

South African guideline on deep brain stimulation for Parkinson's disease

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Background. Parkinson's disease (PD) is a common neurodegenerative disease, associated with severe impairment of quality of life. Although the motor aspects of the illness are typically successfully treated with medications acting on the dopaminergic system, a number of patients encounter progressive difficulties associated with their medical treatment.

Recommendations. Carefully selected patients will benefit from deep brain stimulation (DBS) treatment for their PD. Selection requires dopamine challenge testing and neuropsychological testing for the presence of cognitive impairment. Careful follow-up and programming of the DBS system are mandatory, and a major reason for DBS failure is inadequate programming and management of medication.

Conclusion. DBS is a useful component of standard therapy for PD and may reduce symptoms, improve quality of life, promote patient independence and reduce healthcare costs by reducing requirements for medicine.

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1. Introduction

Parkinson's disease (PD) is a progressive, disabling neurodegenerative movement disorder. Medical treatments that treat many of the motor symptoms of the disease are available.^[1] Unfortunately, after prolonged exposure to oral levodopa, motor complications may arise with patients rapidly changing from periods of limited movement (akinesia/'off') to periods of excessive movements that may range from mild to severe and disabling (dyskinesias). Although there are several medication-based strategies to reduce these levodopa-induced motor complications, ultimately the majority of these fail or become excessively burdensome to the patient.^[2]

The history of deep brain stimulation (DBS) began in the 1940s, when because there was limited medication available for the treatment of PD, emphasis came to be placed on the use of surgically induced lesions of the thalamus and internal segment of the globus pallidus (GPi). With the advent and widespread use of dopamine in the 1960s, surgery fell out of favour until the reintroduction of pallidotomy by Laitinen.^[3] It was subsequently shown that high-frequency DBS was able to simulate the effects of ablation surgery of basal ganglia targets in a reversible and adjustable manner. With the renaissance of functional neurosurgery in this field, DBS is now considered an important treatment for PD, dystonia and tremor. DBS has been used for the treatment of movement disorders in South Africa (SA) since Dr Roger Melvill did the first procedure in 2000, and DBS procedures have been performed at a wide range of hospitals in both the private and the state sectors.

2. Stakeholder involvement

DBS guidelines were discussed at a meeting held on 4 July 2013 in Johannesburg, SA. At the time of writing, DBS has been provided at five academic centres in the state sector: Inkosi Albert Luthuli Central Hospital (KwaZulu-Natal), Universitas Hospital (Free State) and Red Cross Children's, Groote Schuur and Tygerberg hospitals (Western Cape), although financial constraints for obtaining DBS equipment

are significant in the state sector. DBS has also been carried out at a number of private hospitals (where the bulk of procedures have been performed). Potentially, all patients in SA with PD, severe tremor and dystonia who meet appropriate criteria for undergoing DBS should be eligible for the procedure. However, restrictions due to cost, including the cost of battery replacement, as well as limitations arising from the need for trained experts in the field, impact on the potential sites where DBS may be carried out.

At the meeting, the public and patients with dystonia and PD were represented through the Parkinson's and Related Movement Disorders Association of South Africa. All the known role players who were involved with DBS at the time were invited. The following, including neurologists, neurosurgeons, neurophysiologists and neuropsychologists, and the director of the Parkinson's and Related Movement Disorders Association of South Africa were in attendance: Ms C Bottcher (Life Entabeni Hospital), Dr D G Anderson (University of the Witwatersrand Donald Gordon Hospital), Prof. N Cassimjee (University of Pretoria), Prof. J Carr (Stellenbosch University, by correspondence), Dr D Giampaolo (Netcare Rosebank Hospital), Prof. M Lucas (University of the Witwatersrand), Dr R Melvill (Mediclinic Constantiaberg and University of Cape Town), Ms I Nepal (Milpark Hospital), Dr P Slabbert (Netcare Rosebank Hospital and University of Pretoria), Dr F Snyckers (Milpark Hospital), Dr J Smuts (Life Wilgers Hospital and University of Pretoria), Dr J Vaidyanathan (Medtronic Scientific Representative), Dr R van Coller (Life Wilgers Hospital and University of Pretoria), Ms K Willemsse (Parkinson's and Related Movement Disorders Association of South Africa), Dr C Wolpe (Hillcrest Private Hospital) and Dr M Zorio (Milpark Hospital).

