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Review article

Surgical treatment of Parkinson's disease

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Abstract

Stereotaxic surgery is an effective therapeutic maneuver in the management of advanced Parkinson's disease (PD). Thalamotomy is an effective measure to control tremor but other PD symptoms are not changed. Bilateral operations are associated with a risk of severe speech impairment. Deep brain stimulation (DBS) of the thalamus is as effective as thalamotomy and is associated with fewer side effects. Pallidotomy is effective in reducing contralateral dyskinesias and the cardinal symptoms of PD. Bilateral pallidotomy often results in cognitive dysfunction. Deep brain stimulation of the pallidum replicates the positive effects of pallidotomy and appears to be safer than ablative lesions. Subthalamic DBS is currently under investigation. This procedure may control all PD symptoms, and the dose of levodopa can often be dramatically reduced. Neurotransplantation is a promising surgical approach to PD. However, further investigation is needed to optimize this approach. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Stereotaxic surgery has gained increasing importance in the treatment of Parkinson's disease (PD). This is mainly because patients are seen with advanced parkinsonism in whom pharmacologic treatment is no longer effective in reducing disability [1]. The quality of life of these patients is deteriorating, and the patients and their families plead for some positive intervention. Importantly, we have a better understanding of the physiology and circuitry of the basal ganglia and recognize their importance in PD. Globus pallidus (GP) and subthalamic nucleus (STN) are thought to be hyperactive in PD [2–4]. Furthermore, advances in surgical techniques, neuroimaging and electrophysiologic recordings allow stereotaxic maneuvers to be done more accurately.

2. The history of stereotaxic surgery

Early surgery for movement disorders treated tremor by means of a variety of lesions, such as the ablation of the cerebral cortex [5,6], sectioning of the pyramidal tract at the cervical level [7], sectioning of the cerebral peduncles in the midbrain [8], and ablation of the basal ganglia [9,10]. These open surgical operations, which produced improvement of tremor at the expense of motor deficits, did not allow for the identification of a brain site that specifically controls tremor.

Human stereotaxic neurosurgery, introduced in the 1940s [11], allowed for the placement of an electrode or probe in the brain using a brain atlas for reference and brain imaging (originally ventriculography, later computer tomography [CT] and magnetic resonance imaging [MRI]). Target choice was originally based on the results of open brain surgery, with the aim of placing discrete lesions in deep brain structures, particularly the basal ganglia. Early targets were the ansa lenticularis [12], the globus pallidus [13], and the ventrolateral thalamus [14]. A series of thalamic lesions performed by Hassler and Reichert [14]

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Table 1

Classic stereotaxic operations performed in parkinsonian patients in the pre-levodopa era

Classic terminology	Site	Indication
Ansotomy	Ansa lenticularis	Akinesia, rigidity
Campotomy	Forel's fields (H1 and H2)	Rigidity
Pallidotomy	Globus pallidum	Dyskinesia, rigidity, akinesia, balance
Subthalamotomy	Zona incerta and Forel's fields	Rigidity
Thalamotomy	Thalamus (Vim)	
Thalamus (Vop)	Tremor	
Akinesia, rigidity		

led to the identification of a site in the ventrolateral thalamus to control parkinsonian tremor. This region was called the nucleus ventralis intermedius (VIM). Its anatomical boundaries were not clearly delimited, but the region could be recognized using perioperative physiological techniques, such as microelectrode recordings or stimulation [15]. Some alternative non-stereotaxic techniques were developed at about the same time by Cooper, who ligated the anterior choroid artery to treat tremor and rigidity [16], and performed chemical and cryogenic lesions of the basal ganglia [17].

Stereotaxic neurosurgery rapidly gained attention. It was implemented in many countries, methodological innovations were introduced, and different targets were tested. The best known pioneers of stereotaxy were Spiegel and Wycis in the United States, Narabayashi in Japan, Guyot in France, Reichert in Germany, and Leksell in Sweden. Many of them published only a limited part of their observations so that, with the notable exception of Hassler, large controlled series were not available during this early period. Leksell performed lesions in different parts of the pallidum and observed that posteroventral pallidotomy significantly improved parkinsonian symptoms, including akinesia, rigidity and tremor [18,19].

