advanced PD who underwent posteroventral pallidotomy with very good clinical improvement. Of these 38 patients, 34 had marked clinical improvement with nearly complete relief of contralateral tremor in 81% and significant improvement of rigidity and hypokinesia on the contralateral side in 92% of the patients. Moreover, patients experienced dramatic relief of levodopa-induced dyskinesia and painful muscle spasms in the contralateral side, with amelioration of almost all "off" symptoms. This report caught the attention of the neurological community at a point when the care of PD patients with severe motor response fluctuations and troublesome dyskinesias was difficult, complex and mostly frustrating. The possibility of offering some relief to those complicated and poorly managed patients prompted a large wave of referrals of advanced PD patients to the centers that performed posteroventral pallidotomies. Well-controlled studies have confirmed the initial report of Laitinen's group that unilateral posteroventral pallidotomy can significantly improve (by about 30%) the severity of parkinsonian symptoms at the "off" state [16–18]. This improvement was still significant after 2 years of follow-up [17]. It seems that symptomatic relief is most pronounced at the contralateral side, but ipsilateral improvement has also been documented [16]. Axial symptoms such as gait and postural disturbances also initially improved, but at 1 and 2 years follow-up this improvement was partially lost [16,18]. Pallidotomy was reported to increase the time a patient spent in "on" and to decrease motor fluctuations [16]. One of the most striking effects of pallidotomy is the contralateral amelioration of levodopa-induced dyskinesias, an effect that is persistent even at 2 years of follow-up. Other "on" related symptoms did not improve and the daily dosage of levodopa post-operatively did not decrease much.

A survey of current practice regarding pallidotomy among 28 centers in the United States that performed 1,219 pallidotomies confirmed previous studies that dyskinesias and "off" symptoms can indeed be alleviated with low morbidity and mortality [19]. The rate of complications after pallidotomy is low, and early reports of visual field defects have become rare ever since neurosurgeons began to place the lesion at the posterior globus pallidum internus and slightly laterally to avoid the optic tract. Dysfunction of the frontal lobe detected by neuropsychological tests gave inconsistent results. One group did not observe any changes [16], while others reported cognitive changes as well as marked weight gain [18]. Demented patients did worse after pallidotomy, while younger patients had more favorable results [20]. Bilateral pallidotomy has been performed only in limited numbers, but anecdotal reports suggest serious complications such as pronounced hypophonia, pseudobulbar syndrome, and in several cases, severe cognitive disturbances.

Stimulatory surgery

Deep brain stimulation within the subthalamic nucleus and GPi through implanted electrodes by external or implanted stimulators was first used in the 1950s by Heath [21] in the USA for intractable pain and a variety of psychiatric and neurologic disorders. Mazars et al. [22] noticed that deep brain stimulation, when applied for pain, also reduced involuntary movements in the painful limb. Bechtereva in Leningrad, and later Mundinger and Neumüller at the beginning of the 1970s, were the first to apply the deep brain stimulation technique for the treatment of movement disorders [23]. In 1980, Schvarz et al. [24] introduced chronic cerebellar dentate nucleus stimulation for the treatment of spasticity. At the same time Brice and McLellan [25] reported symptomatic and functional improvement of action tremor in three multiple sclerosis patients with chronic subthalamic nucleus stimulation. Others confirmed Mazars' earlier observation that stimulation of the sensory thalamus (VPL) can suppress both tremor and dyskinesias in patients with parkinsonism or thalamic infarction.