At the meeting, it was decided to summarise the current DBS literature and provide a practical guideline of best care for DBS in patients with PD for general practitioners, neurosurgeons, neurologists, neurophysiologists, anaesthetists and healthcare funders. The guideline was written and edited by Dr Anderson, Dr Van

Coller and Prof. Carr, representing the private and state sectors. The completed text was reviewed by Prof. J Volkmann (Department of Neurology, Würzburg, Germany), an international authority on DBS. The Parkinson's and Related Movement Disorders Association of South Africa, the Neurological Association of South Africa and the South African Neurosurgical Association reviewed and endorsed the guideline. Annual review of the guideline will be carried out by the Movement Disorders Interest Group of South Africa.

Role of sponsor. The guideline has been the voluntary effort of Dr Anderson, Dr Van Coller and Prof. Carr. The meeting was sponsored by Medtronic.

3. Cost-effectiveness

Treating PD is complex and expensive, reflecting the complexities of the disease and the many complications of therapy. It must be noted that DBS with best medical treatment (BMT) is superior to BMT alone, and depending on the study, the cost of the DBS device is recouped in medication savings alone in 3 - 5 years in the case of subthalamic nucleus (STN) DBS.^[4] Three studies were published in 2016 addressing the issue of cost-effectiveness of DBS for PD. These included a systematic review of the literature on economic studies of the use of DBS in patients with PD, including cost studies or economic evaluations expressed as cost per improvement in quality of life.^[5] Nine studies were identified, and the quality-adjusted life year (QALY) gain was higher for DBS than for BMT after 2 years. A recent study on cost-effectiveness in the USA^[6] found DBS to be cost-effective. DBS therapy resulted in a discounted QALY gain of 1.69 more than BMT (3.19 v. 1.50 QALYs). The corresponding 10-year costs for DBS and BMT were USD130 510 and USD91 026, respectively, leading to an incremental cost-effectiveness ratio of USD23 404. DBS was associated with cost increases of ~USD40 000 over 10 years. However, the cost-effectiveness profile (ratio of incremental costs to gained QALYs) was favourable. The authors concluded that 'DBS yields substantial improvements in health-related quality of life at a value profile that compares favorably to

other well-accepted therapies.'^[6] A study specifically addressing cost-effectiveness in the early motor complications group found that STN DBS was cost-effective in patients aged <61 years compared with BMT.^[7] The incremental cost-utility ratio for STN DBS compared with BMT was EUR22 700 per QALY gained. Overall, DBS reduces pharmacological treatment costs and is likely to reduce the direct, indirect and social costs of PD in the long term.

4. Evidence for DBS

The authors reviewed the available evidence for DBS with respect to benefit and harm by performing a MEDLINE search using the terms 'deep brain stimulation' and 'Parkinson', selecting the following article types: clinical trial, randomised controlled trial and review. In addition, material from personal sources and relevant textbooks was consulted.

DBS was first used for PD in 1990,^[8] and was recognised as a way to improve tremor, rigidity and bradykinesia, allowing for a reduction in levodopa use.^[9] Subsequently, DBS was believed to improve 'off'-time disability, reduce dyskinesia, improve quality of life and lead to reduction of the levodopa dose^[10] (Table 1). However, it was only in 2009 that a randomised controlled trial found DBS to be superior to BMT in improving 'on' time, reducing dyskinesias and improving quality-of-life scores.^[11] A year later, in a trial of DBS and BMT v. BMT alone for advanced PD (PD SURG), it was found that DBS and BMT were superior to BMT alone when assessing self-reported quality-of-life scores at 1 year^[12] (Table 1). Although DBS is accepted as an alternative treatment option in patients with advanced PD, the EARLYSTIM study showed a substantial benefit in younger patients (mean age 52 years) with shorter-duration PD when comparing DBS with BMT, and found significant improvement in the primary outcome of quality of life^[13] (Table 1).