The efficacy of thalamotomy for tremor was particularly impressive. This procedure rapidly became a standard treatment for tremor and allowed stereotaxic surgery to be

accepted worldwide as a therapeutic procedure for PD. However, consensus was not reached on the indications for other stereotaxic operations (Table 1). The ideal site for thalamotomy was also a subject of long-standing debate. There was evidence that a lesion extending beyond the VIM could also improve rigidity, but a general agreement was not reached. The discovery that levodopa provided a powerful medical treatment [20,21] dramatically reduced the spectrum of indications for stereotaxic surgery in PD. However, during the levodopa era, it soon became clear that a percentage of tremulous patients did not improve adequately with drug treatment [22].

3. Thalamotomy

Hassler and Reichert [14] were among the first to select the ventral nucleus of the thalamus and its surrounding area as the favored site for tremor reduction. Selby [23] estimated that 10 000 patients had been subjected to basal ganglia surgery before the widespread use of levodopa in PD in the 1970s. Table 2 summarizes representative reported series on the effect of thalamotomy on parkinsonian tremor. Improvement in tremor and rigidity of the limbs contralateral to the side of the lesion occurred in more than 90% of patients [22–32]. However, assessments

Table 2

Thalamotomy in Parkinson's disease

Investigation (year)	Number improved/ total no. patients	Persistent morbidity
Cooper (1961) [24]	425/500	Paresis, dysarthria
Krayenbuhl et al. (1961) [25]	23/23	None
Markham and Rand (1963) [26]	53/79	Paresis, dysarthria, dysphagia
Selby (1987) [23]	158/158	Dysarthria, cognitive impairment, paresis, incoordination
Bertrand et al. (1969) [27]	114/115	Dysarthria
Kelly and Gillingham (1980) [28]	51/57	Dysarthria
Ohye (1982) [29]	20/20	Dysarthria
Tasker et al. (1983) [30]	61/75	Dysarthria, dystonia, hemianesthesia
Matsumoto et al. (1984) [31]	79/86	Dysarthria
Nagaseki et al. (1986) [32]	25/27	Paresthesia, dysarthria
Jankovic et al. (1995) [22]	42/42	Paresis, dysarthria

were often more qualitative than quantitative, because currently used standardized rating scales for parkinsonism were not yet developed or widely used. At autopsy the lesions were sometimes not in the intended target [23]. Nevertheless, the reported studies and clinical anecdotal experience indicate that unilateral thalamotomy is an effective treatment for parkinsonian tremor.

Long-term follow-up studies have been uncontrolled and unblinded, however, it appears that thalamotomy has a lasting beneficial effect. Kelly and Gillingham [28] reported that 90% of 57 parkinsonian patients were free of contralateral tremor 2 years after surgery and that 57% were still free 10 years after the operation. Kelly et al. observed abolition of tremor in 86% of 36 patients with a mean follow-up of 33 months. Nagaseki et al. [32] found minimal recurrence of tremor in 27 parkinsonian patients after a mean of follow-up of 6.6 years. Jankovic et al. [22] reported no recurrence of tremor in 36 patients followed for a mean of 60 months. Diederich and colleagues [33] examined a defined group of patients treated 10 to 15 years previously with unilateral operations. They found that tremors were significantly better on the side contralateral to surgery, implying long-term benefit. Other parkinsonian symptoms such as bradykinesia and the tremor ipsilateral to the surgery were noted to progress [33]. Hughes et al. [34] reported that a previous thalamotomy did not alter the degree of responsiveness to levodopa therapy.

It is estimated that the mortality rate for thalamotomy in PD is less than 0.3% [23]. Death is usually the result of basal ganglia hemorrhage or indirect postoperative complications such as pulmonary embolism or infection. Transient postoperative adverse events have included somnolence, confusion, hemiparesis, limb ataxia, truncal deviation, seizure, dysarthria and expressive aphasia after operations on the dominant hemisphere. Persistent morbidity is uncommon, consisting mainly of dysarthria, dysphagia, and mild paresis (Table 2). Complications from bilateral thalamotomy were more common, more than 25% of patients experienced speech impairment [23]. Mental changes and involuntary movements could also persist after bilateral surgery. Therefore, we do not recommend bilateral thalamotomy. Nevertheless, it has been suggested that with advances in stereotaxic techniques, bilateral operations can be performed with reduced morbidity.

