Update on surgery for Parkinson's disease

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Purpose of review

The clinical effectiveness and limitations of subthalamic nucleus deep brain stimulation for Parkinson's disease are summarized and recent developments concerning alternative brain targets for deep brain stimulation or restorative surgical therapies are discussed.

Recent findings

In a controlled study subthalamic nucleus deep brain stimulation was superior to best medical management in improving quality of life of patients with advanced Parkinson's disease. The benefits of the procedure on levodopa-sensitive motor symptoms are sustained for up to 5 years, but it does not halt disease progression. Cognitive decline and worsening of axial motor symptoms may limit the overall benefit. Age at the time of surgery is an important factor for long-term stability and safety. Psychosocial aspects of Parkinson's disease can profoundly impact on the ability of a patient to reintegrate after surgery and have to be considered in patient selection. Stimulation of the pedunculopontine nucleus may have an additive effect on postural and gait symptoms, which do not respond to levodopa or subthalamic nucleus deep brain stimulation.

Summary

Deep brain stimulation is emerging from an empirical to an evidence based therapy. The safety and efficacy of the procedure may legitimize surgery at a younger age before social maladjustment prevents reintegration of the patient into a normal life.

Keywords

deep brain stimulation, Parkinson's disease, subthalamic nucleus, transplantation

Curr Opin Neurol 20:465–469. © 2007 Lippincott Williams & Wilkins.

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Current Opinion in Neurology 2007, 20:465–469

Abbreviations

DBS	deep brain stimulation
GDNF	glial cell line-derived neurotrophic factor
GPi	globus pallidus
PPN	pedunculopontine nucleus
STN	subthalamic nucleus

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Introduction

Deep brain stimulation (DBS) is increasingly accepted as an adjunct therapy for Parkinson's disease. High-frequency DBS was pioneered by Benabid and colleagues in Grenoble in the late 1980s [1] as an alternative to ablative stereotaxy. DBS is based on the observation that high-frequency electrical stimulation of specific brain targets can mimic the effect of a lesion without the need for destroying brain tissue. For chronic stimulation a permanent lead is implanted into the target area within the brain and connected to a fully implanted neurostimulation device. The stimulator settings can be adjusted telemetrically with respect to electrode configuration, current amplitude, pulse width and pulse frequency. DBS has rapidly replaced ablative stereotactic surgery in movement disorders due to several advantages: DBS does not require making a destructive lesion in the brain; it can be performed bilaterally with relative safety in contrast to most lesioning procedures; stimulation parameters can be adjusted postoperatively to improve efficacy, to reduce adverse effects and to adapt DBS to the course of disease; and DBS is in principle reversible and does not preclude the use of possible future therapies in Parkinson's disease, which may require the integrity of the basal ganglia circuitry.

Candidates for surgery suffer from intractable tremor or from long-term complications of levodopa therapy, such as motor fluctuations and severe dyskinesias [2]. Thalamic stimulation in the ventral intermediate nucleus (Vim) leads to a marked reduction of contralateral tremor, but has no beneficial effect on other symptoms of Parkinson's disease. The subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi) are targeted for the treatment of advanced Parkinson's disease. STN-DBS is currently considered superior to GPi-DBS because the antiakinetic effect seems to be more pronounced, it allows a more marked reduction of antiparkinsonian medication and requires less stimulation energy [2], but a formal comparison in sufficiently powered comparative trials is still pending [3,4].

Subthalamic nucleus deep brain stimulation

As of 2006 more than 20 000 patients were treated by STN stimulation worldwide. This number underlines the present routine character of surgical Parkinson's disease therapy. The principle efficacy of STN-DBS in reducing all cardinal motor symptoms of Parkinson's disease is well established. A recent systematic review commissioned by the Movement Disorder Society identified a total of 34

articles using Medline and Ovid databases from 1993 until 2004, which reported on the outcome from 37 cohorts comprising 921 patients [5••]. The estimated decreases in absolute Unified Parkinson's Disease Rating Scale (UPDRS) II (activities of daily living) and III (motor) scores after surgery in the stimulation on/medication off state compared with preoperative medication off state were 50% and 52%, respectively. Average reduction of the levodopa equivalent daily dosage of dopaminergic drugs following surgery was 55.9%. Average reduction in dyskinesia following surgery was 69.1%. Average reduction in daily off periods was 68.2%. Higher baseline UPDRS III off scores and higher baseline L-dopa responsiveness were independent predictors of greater change in motor score after surgery. The most common serious adverse event related to surgery was intracranial hemorrhage in 3.9% of patients. Psychiatric sequelae were common. The authors conclude that the current literature suggests a consistent beneficial effect of STN-DBS on motor symptoms and activities of daily living. The safety assessment, however, is limited by the small sample sizes and the uncontrolled nature of the open-label studies.