The long-term benefit of DBS has now been shown in 5- and 10-year follow-up studies.^[10] DBS is still effective in managing motor symptoms 10 years after implantation. The usefulness of DBS in managing axial features of advanced PD seems to be less

Table 1. Assessment of evidence for effectiveness of DBS in PD by the PICO approach*

Reference	Population	Intervention	Outcome
Deuschl <i>et al.</i> ^[10]	156 patients with advanced PD and severe motor symptoms	DBS v. BMT	PDQ-39 Summary Index (50 of 78 pairs; $p=0.02$) improved 9.5 points UPDRS-III (55 of 78; $p<0.001$) improved 19.6 points
Williams <i>et al.</i> ^[12]	366 patients with PD not adequately controlled by medical therapy	DBS/pallidotomy v. BMT	PDQ-39 Summary Index compared with baseline: difference of -4.7 points in favour of surgical group ($p=0.001$) UPDRS-III motor 'off' (-16.8) ($p<0.0001$) 43 SAEs were surgically related
Weaver <i>et al.</i> ^[11]	PD patients with persistent disabling symptoms	121 patients randomised equally to pallidotomy or DBS v. 134 on BMT	DBS group had 4.6 hours daily improvement in 'on' time (no change in BMT group) Significant improvements in the summary measure of quality of life and in 7 of 8 PD quality-of-life scores ($p<0.001$) Largely in first 3 months, significantly greater SAEs for surgical group for falls, gait, depression and dystonia
Schuepbach <i>et al.</i> ^[13]	251 PD patients with disabling motor complications present for 3 years at most	DBS v. BMT	PDQ-39 Summary Index improved from baseline to 24 months by 26% in DBS group; worsened by 1% in the medical therapy group 26 SAEs were surgically related, all but one resolved completely

DBS = deep brain stimulation; PD = Parkinson's disease; PICO = population, intervention, comparison and outcome; BMT = best medical therapy; PDQ-39 = 39-Item Parkinson's Disease Questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale; SAEs = serious adverse events.
*In all trials, the comparison was with BMT.

robust. A neuroprotective effect from DBS could not be demonstrated.^[14]

DBS surgery is relatively safe, the commonest complications being infection, haemorrhage and transient post-surgical confusion. The reported complication rate varies widely. In a study of 526 consecutive patients with DBS implantation, haemorrhage occurred in 8.4% of all cases.^[15] Bleeds occurred at the entry point or subcortically, but rarely in the target, and more often in hypertensive patients. Asymptomatic haemorrhage occurred in 3.4% of this series of patients, and symptoms were transient in 4.4% of patients and permanent in only 0.6%.^[15] Approximately 10% of patients were reported to have transient postoperative confusion. This has been attributed to intracranial contusion, long surgery duration and dopamine withdrawal.^[16]

5. Target site

Three anatomical basal ganglia targets are suitable for stimulation in PD. The target adopted initially was the ventral intermediate (VIM) thalamus, which showed a degree of efficacy that was similar to thalamotomy for PD-related tremor, but less so for other motor features.^[17] Altering the target to the GPi resulted in improvement in all the major motor features of PD and a reduction in dyskinesia. The GPi was then replaced by the STN based on lesion studies in primates showing possibly greater efficacy.^[18]