The mechanisms of action of thalamotomy are not known, but may be due to destruction of autonomous neural activity, i.e. to synchronous bursts that fire at the same frequency as limb tremor. Lenz et al. [35] reported that a small lesion targeting neurons that fire at tremor frequency ('tremor cells'), is uniformly effective in relieving parkinsonian tremor. Two major pathways are interrupted by a thalamic lesion: the pallidofugal, which arises from the globus pallidus (GP) and enters the inferior part of the nucleus ventralis oralis via the ansa lenticularis, and the cerebellothalamic pathway, which arises from the cerebellum. The VIM projects to the motor cortex. As a

result of its connections, the VIM could become passively entrained by oscillations from other sites, and this entrainment could, in turn, promote abnormal oscillations throughout the motor system. Thus, lesions in the VIM would reduce tremor by curtailing this entrainment. It should be noted that these two hypotheses, viz., VIM inherent rhythmicity and passive entrainment by distant structures, are not mutually exclusive.

4. Deep brain stimulation (DBS)

In the United States, the Food and Drug Administration (FDA) approved the use of the Activa Tremor Control therapy in August 1997. It uses a deep brain stimulation (DBS) lead, an extension which connects the DBS lead to an Implantable Pulse Generator (IPG), and the Itrel II IPG. The intracranial end of the DBS lead has four platinum-iridium contacts that are 1.5 mm in length, and separated by 1.5 mm. The DBS lead is connected to the IPG device by means of the extension that is tunneled under the skin. The IPG is implanted subcutaneously in the infraclavicular area. Any one of the stimulating contacts can be used for monopolar stimulation or any two or more can be used in combination for bipolar stimulation. Stimulation is usually initiated 1 day postoperatively and is programmed by using an external programming device. Adjustable parameters include pulse width, amplitude, stimulation frequency, and a choice of active contacts. The patient can turn the stimulator on or off using a hand held magnet. The usual stimulation parameters are a stimulation frequency of 135 to 185 Hz, a pulse width of 60 to 120 μ s, and an amplitude of 1 to 3 V.

4.1. DBS of the VIM nucleus of the thalamus

Since high frequency stimulation (greater than 100 Hz) of the VIM nucleus of the thalamus results in both decreased neuronal activity and suppression of tremor, Benabid and coworkers [36] decided to implant electrodes in the VIM nucleus and to test the effect of chronic stimulation. Several studies have reported the efficacy of DBS of the thalamus for the tremor of PD (Table 3) [36–42]. A variety of study designs were used and several investigations employed blinded evaluations. For the most part, unilateral stimulation was evaluated. The usual outcome variable was a clinical rating scale of tremor severity (0 to 4 on Unified Parkinson Disease Rating Scale [UPDRS]). Follow-up was as long as 12–16 months in most studies.

Collectively, 152 of 162 patients (94%) were reported to have tremor reduction. The largest series was that of Benabid and colleagues [40] in which 78 of 80 patients were said to have benefited. Some patients show a 'micro-

Table 3

High frequency thalamic stimulation for parkinsonian tremor

Investigation (year)	Number improved/ total no. patients	Persistent morbidity
Blond et al. (1992) [37]	10/10	None
Speelman and Bosch (1995) [38]	5/5	Hemi-inattention
Alesch et al. (1995) [39]	18/23	Dysarthria, paresthesia, disequilibrium
Benabid et al. (1996) [40]	78/80	Dysarthria, paresthesia, dystonia of foot, disequilibrium
Koller et al. (1997) [41]	22/24	Paresthesia, dysarthria
Ondo et al. (1998) [42]	18/19	Disequilibrium, paresthesia, dysarthria, diplopia

thalamotomy' effect, i.e. a reduction of tremor after implantation of the electrode, but before the stimulator is turned on. This effect presumably is due to swelling at the electrode site. It usually lasts only several weeks but occasionally persists. Several of the studies demonstrated long-term efficacy of the procedure, e.g. 1 year or greater. While tremor is reduced, other parkinsonian symptoms such as bradykinesia, are not improved with DBS of the thalamus. Therefore, patients continue medications usually in the same amounts as before surgery. It is also not surprising that measures of activities of daily living (ADL) and of quality of life are not dramatically changed by DBS of the thalamus.