Patients will only accept DBS as a noncurative therapy if the symptomatic benefits outlast the inherent surgical risks and lead to a more effective reduction of the burden of disease than optimal drug therapy. This fundamental problem was recently addressed in a large randomized controlled multicenter study comparing neurostimulation with best medical management over a 6-month period [6••]. The study included 156 patients with severe motor symptoms of Parkinson's disease, who were randomly assigned in pairs to receive either bilateral DBS of the STN in combination with medical treatment or best medical therapy alone. Primary outcome of the trial was the change in health-related quality of life [Parkinson's Disease Questionnaire-39 (PDQ-39) score] after 6 months. The PDQ-39 summary index was 41.8 ± 13.9 of 100 at baseline and 31.8 ± 16.3 at 6 months in the neurostimulation group compared with 39.6 ± 16.0 and 40.2 ± 14.5 in the medication group. This corresponded to an improvement of about 25% in the neurostimulation group versus practically no change in the medication group. While serious adverse events were more common with neurostimulation than with medication alone and included a fatal intracerebral hematoma, and a suicide, the total number of adverse events was higher among medication-only patients. One patient in the medication-only group died from a car accident during a psychotic episode.

This study is ground breaking for several reasons. First, it provides a realistic risk assessment of DBS in patients with advanced Parkinson's disease, whose natural course is already associated with major risks of disease or treatment-related complications. Second, it proves that the symptomatic benefits of DBS outlast potentially negative effects of the surgery on disability and quality of life. There is an ongoing discussion if detrimental effects of surgery on cognition [7,8], mood [9] or behavior [10] in some patients could be related to surgery, stimulation itself, or rather to the disease, medication or a potential selection bias. Depression has a higher impact on quality of life than motor symptoms [11], such that neuropsychiatric adverse effects of neurostimulation may cancel out the motor benefits. This study [6••], however, found no evidence for an increased risk of cognitive or neuropsychiatric complications in the neurostimulation group, but confirmed a 25% improvement of quality of life with STN-DBS, which was within the range of the improvements previously found in uncontrolled case series [12–19]. A shortcoming of the study is the limited follow-up period of only 6 months. Other ongoing trials with a longer parallel group comparison such as the UK PD SURG trial (http://www.pdsurg.bham.ac.uk) may help to determine the longevity of the results.

Long-term effects

The open-label follow up of two large cohorts suggests that postoperative improvements in motor disability are sustained for up to 5 years after STN-DBS [20,21]. Parkinson's disease, however, progresses as reflected by a slight but significant worsening of the 'on' period motor score, in particular of axial symptoms including dysarthria, gait freezing or postural imbalance. Cognitive decline, apathy and frontal dysexecutive symptoms pose additional problems in the long-term management of DBS-treated patients [20,22], but in the absence of control groups, one cannot discern whether the neuropsychiatric problems are related to disease progression, surgical treatment, postoperative medication changes or a combination of all these factors.

Issues of patient selection

The preoperative responsiveness of motor symptoms to levodopa is a well established predictive factor for the motor benefit after STN-DBS [23]. Another important factor seems to be the age at surgery [23,24]. Patients over age 70 may carry an increased risk of cognitive decline after surgery and in their 'stimulation-on' state do not reach the 'best-medical-on' state in contrast to younger patients [24]. Russmann and colleagues [24] found in a retrospective analysis of their results, that especially axial symptoms (gait and balance) worsened in the older patient group after surgery and were the reason for institutional care in 25%.