A debate has persisted for some time about which site is preferable, the STN or the GPi. Randomised controlled trials indicate that compared with bilateral GPi DBS, bilateral STN DBS is equally effective in treating PD motor symptoms.^[19,20] The advantages of targeting the STN include good clinical effect on tremor and bradykinesia, improvement in dyskinesia and motor fluctuations, and the potential to reduce medications.^[21] The GPi continues to be a potential target, since there remain concerns that STN stimulation has a potentially greater effect on cognition and may exacerbate neuropsychiatric conditions, and programming and follow-up are typically more straightforward for GPi stimulation.^[22]

The recommended target in PD is currently the STN. In special circumstances, thalamic targets and the GPi may be considered, e.g. in elderly patients with dominant PD tremor and little progression of akinetic-rigid symptoms (VIM), or frail patients with prominent dyskinesia, who might not tolerate the complex and lengthy postoperative adjustment of medication and stimulation required in STN-DBS.

6. Referral of patients for DBS

The decision when to refer for DBS is not based on level 1 evidence and is currently the subject of ongoing debate and investigation. Most specialists agree that the optimal time to refer is when patients have medication-refractory motor fluctuations, or dyskinesias or tremor that are resistant to treatment.

It is important to emphasise that delaying referral may cause harm, since it is accepted that the best DBS outcomes are seen in patients who are younger, responsive to dopamine and do not have significant gait problems. PD patients should be considered for DBS if:

- PD diagnosis is established
- Age at time of surgery is (ideally) <75 years
- Troublesome motor fluctuations or resistant tremor are present
- Dopamine responsiveness is present
- Cognition is normal or minimally impaired
- Gait is impaired, but shows dopamine responsiveness.

Most units will require patients to be known to have PD for >5 years in order to exclude patients with atypical parkinsonism. Patients with

atypical parkinsonism respond poorly to DBS even when there was previously documented response to levodopa.

Although age has not been found to be a specific prognostic indicator in DBS for PD, increasing age is associated with a number of factors that should be considered: medical comorbidity, decreased cognitive ability, levodopa resistance and increased surgical risk. The recommendation is that patients aged >75 years should only be considered in special circumstances.

Accumulating long-term evidence in DBS treatment of PD shows poor response of gait and postural instability to stimulation treatment. Some aspects of gait and posture may improve initially after DBS surgery owing to lengthening of stride and improvement of initiation of gait, but rhythmicity and cadence do not seem to improve. The gait features that do improve are usually responsive to levodopa, and these can be used to predict improvement following surgery. Of note, in some patients, gait may even deteriorate after surgery.^[23] In the long term, patients with advanced PD may have progressive issues with gait, freezing of gait, and balance and posture, and these features are not effectively addressed by STN DBS.^[24] DBS should only be considered in patients with gait and balance impairment where there is proven levodopa response in these domains prior to surgery. Patients should be informed of the possible deleterious effect on gait and balance after surgery, and similarly should be made aware that gait and balance will not respond well to DBS in many cases.

Alternative targets for patients with gait-predominant PD are being explored, but no alternative target has been shown to be effective.^[23]

7. Patient selection/assessment

The patient selection process consists of assessing the patient for suitability for surgery and dopamine responsiveness, and a neurocognitive evaluation (sometimes with psychiatric assessment).

7.1 The DBS team

More than 30% of DBS surgery failures can be attributed to inappropriate patient selection.^[25] Each patient needs to be selected according to their individual risk-benefit profile at an expert centre, by a multidisciplinary team consisting of an experienced neurologist, neurosurgeon and neuropsychologist. This also allows for the patient's expectations to be managed realistically. An expert centre should be able to produce an audit of results. Other members of the team, but not necessarily seen by every patient, are a neurophysiologist, psychiatrist, anaesthetist and neuroradiologist, and ideally a nurse with experience in movement disorders.^[26]