In general, morbidity and mortality of DBS of the thalamus is low. Adverse reactions related to surgery include intracerebral hemorrhage, seizures, and confusion. Complications related to the device include wire erosion, lead friction, infection of the IPG, malfunction of the IPG, electrical shock, and lead migration. These events occur only rarely. Side effects related to stimulation are reversible with stimulation reduction and are usually well tolerated. Transient paresthesias, lasting several seconds, are particularly common. Other complications due to stimulation that may occur include dysarthria, disequilibrium, paresis, and gait disorder (Table 3).

The mechanism of action of DBS is unknown. Persistent depolarization, stimulation of inhibitory systems, and neuronal jamming have been proposed as possible mechanisms of action. The advantages of DBS over ablative surgery include reversibility (no destructive lesion) and adaptability (changing of stimulus parameters to increase efficacy or decrease adverse reactions). Disadvantages include the added cost of the device, battery replacement (estimated 3 to 5 years of life), equipment failure and the risk of infection.

4.2. Thalamotomy vs. DBS of the thalamus

A randomized trial of thalamotomy vs. DBS of the thalamus is currently underway in Denmark. Initial results suggest that the two procedures have equal efficacy. However, DBS was associated with fewer adverse reactions [personal communication].

5. Pallidotomy

In 1952, Cooper [43] accidentally ligated the anterior choroidal artery in a parkinsonian patient and noticed improvement in his symptoms. This improvement was due to an ischemic lesion in the globus pallidus internus (GPi). Subsequently, multiple attempts to create lesions in the GPi were met with inconsistent results [44] until the use of stereotaxic frames. In 1960, Svinnilson et al. [18] reported improvement in 19 of 20 PD patients with lesions in the posteroventral region of the GPi. However, with the advent of levodopa in the 1960s, the use of surgery for PD waned until the late 1980s.

Laitinen and his colleagues [19] were among the first to reexamine Leksell's posteroventral pallidotomy in 38 PD patients and reported significant improvement in bradykinesia, rigidity, tremor, ambulation, speech, and drug-induced dyskinesias. This study was criticized due to the lack of standardized clinical examinations and the absence of radiologic follow-up ascertaining precise lesion placement. However, multiple studies [45–55] used standardized clinical rating scales and have reported significant improvement in parkinsonian symptoms after unilateral pallidotomy in PD (Table 4). Dogali et al. [45] reported their initial findings in 18 PD patients with medically intractable parkinsonian symptoms. When compared to a preoperative baseline, all quantifiable test scores improved significantly. When the patient was off medications, the UPDRS improved by 65%, while walking scores improved by 45%. Core Assessment Program for Intracerebral Transplantation (CAPIT) subscores on the contralateral side improved by 38%, and there was a significant reduction in the contralateral 'on' dyskinesias.

Lozano et al. [46] studied the effect of GPi pallidotomy in 14 PD patients. Six months after surgery, total motor scores in the 'off' state improved by 30%, and gait scores by 23%. Drug-induced involuntary movements were almost totally eliminated. Three patients had mild facial droop for 2–3 weeks, and four patients were euphoric for several weeks.