Psychosocial aspects of Parkinson's disease surgery

Despite optimal motor outcome and the absence of complications, some patients are not satisfied with their condition after STN-DBS [25]. Schupbach and colleagues [26••] recently analyzed the factors of psychosocial distress

after surgery in 29 patients. These patients experienced marked improvements in Parkinsonian motor symptoms, activities of daily living and quality of life and had no signs of psychiatric disease. Social adjustment as measured by the social adjustment scale, however, did not improve after STN-DBS. Three types of maladjustment were observed. Nineteen of 29 patients expressed a feeling of strangeness and unfamiliarity with themselves. They had difficulties adopting to the new role after surgery and defining new goals in life after overcoming the burden of Parkinson's disease. Marital conflicts occurred in 17/24 patients living in couples before surgery and led to divorce in three couples. Only nine of 16 patients who were working before surgery resumed their professional activity after surgery. Five of these patients preferred to engage in leisure activities instead of working, while others felt unable to work despite excellent motor improvement. This study underlines that DBS is a therapy with profound impact on a patient's life, comparable to epilepsy surgery or organ transplantation [27]. Maladjustment had previously been observed after these life-changing medical procedures and multidisciplinary programs have been developed to help patients cope with reintegration [27]. Such programs need to be adopted to the special needs of patients undergoing movement disorder surgery.

Currently surgery is performed in very advanced stages of Parkinson's disease after an average of 14 years of disease duration, when the psychosocial burden of the disease has been marked for many years. The majority of patients have retired from professional life and are dependent on help in their activities of daily living. The low morbidity and impact of STN-DBS may justify operating on patients at an earlier stage to prevent the inevitable decline in quality of life and social participation. In a small pilot study the Paris group [28••] randomized 20 patients with a short duration of Parkinson's disease (6.8 ± 1 year) to either immediate surgery or best medical treatment for a period of 18 months. Quality of life was significantly improved by 24% in the surgical group but did not change in nonsurgical patients. After 18 months, the severity of parkinsonian motor signs 'off' medication, levodopa-induced motor complications, and daily levodopa dose were reduced by 69%, 83%, and 57% in operated patients and increased by 29%, 15%, and 12% in the group with medical treatment only. Adverse events were mild or transient, and overall psychiatric morbidity and anxiety improved in the surgical group. This small pilot study suggests that DBS may be considered in suitable patients at the end of the drug honeymoon period, when the first motor complications start to emerge. This concept is currently being investigated in a large binational multicenter trial in France and Germany.

It is important to keep in mind that the low morbidity and high efficacy of DBS, which may justify surgery at an earlier stage, was observed by multidisciplinary teams with extensive experience in movement disorder surgery. The increasing number of centers now offering DBS – sometimes with little previous experience in stereotactic and functional surgery or the neurological management of patients with advanced Parkinson's disease – increases the risk of poor outcomes and apparent DBS failures [29]. Expert centers may be able to correct some of these treatment failures [29,30] by adjustments in medication or programming or lead repositioning, but poor outcomes after surgery impose an unnecessary burden on patients and threaten the general acceptance of DBS by the neurological community and patient advocacy groups.

Alternative targets for deep brain stimulation

Current pathophysiological concepts of Parkinson's disease emphasize the abnormal increase in neuronal activity in the STN. The overactive STN then drives the internal pallidum (GPi) to inhibit thalamocortical motor pathways [31]. High-frequency stimulation (HFS) of the STN or GPi is thought to be effective by releasing the ventrolateral thalamus and its cortical projection areas from the abnormal basal ganglia input [32]. More recently, a number of reports suggest an equally important role for the upper brainstem, and in particular, the pedunculopontine nucleus (PPN), in the genesis of Parkinson's disease motor symptoms, like akinesia, gait dysfunction and postural instability [33,34]. The PPN is part of the mesencephalic locomotor reticular region [35] and maintains dense interconnections with the basal ganglia and several other pontine and medullar areas [36,37]. Local injections of the γ-aminobutyric acid antagonist bicuculine into the PPN of two nonhuman primates reversed the Parkinsonian motor symptoms induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [33]. Two recent case reports [38,39] have demonstrated the feasibility of electrode implantations into the human PPN. The target is located lateral to the decussation of the superior cerebellar peduncle at the level of the inferior colliculus [39]. Low-frequency stimulation of the PPN resulted in up to 57% reduction of Parkinson's disease motor symptoms [39]. The first blinded comparison of STN and PPN stimulation in six patients with electrode implantations into both targets, however, provides a less enthusiastic view [40•]: PPN stimulation alone was significantly inferior to STN-DBS (32% versus 54% motor score improvement). Combined stimulation of PPN and STN did not improve the overall motor score, but led to a significant additive effect on gait and balance symptoms and further improvement in the activities of daily living. A longer follow up and larger sample size will be necessary to prove whether combined STN-PPN-DBS may overcome some of the limitations of STN-DBS, in particular the progression of levodopa resistant axial symptoms.