7.2 Dopamine challenge test

The degree of responsiveness to levodopa is considered to be the best predictor for DBS outcomes.^[15] The dopamine challenge test is performed after a period of dopamine withdrawal (at least 12 hours) with the patient in the worst 'off' state. Special attention must be paid to dopamine agonist withdrawal, since these drugs have relatively long half-lives that may affect the assessment of the response to the dopamine challenge test. A Unified Parkinson's Disease Rating Scale (UPDRS) III is scored in this state. The patient is then given levodopa orally. The dose can vary from 100 to 250 mg. After at least 1 hour, the UPDRS is scored in the best 'on' state. A 30% improvement is generally considered acceptable to proceed to surgery.^[27] This has been the operational definition for many clinical trials. In clinical practice, however, the quality of the 'best on' is more important. In particular, the degree of levodopa-resistant symptoms should be critically evaluated and then discussed with the patient.

7.3 Neuropsychological testing

Cognitive dysfunction is common in PD, and ranges from mild cognitive impairment to dementia.^[28] As DBS can impact variably on post-surgical cognitive functioning, and frequently worsens functions that are associated with the frontostriatal areas, cognitive status should be known before surgery.^[29-32] It is recommended that all patients should be assessed before deciding about surgery, and that the assessment of cognitive functioning be carried out by a clinical psychologist with specialist knowledge of neuropsychology, or a neuropsychologist. Recommendations for the assessment of cognitive function in PD have been published.^[28,33]

In SA, there are few local normal values for standard neuropsychological tests. Education level and not speaking English as a first language can influence the outcome of these tests by as much as two standard deviations. The neuropsychologist should therefore use both quantitative and qualitative approaches where appropriate. The underlying mood of the patient, other medical conditions, and whether the patient is in the treatment 'on' or 'off' state can all affect the test outcome.^[33]

The presence of significant cognitive impairment in a PD patient is an exclusion factor for DBS surgery, particularly if a patient's test profile on a comprehensive battery of neuropsychological tests indicates impairment of one or more measures of executive function. The presence of mesiotemporal memory impairment (poor encoding rather than impaired recall) should alert the neuropsychologist to cognitive impairment of a different type to that usually observed in executive dysfunction, and suggest further caution regarding a decision to proceed to surgery. Individuals with PD who score in the borderline range are more susceptible to subtle decline in cognitive functioning after surgery,^[34] and caution is advised.

8. Surgery

DBS can be done awake with radiological (magnetic resonance imaging (MRI)/computed tomography (CT)), electrophysiological and clinical guidance or asleep with MRI-based guidance and verification of the anatomical target. Both forms of surgery are acceptable and have proven outcomes, and units should use the method with which they are most familiar.

Awake surgery is performed in two phases. The first phase is the stereotactic implantation of the stimulating electrodes in the STN. This is usually performed in the awake state to allow for electrophysiological recording and stimulation to assess for benefits and side-effects. A stereotactic system that maps image space to physical space is used to deliver the stimulating electrodes to the STN. The trajectory of the electrode is set to avoid critical structures of the brain, including blood vessels, sulci and ventricles. Microelectrode recording (MER) from individual neurons is typically used to identify the neuronal firing patterns during surgery to confirm correct positioning. The second phase is the internalisation of the neurostimulator, performed under general anaesthesia. This involves connecting the stimulating electrodes to the neurostimulator. Both phases can be done in one session.

In MRI-guided and verified surgery, the patient receives full anaesthesia throughout the surgery, and planning and verification of lead placement is done by MRI with the stereotactic frame on.^[35] In this case, there is no requirement for intraoperative neurophysiological recordings, resulting in possible benefits in terms of surgical adverse effects and theatre time.

Pre- and post-surgical imaging form an essential part of both surgical techniques and are discussed in section 10. Both techniques (awake and asleep) have similar outcomes with regard to motor function and reduction in dyskinesia.^[11,35]

9. Neurophysiology (MER and macroelectrode stimulation (MES))

Despite advances in imaging, most units around the world rely on electrophysiological and clinical localisation to confirm and refine the radiological target.^[36] The first phase in intraoperative electrophysiology is to perform MER. Up to five test electrodes can be advanced simultaneously in micrometric steps to the radiological target and beyond. The different anatomical targets in the basal ganglia each have a unique electrophysiological footprint that defines the boundaries of the target.