Baron et al. [47] reported the results of a 1-year pilot study regarding the effects of GPi pallidotomy in 15 advanced PD patients. The mean total UPDRS score improved by 30% at 3 months and remained improved at

Table 4
Pallidotomy for Parkinson's disease

Investigation (year)	n	Percentage improvement				Persistent morbidity
		OFF		ON		
		ADL	Motor	ADL	Motor	
Lozano et al. (1995) [46]	14	33	25	44	16	None
Baron et al. (1996) [47]	15	15	21	−7	13	Asymptomatic bleed, Dysarthria, quadrantanopia
Kishore et al. (1997) [48]	24	27	46	2	−10	Hemiparesis, scotomas, facial paresis
Lang et al. (1997) [49]	40	30	31	30	5.2	Facial weakness, dysarthria, dysphagia, impaired concentration, personality change, worsening of balance, worsening of dementia
Samuel et al. (1998) [54]	26	17	18	0	5.6	Fatal intracranial bleed, fatal hemorrhagic infarct, intracranial bleed, hemineglect, dysarthria, dysphagia

1-year follow-up. The 3-month mean ADL 'off' score improved by 34%. Similarly, the motor 'off' score improved by 25% at 3 months and remained improved at 1-year evaluations. The motor 'on' score improved by 13% at 3 months and 6 months, but worsened at 1-year follow-up. There was a dramatic improvement in contralateral drug-induced dyskinesias and tremor. Postural instability, freezing and pain were improved at 3-month evaluations but not 1 year after surgery. Two patients developed dementia and did not improve, suggesting that persons with moderate to severe dementia may have poor surgical outcomes. Adverse events included asymptomatic hemorrhage, moderate dysarthria, superior quadrantanopsia and transient postoperative confusion.

Lang et al. [49] performed a 2-year prospective study of 40 PD patients who underwent GPi pallidotomy. All patients had preoperative evaluations, 39 patients were examined at 6 months, 27 were examined at 1 year and 11 were examined at 2 years. At 6 months, there was a 28% improvement in the 'off'-period motor scores, 29% improvement in 'off'-period ADLs, 82% improvement in contralateral dyskinesia and 44% improvement in ipsilateral dyskinesia. The improvement in dyskinesia, 'off'-period scores, bradykinesia, and rigidity were sustained in the 11 patients examined after 2 years. Persistent complications included contralateral facial weakness, dysarthria, dysphagia, impaired concentration, changes in personality or behavior, worsening of handwriting, worsening of balance, word finding difficulty, and worsening of dementia.

One concern regarding postoperative improvement is the age of the patient. According to Baron et al. [47] total UPDRS scores improved an average of 52% in the younger patients (ages 38–52 years) and 14% in older patients (ages 58–69 years). Similarly, Lang et al. [49] reported a 36% improvement in the younger group (60 years or younger) and a 16% improvement in the older group at 6 months. Uitti et al. [51] compared pallidotomy in patients younger and older than 65 years of age. In patients younger than 65 years, the total UPDRS improved 26%, the 'off' motor score 29% and the 'on' motor score 21%. In patients older than 65 years, the total UPDRS

improved 20%, the 'off' motor score 16% and the 'on' motor score 24%. Although it is believed at the present time that younger patients do better with stereotaxic procedures, age should not be the only factor in deciding for or against surgery.

Bilateral pallidotomy is rarely recommended. While it results in modest improvement in parkinsonian symptoms, it causes a striking reduction in levodopa-induced dyskinesias [56]. The complications of bilateral pallidotomy are significant and include speech difficulties, dysphagia and cognitive difficulties [56,57]. Indications for a staged second side pallidotomy are limited and may include an excellent response to the first operation without any persistent complications, unchanged neuropsychological testing and persistent disabling dyskinesias on the contralateral side [58].

Centers performing pallidotomy use various techniques for target localization. They employ anatomical (stereotaxic CT or MRI) and electrophysiological techniques such as electrical stimulation. Some centers also use microelectrode recordings. Microelectrode-guided pallidotomy is time consuming and involves risks associated with multiple needle passes through the brain [59]. Furthermore, purchase and maintenance of the equipment involve increased costs associated with the surgery. However, microelectrode recordings lead to precise target localization and a reduced risk of complications [60]. On the other hand, good results have been reported in patients who underwent only macrostimulation during pallidotomy [19,48,61].