A recent report suggests that the rostral zone of the zona incerta may be a better target for the cardinal motor symptoms of Parkinson's disease than the STN [41•]. The subthalamic area dorsomedial to the STN contains pallidofugal fiber tracts and the zona incerta, whose function within the basal ganglia–thalamocortical circuitry is not well established. The observation by Plaha and colleagues [41•] underlines the necessity for a better delineation of the optimal 'STN' target. Since the authors did not use intraoperative neurophysiology to confirm their anatomical targeting, one cannot decide whether the superior results of the 'zona incerta' target related to a suboptimal placement of the STN electrodes. Due to the intraindividual variability in the severity of motor symptoms and their responsiveness to levodopa, comparative trials of targets should rather use a relative score (e.g. percentage of the preoperative levodopa response achieved by stimulation alone after surgery) than comparing average stimulation responses of two or more groups. Stimulation of optimally placed STN electrodes should 1:1 mimic the preoperative levodopa response. Using this approach in combination with intraoperative neurophysiology, Herzog *et al.* [42] demonstrated that stimulation of the subthalamic area was clinically inferior to stimulation of the dorsal STN border or the STN proper.

Other surgical therapies for Parkinson's disease

After the publication of two large controlled trials [43,44] demonstrating the clinical inefficacy of fetal mesencephalic transplantation compared with sham-surgery, cell replacement therapies have returned to an experimental stage. In the meantime, two small pilot trials evaluated the feasibility of alternative donor material for transplantation. Autotransplantation of dopaminergic carotid body cell aggregates into the striatum resulted in modest clinical benefit (23% motor score reduction at 6 months) in 13 patients with advanced Parkinson's disease [45•]. None of the patients developed off-period dyskinesias. Based on the favorable results of a pilot study [46] a double-blind, sham-controlled multicenter trial is currently investigating the safety and efficacy of intraputaminal implantation of human retinal pigment epithelial (RPE) cells. RPE cells produce levodopa and can be isolated from postmortem human eye tissue, grown in culture, and implanted into the brain attached to microcarriers. In an open-label pilot study [46], six patients with advanced Parkinson's disease were followed after unilateral implantation and had an average improvement of 48% in the motor score after 12 months. This benefit was sustained at 24 months. No neurological side effects were observed.

Despite very favorable reports on the beneficial effects of intraputaminal infusion of glial cell line-derived neurotrophic factor (GDNF) in open studies [47,48], a recent randomized controlled clinical trial [49••] failed to prove the superiority of GDNF over placebo infusion in 34 Parkinson's disease patients. Serious, device-related adverse events required surgical repositioning of catheters in two patients and removal of devices in another. Neutralizing antibodies were detected in three patients. Despite some issues on differences in methodology raised by the proponents of GDNF infusions, this study again demonstrates the need for a placebo control in surgical trials of Parkinson's disease. The magnitude of the placebo effect with any invasive therapy of Parkinson's disease must not be underestimated and may influence subjective patient ratings, such as quality of life, but also single-blinded physician ratings of motor symptoms, as demonstrated in a remarkable secondary analysis of a sham-controlled transplantation trial [50].

Conclusion

STN-DBS has evolved to an evidence-based, routine therapy for patients with severe tremor or long-term complications of levodopa therapy. A recent controlled trial confirmed the superiority of this surgical therapy over medical treatment alone in improving quality of life of patients with advanced Parkinson's disease. The role of surgery within the treatment algorithm, however, may need to be redefined in the near future, because the goal of maintaining quality of life and preventing the psychosocial decline associated with Parkinson's disease may be better achieved in younger patients operated at an earlier stage of disease. No other surgical treatment is currently available, which could challenge the clinical benefit of STN-DBS in well selected Parkinson's disease patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 506–508).

1 Benabid AL, Pollak P, Seigneuret E, *et al.* Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. Acta Neurochir Suppl (Wien) 1993; 58:39–44.

2 Volkmann J. Deep brain stimulation for the treatment of Parkinson's disease. J Clin Neurophysiol 2004; 21:6–17.

3 Anderson VC, Burchiel KJ, Hogarth P, *et al.* Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. Arch Neurol 2005; 62:554–560.

4 Okun MS, Foote KD. Subthalamic nucleus vs globus pallidus interna deep brain stimulation, the rematch: will pallidal deep brain stimulation make a triumphant return? Arch Neurol 2005; 62:533–536.