The modern era of deep brain stimulation began in 1987 when Benabid, Pollak and their colleagues in Grenoble, France, first reported their experience with thalamic ventral intermediate nucleus stimulation for tremor [26]. They introduced the technique of micro-recording extracellular neuronal activity at the tip of the inserted electrode for better localization of the stimulator, which has become the gold standard in many centers. Several groups from Europe and the USA [27–29] have reported excellent tremor suppression with bilateral Vim stimulation in parkinsonism and essential tremor. The low complication rate and the good symptomatic improvement were the reasons that this technique for tremor suppression was approved by the American Food and Drug Administration in 1998. Vim stimulation seems to suppress tremor, at least in part, by inactivation of the cerebellum, as was shown by a positron emission tomography study of cerebral blood flow [30]. The major complication of thalamic stimulation was dysarthria, which is completely reversible when the stimulators are turned off and partially reversible when the stimulation parameters are adjusted. A successful Vim stimulation enables patients to control their tremor by switching the stimulators on or off with a personal magnet. Such an option has an important impact on the well being, confidence, independence and sense of self-control in patients having to deal with a very disturbing and socially embarrassing symptom. However, Vim stimulation is of limited value for PD patients in that it has no effect on any of the parkinsonian symptoms other than tremor, such as slowness and rigidity.

Vim = ventral intermediate nucleus

It was Siegfried who first implanted electrodes in the internal globus pallidum for PD in 1992 [31]. His rationale was that deep brain stimulation had a similar effect as lesioning in the thalamus. Combining the reversibility of that procedure with the effectiveness of pallidotomies made this approach clinically feasible. GPi stimulation has become an effective alternative target for PD patients where rigidity and bradykinesia as well as levodopa-induced dyskinesias were the main troublesome symptoms [32]. To date, no large-scale prospective studies with long-term follow-up for assessment of GPi deep brain stimulation have been conducted. Interestingly, Bejjani et al. [33] have shown that stimulation of the ventral part of the GPi relieved levodopa-induced dyskinesias and rigidity but worsened gait and bradykinesia. By contrast, stimulation of the dorsal part of the GPi (at the border with the external globus pallidum) improved gait and reduced rigidity and bradykinesia without an effect on levodopa-induced dyskinesias. Since GPi stimulation did not reduce tremor, patients had to stay on their regular dose of anti-parkinsonian medication. Overall, GPi stimulation can provide definite relief to some patients, but long-term follow-up is not available and further experience is needed especially in light of the complex clinico-anatomical relationships at the exact site of stimulation in the GPi.

While some groups have explored the GPi as an alternative target for deep brain stimulation in PD, the Grenoble group has concentrated on the subthalamic nucleus as the most promising target for stimulation. Their initial report that demonstrated significant alleviation of rigidity and bradykinesia with bilateral high frequency subthalamic nucleus stimulation was very encouraging [34]. Later studies demonstrated that bilateral subthalamic nucleus stimulation can also reduce parkinsonian tremor as effectively as with thalamic stimulation to make it a preferable treatment site for PD [34–36]. Subthalamic nucleus stimulation does not directly affect the levodopa-induced dyskinesia. However, the symptomatic beneficial effect on parkinsonian signs at a magnitude similar to that obtained by levodopa made it possible to reduce and occasionally even stop treatment with levodopa and other anti-parkinsonian medications. The majority of subthalamic nucleus-stimulated patients remained on 20–40% of the total pre-operative levodopa dosage [37,38]. Levodopa-induced dyskinesia and psychosis, which are closely related to dosage of dopaminomimetic treatment, are alleviated in most patients as a result of the lower dosages of anti-parkinsonian medications required post-operatively. Generally, amelioration of all levodopa-responsive parkinsonian symptoms, together with the increase in "on" time with improvement of the "off" state in conjunction with a significant decrease of anti-parkinsonian medications and decreased dyskinesias, provided most patients with a dramatic improvement of function and quality of life. Subthalamic nucleus stimulation is as safe as other deep brain stimulation procedures, and if performed correctly by an experienced experienced group of neurosurgeons and neurophysiologists has a low rate of morbidity and mortality. It should be noted that involuntary movements were sometimes observed secondary to subthalamic nucleus stimulation, a side effect that could be controlled by modifying the stimulation parameters in most cases. The technique seems to be safer in younger patients, but there is lack of objective and prospective assessment of the effect of subthalamic nucleus stimulation in older patients.