Patients with a diagnosis of idiopathic PD who are levodopa-responsive and have levodopa-induced dyskinesias are good candidates for pallidotomy. We do not recommend this procedure in patients with cognitive difficulties or patients suspected of having other forms of parkinsonism. Kazumata et al. [62] assessed the utility of preoperative clinical assessment and functional brain imaging with ^{18}F -fluorodeoxyglucose (FDG) and positron emission tomography (PET) in predicting the clinical outcome of stereotaxic pallidotomy. Twenty-two PD patients undergoing pallidotomy were clinically assessed preoperatively and also underwent quantitative FDG/PET

scans. Clinical outcome following surgery correlated significantly with preoperative measures of CAPIT score change from levodopa administration and with preoperative FDG/PET measurements of lentiform glucose metabolism. In clinical practice, levodopa responsiveness is usually used as an indication for pallidotomy, however, FDG/PET scans are not routinely employed.

6. Pallidal stimulation

Based on the success of deep brain stimulation for tremor and of pallidotomy for parkinsonian symptoms, Siegfried and Lippitz [63] used the technology of deep brain stimulation for continuously stimulating the ventroposterolateral pallidum. They implanted bilateral GPi electrodes in three PD patients. Follow-up in these three patients ranged from 3 months to 1 year. The investigators reported improvement in Webster Rating Scale scores and ‘on’–‘off’ motor fluctuations.

Pahwa et al. reported five patients who underwent pallidal stimulation [64] (Table 5). Three patients had bilateral implants and two had a unilateral implant. Four patients were markedly improved and one was moderately improved after surgery. The ADL subscores of the UPDRS improved by 19% in the ‘off’ state and by 42% in the ‘on’ state. Motor evaluations in the ‘off’ state also improved at the 3-month follow-up. Patient diaries demonstrated an increase in ‘on’ time with a decrease in ‘off’ time and ‘on with dyskinesias’. One patient had an asymptomatic intracranial bleed. Another patient had facial dystonia and paresthesia which required surgical repositioning of the lead.

Gross et al. [63] reported seven PD patients who had unilateral electrode implantation in the GPi. One year after surgery, ‘on medication/stimulator on’ motor subscores of the UPDRS were improved by 43% compared to baseline motor scores on medication. There was a marked decrease in levodopa-induced dyskinesias.

Kumar et al. [68] studied eight PD patients who underwent GPi stimulation (four unilateral, four bilateral). At 3-month follow-up, UPDRS total motor scores while

off medication but active stimulator improved by 27% as compared to the baseline. In the ‘off’ state, the ADL subscores improved by 26% and the ‘on’ ADL subscores by 40%. Levodopa-induced dyskinesias were improved by 60%.

In five patients who underwent GPi stimulation, Krack et al. [66] reported a 46% improvement in ADL ‘off’ subscores of the UPDRS at 6-month follow-up. Similarly, there was a 39% improvement in the motor UPDRS ‘off’ subscores.

7. Pallidotomy vs. pallidal stimulation

Although pallidal stimulation has advantages over pallidotomy, such as fewer long-term complications, ability to perform bilateral procedures with lower risks and the ability to respond to future therapies, there are certain disadvantages of stimulation surgery. The disadvantages include the high cost of the hardware, the need for the second procedure performed under general anesthesia, the higher risk of infection due to the presence of a foreign body and the risk of hardware failure and breakage. Unfortunately, there has been a lack of randomized studies that compare these procedures. Kumar et al. [67] compared the effects of pallidotomy and GPi stimulation. They reported similar objective improvements in the medication-off state with regard to UPDRS motor scores, rigidity, gait and postural instability. Persistent complications with the pallidotomy group included hemorrhage with hemiplegia and dysphasia. Neuropsychological testing after pallidotomy revealed mild, but significant, deficits in verbal and nonverbal memory. In contrast, neuropsychological testing after GPi stimulation did not reveal any decline in cognitive function. Merello et al. [68] conducted a prospective randomized study of two unilateral procedures in 13 PD patients. Both procedures showed a comparable effect on UPDRS and ADLs. No significant changes in neuropsychological parameters were observed, and the complications were also similar in the two groups. These results are preliminary, and further investigations are required to compare the two procedures.