5 •• Kleiner-Fisman G, Herzog J, Fisman DN, *et al.* Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Mov Disord 2006; 21 (Suppl 14):S290–S304.
This paper provides a systematic review and metaanalysis of clinical trials on STN-DBS. It is the most recent and comprehensive summary of clinical DBS effects.

6 •• Deuschl G, Schade-Brittinger C, Krack P, *et al.* A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006; 355:896–908.
The authors report on a randomized controlled, multicenter trial of STN stimulation versus best medical treatment in patients with advanced Parkinson's disease. This study proves the superiority of surgery to medical treatment alone in improving quality of life, activities of daily living and motor symptoms.

7 Saint-Cyr JA, Trepanier LL, Kumar R, *et al.* Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain 2000; 123:2091–2108.

8 Ardouin C, Pillon B, Peiffer E, *et al.* Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann Neurol 1999; 46:217–223.

9 Berney A, Vingerhoets F, Perrin A, *et al.* Effect on mood of subthalamic DBS for Parkinson's disease: a consecutive series of 24 patients [comment]. Neurology 2002; 59:1427–1429.

10 Houeto JL, Mesnage V, Mallet L, *et al.* Behavioural disorders, Parkinson's disease and subthalamic stimulation [comment]. J Neurol Neurosurg Psychiatry 2002; 72:701–707.

11 Committee GPsDSS. Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov Disord 2002; 17:60–67.

12 Drapier S, Raoul S, Drapier D, *et al.* Only physical aspects of quality of life are significantly improved by bilateral subthalamic stimulation in Parkinson's disease. J Neurol 2005; 252:583–588.

13 Erola T, Karinen P, Heikkinen E, *et al.* Bilateral subthalamic nucleus stimulation improves health-related quality of life in Parkinsonian patients. Parkinsonism Relat Disord 2005; 11:89–94.

14 Lezcano E, Gomez-Esteban JC, Zarranz JJ, *et al.* Improvement in quality of life in patients with advanced Parkinson's disease following bilateral deep-brain stimulation in subthalamic nucleus. Eur J Neurol 2004; 11:451–454.

15 Lyons KE, Pahwa R. Long-term benefits in quality of life provided by bilateral subthalamic stimulation in patients with Parkinson disease. J Neurosurg 2005; 103:252–255.

16 Martinez-Martin P, Valldeoriola F, Tolosa E, *et al.* Bilateral subthalamic nucleus stimulation and quality of life in advanced Parkinson's disease. Mov Disord 2002; 17:372–377.

17 Just H, Ostergaard K. Health-related quality of life in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nuclei. Mov Disord 2002; 17:539–545.

18 Spottke EA, Volkmann J, Lorenz D, *et al.* Evaluation of healthcare utilization and health status of patients with Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus. J Neurol 2002; 249:759–766.

19 Lagrange E, Krack P, Moro E, *et al.* Bilateral subthalamic nucleus stimulation improves health-related quality of life in PD. Neurology 2002; 59:1976–1978.

20 Schupbach WM, Chastan N, Welter ML, *et al.* Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. J Neurol Neurosurg Psychiatry 2005; 76:1640–1644.

21 Krack P, Batir A, Van Blercom N, *et al.* Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003; 349:1925–1934.

22 Rodriguez-Oroz MC, Obeso JA, Lang AE, *et al.* Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. Brain 2005; 128:2240–2249.

23 Charles PD, Van Blercom N, Krack P, *et al.* Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 2002; 59:932–934.

24 Russmann H, Ghika J, Villemure JG, *et al.* Subthalamic nucleus deep brain stimulation in Parkinson disease patients over age 70 years. Neurology 2004; 63:1952–1954.

25 Agid Y, Schupbach M, Gargiulo M, *et al.* Neurosurgery in Parkinson's disease: the doctor is happy, the patient less so? J Neural Transm Suppl 2006; 70:409–414.

26 •• Schupbach M, Gargiulo M, Welter ML, *et al.* Neurosurgery in Parkinson disease: a distressed mind in a repaired body? Neurology 2006; 66:1811–1816.

This article introduces the concept of psychosocial maladaptation to outcome research in movement disorder surgery. The authors describe different patterns of difficulties to reintegrate into social life after STN stimulation despite excellent motor benefit and the absence of psychiatric adverse effects.

27 Wilson S, Bladin P, Saling M. The 'burden of normality': concepts of adjustment after surgery for seizures. J Neurol Neurosurg Psychiatry 2001; 70:649–656.