Increasing attention has been given over the past 5 years to the effect of pallidotomy or deep brain stimulation on cognitive functions of PD patients. The concern arose because of repeated complaints by patients, their families, caregivers and medical staff about behavioral changes post-pallidotomies. The development of environmental dependency, disturbed psychological/emotional control, and executive/cognitive changes in some cases have outscored the motor improvement [18,39]. Bilateral pallidotomies were discarded by most centers due to the impression of a significant deterioration in cognitive functions. The recommended bilateral approach for Gpi, subthalamic stimulation or deep brain stimulation elicited much concern regarding its possible effect on cognitive and behavioral functions. A recent study [40] did not find any significant long-term cognitive disturbances 3–6 months after bilateral subthalamic nucleus or GPi stimulation in 62 PD patients whose mean age at operation was the early fifties. However, in older patients with significant cognitive disturbances deep brain stimulation can worsen their mental state.

The mechanism of action of subthalamic nucleus stimulation to alleviate parkinsonian signs is still poorly understood. Limousin and her colleagues from the Grenoble group recently demonstrated that the effect of subthalamic nucleus stimulation on the motor control areas is different from the effect of GPi stimulation. Using PET and assessing regional cerebral blood flow, they were able to show that in age-matched healthy controls, subthalamic nucleus stimulation partially increased cortical activity at the supplementary motor area, cingulate cortex and most significantly at the dorsolateral prefrontal cortex. Similar normalization of cortical activity was observed with apomorphine (a powerful dopamine agonist drug). GPi stimulation did not affect any of these cortical areas. The above observation and the clinical outcome of subthalamic nucleus stimulation suggest that it is of primary importance for motor control and that high frequency stimulation causes changes in brain circuits that are different from those associated with thalamic or GPi stimulation.

Bilateral subthalamic nucleus stimulation is potentially an excellent therapeutic option for advanced PD. However, one should be cautious because of the lack of a long-term, well-controlled follow-up of a large group of patients. This is especially true in light of the history of functional neurosurgery for PD over the last 50 years.

PET = positron emission tomography

From a practical point of view, deep brain stimulation is a possible therapeutic option for a limited number of patients who have access to medical centers where experts can deal with the complex management and technical issues associated with stimulator control. Although still unclear, the place of subthalamic nucleus stimulation in the older age groups is of great importance and will undoubtedly affect its future use. Another question that should be explored is the right timing for surgical intervention. Could subthalamic nucleus stimulation take the place of levodopa treatment in the early stages of the disease? The future will provide us with answers to some of these questions.

Functional neurosurgery is a very potent tool for the amelioration of parkinsonian symptoms in PD. However, in spite of the dramatic improvement in stereotactic targeting of basal ganglia and the introduction of the deep brain stimulation technique, it is still an intervention that can be used only in a selected group of PD patients.

At the present time, the "ideal" PD patient for functional neurosurgical intervention is a relatively young person who responds well to levodopa treatment but has already developed severe response fluctuations and dyskinesias with short periods of "on" time and disabling "off"s. He or she should be behaviorally well balanced, cognitively fully intact, and with the mental status that will allow continuous follow-up and adjustment of stimulator parameters and medications according to the clinical status.

The two main reasons why this approach cannot be used in the entire PD population are the high cost and the risk of side effects. The present approach using deep brain stimulation bilaterally aiming at the subthalamic nucleus requires a highly professional team of neurosurgeons who are experienced with stereotactic techniques, neurophysiologists who can help with the final targeting by extracellular deep brain micro-recording, and neurologists who are experienced with the later frequent adjustments of the stimulators. In addition, in view of the cost of a single stimulator ($13,000), the long hospitalization period, and the time-consuming work to follow these patients in an outpatient clinic, it is clear that such an approach can be used only in a limited number of patients. The risk of side effects such as intracranial hematoma, infection, secondary behavioral or cognitive changes, as well as speech problems, also restrict the application of the neurosurgical approach.

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