Table 5
Globus pallidus stimulation for Parkinson’s disease

Investigation (year)	n	Improvement in UPDRS scores			
		OFF		ON	
		ADL	Motor	ADL	Motor
Pahwa et al. (1997) [64]	5	19%	24%	41%	60%
Gross et al. (1997) [65]	7	N/A	30%	N/A	43%
Kumar et al. (1998) [67]	8	26%	27%	40%	8% worse
Krack et al. (1998) [66]	5	46%	39%	22%	14% worse

8. Subthalamotomy

The subthalamic nucleus (STN) has gained importance in PD. The STN has many connections, including excitatory glutaminergic input directed toward both segments of the GP and the substantia nigra. In PD, the STN appears to be hyperactive, suggesting that modulation of STN activity may have therapeutic benefit in PD [2]. Surgical treatment aimed at the STN has only recently been investigated.

Unilateral STN lesions (three left and two right) have recently been performed in five patients whose PD was characterized by severe gait freezing and axial akinesia [69]. One of these five cases was complicated by a large subthalamic infarction causing hemichorea. It appeared 7 days after surgery. The cardinal PD symptoms of the other patients continued to improve even after reduction of the levodopa dosage 3 months after surgery. Dyskinesias elicited by apomorphine remained unchanged. In another report of two patients, efficacy was seen after bilateral lesions that caused no serious adverse reactions or hyperkinesias [70].

9. Subthalamic stimulation

Because of the potential dangers of lesioning the STN, it seemed reasonable to use DBS of this structure. While experience of DBS of the STN is preliminary, this approach may have considerable potential. Two reports have been published [71,72] (Table 6). Only 31 patients were evaluated in these studies, but efficacy was clearly apparent. ‘Off’ motor scores were improved by approximately 60% and ADL scores by 30–58%. Bradykinesia, tremor, and rigidity were all diminished. A positive effect on postural instability and gait was also apparent. Dyskinesias were reduced dramatically, most likely due to the marked reduction of levodopa dosage (40–50%). Adverse reactions were not uncommon, perhaps related in part to the lack of experience with this new approach. Several intracerebral hemorrhages occurred and mental status changes frequently occurred postoperatively. Further investigations, particularly in comparison to DBS of the

globus pallidus, are needed to resolve many unanswered questions regarding these procedures.

10. Transplantation

Brain grafting has provided a revolutionary concept for the treatment of PD. The approach is based on the implantation of dopaminergic neurons (or of dopamine-producing cells) into a structure normally innervated by the endogenous dopaminergic system. The degenerated nigrostriatal pathway cannot be reconstituted by grafts that are placed into the neostriatum, the main site of dopaminergic terminals. Grafted neurons are expected to form synaptic connections with the host neostriatum. The resulting neuroanatomical reorganization provides a new network whose function can compensate for the motor deficits associated with the loss of nigrostriatal neurons. This therapeutic strategy requires that neurons from fetal substantia nigra survive when grafted into patients with PD, and that their activity compensates for the lost function. The brain is thought to constitute a privileged transplantation site. Immunosuppressive treatment has been performed in many patients with PD for a variable length of time, and no cases of rejection have been observed. This experimental technique has also been developed to the point of clinical application in other degenerative movement disorders, such as Huntington’s disease [73]. Despite initial enthusiasm, fetal grafts have not gained wide application in clinical practice.

Preclinical data have demonstrated that dopamine cell grafts in animals survive long-term, innervate the host striatum by forming synaptic connections, and improve motor behavior [74,75]. The first observation of neostriatal reinnervation grafts of fetal substantia nigra was made by Björklund and Stenevi [76]. These authors used the 6-hydroxydopamine rat model of PD. The model of restoration of function was quickly characterized by the demonstration that fetal grafts survive, and induce a behavioral and pharmacological recovery with a predictable time window [77]. Adrenal chromaffin cells have also been grafted into the dopamine-depleted striatum of the rat [78].

Table 6
Subthalamic stimulation for Parkinson’s disease

Investigator (year)	n	Clinical outcome	Dyskinesias	Drug dosage	Adverse reactions
Kumar et al. (1998) [71]	7	UPDRS ‘off’ Motor +58% ADL +30% ‘on’ time +20%	–83%	–40%	Surgery: infarction Stimulation: mental changes, paresthesia, diplopia, tonic contraction
Limousin et al. (1998) [72]	24	UPDRS ‘off’ Motor +60% ADL +58%	–63%	–50%	Surgery: intracerebral hemorrhage Stimulation: mental changes, eyelid apraxia, dysarthria Device: infection

This method has prompted the development of autologous adrenal medullary transplantation in man [79,80], though it has been abandoned after the failure of clinical trials [81].