28 •• Schupbach WM, Maltete D, Houeto JL, *et al.* Neurosurgery at an earlier stage of Parkinson disease: a randomized, controlled trial. Neurology 2007; 68:267–271.

This article marks a possible change in the position of surgery within the treatment algorithm of Parkinson's disease. The authors conduct a small pilot trial to demonstrate that surgery in younger patients at a less severe stage of the disease may be better tolerated and more effective in preventing the progression of disability and decline in quality of life than medical treatment alone.

29 Okun MS, Tagliati M, Pourfar M, *et al.* Management of referred deep brain stimulation failures: a retrospective analysis from 2 movement disorders centers. Arch Neurol 2005; 62:1250–1255.

30 Moro E, Poon YY, Lozano AM, *et al.* Subthalamic nucleus stimulation: improvements in outcome with reprogramming. Arch Neurol 2006; 63:1266–1272.

31 DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990; 13:281–285.

32 Limousin P, Greene J, Pollak P, *et al.* Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. Ann Neurol 1997; 42:283–291.

33 Nandi D, Aziz TZ, Giladi N, *et al.* Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus. Brain 2002; 125:2418–2430.

34 Munro-Davies LE, Winter J, Aziz TZ, Stein JF. The role of the pedunculopontine region in basal-ganglia mechanisms of akinesia. Exp Brain Res 1999; 129:511–517.

35 Jordan LM. Initiation of locomotion in mammals. Ann N Y Acad Sci 1998; 860:83–93.

36 Delwaide PJ. Parkinsonian rigidity. Funct Neurol 2001; 16:147–156.

37 Pahapill PA, Lozano AM. The pedunculopontine nucleus and Parkinson's disease. Brain 2000; 123:1767–1783.

38 Mazzone P, Lozano A, Stanzione P, *et al.* Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease. Neuroreport 2005; 16:1877–1881.

39 Plaha P, Gill SS. Bilateral deep brain stimulation of the pedunculopontine nucleus for Parkinson's disease. Neuroreport 2005; 16:1883–1887.

40 • Stefani A, Lozano AM, Peppe A, *et al.* Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 2007; 24 January [Epub ahead of print].

This is the first systematic comparison of the effects of low-frequency pedunculopontine and high-frequency subthalamic stimulation on parkinsonian motor symptoms in six patients with lead implants into both targets.

41 • Plaha P, Ben-Shlomo Y, Patel NK, Gill SS. Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. Brain 2006; 129:1732–1747.

The authors examine the optimal target for deep brain stimulation in advanced Parkinson's disease in a series of patients, in which they progressively moved their target from the STN to the caudal zona incerta.

42 Herzog J, Fietzek U, Hamel W, *et al.* Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's disease. Move Disord 2004; 19:1050–1054.

43 Olanow CW, Goetz CG, Kordower JH, *et al.* A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 2003; 54:403–414.

44 Freed CR, Greene PE, Breeze RE, *et al.* Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 2001; 344:710–719.

45 • Minguez-Castellanos A, Escamilla-Sevilla F, Hotton GR, *et al.* Carotid body autotransplantation in Parkinson disease: a clinical and PET study. J Neurol Neurosurg Psychiatry 2007; 12 January [Epub ahead of print].

The authors describe the symptomatic effects of autologous transplantation of dopaminergic carotid body cells into the putamen in patients with Parkinson's disease.

46 Stover NP, Bakay RA, Subramanian T, *et al.* Intrastriatal implantation of human retinal pigment epithelial cells attached to microcarriers in advanced Parkinson disease. Arch Neurol 2005; 62:1833–1837.

47 Gill SS, Patel NK, Hotton GR, *et al.* Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nat Med 2003; 9:589–595.

48 Patel NK, Bunnage M, Plaha P, *et al.* Intraputamenal infusion of glial cell line-derived neurotrophic factor in PD: a two-year outcome study. Ann Neurol 2005; 57:298–302.

49 •• Lang AE, Gill S, Patel NK, *et al.* Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. Ann Neurol 2006; 59:459–466.

The authors find no evidence for a clinical efficacy of intraputaminal GDNF infusions compared with placebo in patients with advanced Parkinson's disease despite previous encouraging results in open-label studies.

50 McRae C, Cherin E, Yamazaki TG, *et al.* Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. Arch Gen Psychiatry 2004; 61:412–420.