In rodents, dissociated fetal nigral cell suspensions enhance neuron survival after direct introduction into the parenchyma [82]. Single grafts could compensate for specific behavioral abnormalities induced by denervation, whereas multiple graft placements, provided a more complete innervation of the host neostriatum and could reverse all abnormal motor behavior [83]. Observations in the unilateral 6-hydroxydopamine model of PD could not be fully duplicated in rats with a bilateral ablation of the nigrostriatal dopamine system. In the model of bilateral dopamine lesion, transplantation procedures failed to reverse the severe behavioral syndrome. This observation implied placement of dopaminergic neurons in to the neostriatum was not sufficient to compensate for complex behavioral deficits [83]. Morphological studies have shown that fetal neurons form synaptic contacts with host neurons [84,85] and that host-to-graft connections also developed [86]. The development of host-to-graft connections has been confirmed in humans [87]. Experiments in the rodent model have been replicated in non-human primates. Studies in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys have also shown that multiple bilateral placements of intrastriatal grafts of mesencephalic dopaminergic neurons could survive, grow, and improve parkinsonian signs, including tremor [88].

To date, more than 250 PD patients have received grafts of fetal substantia nigra. This procedure has gained unanimous scientific acceptance, but has not become a common treatment. In a few outstanding cases, patients have been able to end levodopa therapy after the graft. However, motor improvement was highly variable and depended in all likelihood on the extent of graft-to-host reinnervation. About two thirds of the patients had a partial recovery of motor function, while a few also had improvement of gait, language, and balance.

Several studies have shown the feasibility of fetal nigral transplantation in patients affected by PD. The first human study reported the implant of nigral tissue from fetuses at 7 to 9 weeks gestational age. The tissue was implanted unilaterally into the caudate nucleus and the anterior putamen in two patients [89]. Based on the methodology developed in rodents, most human protocols have used cell suspensions [90]. They provide a more homogeneous distribution of grafted tissue but also necessitate pooling of fetal tissue. Solid grafts are easy to prepare and preserve their cytoarchitecture though neuronal survival is limited.

The low survival rate of grafted dopaminergic neurons is a critical drawback of the technique. Only 5–20% of the grafted neurons survive, and better cell survival is necessary to reach a satisfactory graft efficiency. Strategies to improve viability of dopaminergic cells include the administration of compounds reducing oxidative stress, or trophic factors. Lazaroids increase the viability of dopa-

minergic neurons in the mouse. Several factors have been identified which promote survival of embryonic rat mesencephalic dopamine neurons in tissue cultures, but only glial cell-derived neurotrophic factor and brain-derived neurotrophic factor have favorably influenced the survival of dopaminergic neurons in animal models of Parkinson's disease [91]. Glial cell-derived neurotrophic factor is particularly efficacious in enhancing survival and function of fetal nigral dopaminergic grafts [92]. Its potency and specificity raise the question of whether it may be used as a sole therapeutic agent to restore the degenerated nigrostriatal tract in PD [93]. Sertoli cells also provide a source of factors improving the survival and maturation of embryonic dopaminergic neurons. They exert a trophic effect on human mesencephalic neurons in vitro [94].

Other strategies involve the administration of free radical scavengers [95], xenografts with readily available fetal tissue from mammals [96], or genetically modified cells or stem cells. Implantation of stem cells is a potentially powerful means to reconstitute damaged nervous tissue. In the mammalian central nervous system, stem cells undergo differentiation in response to an appropriate growth factor [97,98]. The use of human stem cells has several theoretical advantages compared to sources of dopaminergic neurons. The human origin allows a careful quality control (diseases, infections, etc.). A limited batch of stem cells permits the cultivation of unlimited numbers of cells that may be used to treat many patients. Future research will show whether fetal grafts will become a common practice or remain a current theoretical approach.

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