The second phase in the determination of the physiological boundaries of the target involves electrical stimulation with a macro-test electrode. MES is done to assess clinical effect and stimulation-related adverse effects before permanent placement of the DBS lead. Someone trained in movement disorders, such as a neurologist, neurosurgeon or specifically trained PD nurse, should perform the assessments.

Stimulation is performed using a constant-current stimulator on the MER system with standard settings. Monopolar stimulation at predefined intervals is done in incrementing current strengths (generally 1 - 5 mA) to assess the area delineated by MER and imaging.

Clinical benefits of acute intraoperative MES are monitored with contralateral wrist rigidity, tremor and bradykinesia.^[37] When there is little or no clinical effect at amplitude settings of up to 3 mA, it should be considered that the position in the STN is not optimal.

Side-effects secondary to stimulation include contralateral muscle contractions and/or eye deviation. Side-effects are classified as transient or persistent and mild, moderate or severe. Only stimulation-induced side-effects after the supramaximal threshold are considered acceptable to choose a trajectory for implanting the permanent DBS lead. A combination of acceptable clinical effects on tremor, rigidity and bradykinesia without the induction of persisting adverse effects is required to assure optimal lead placement.^[36]

10. Imaging

10.1 Imaging before surgery

Imaging the brain is essential for the preoperative target planning in DBS. Acceptable imaging modalities for targeting include MRI, CT and ventriculography. T2-weighted imaging or susceptibility-weighted imaging (SWI) is generally considered useful to delineate the target and to indicate which neighbouring structures to avoid, and at least 1.5 Tesla field strength is recommended. Whole-brain T1-weighted imaging with contrast is used for planning and ensuring a safe trajectory to the target and verifying the entire course from cortical entry to target.^[26]

10.2 Imaging after surgery

Post-surgical imaging is somewhat controversial. The majority of units agree that some form of imaging is necessary to ensure that the leads are in position. This then acts a reference point in the case of subsequent limited benefit, adverse effects or lead displacement. In a consensus document, a CT scan was judged to be adequate, but MRI was generally seen as superior to CT.^[26] However, there is concern in performing MRI following DBS, as it can result in heating of the leads, magnetic field interactions and movement of the components, induced currents, and functional disruption of the DBS components.^[38] Carefully following manufacturer guidelines permits the use of conditionally safe MRI scans to audit the lead location. Larson *et al.*^[39] demonstrated safety in >1 000 MRI examinations. The DBS Study Group of

the National Parkinson Foundation has scanned >3 304 patients without any complications.^[40]

Our recommendation is that post-surgical imaging with at least CT imaging with a presurgical MRI merge is necessary, although post-surgical MRI is preferred.

11. Programming

Programming of the device is as important as accurate electrode placement in ensuring successful treatment. To ensure the full benefit of this specialised treatment, programming should be done by a trained specialist. Managing programming cannot be done in isolation from medication adjustments and other treatments, so a neurologist with training or experience in DBS should preferably be in charge of programming.

The programming process consists of the initial programming, follow-up sessions in the weeks after surgery, and long-term follow-up once symptom control and medication adjustment are stable.

The standard DBS electrode consists of four 1.5 mm cylindrical contacts each spaced 0.5 mm from one other. Various programming options can be used to maximise the clinical effect. These include the use of different contacts in mono- or bipolar mode and adjusting the voltage/current, pulse width and frequency of stimulation.^[41]

The initial programming is patient specific and depends on the microlesion effect (positive surgical effect that can last several weeks), the side-effects of stimulation, the patient's stamina and whether bilateral stimulation is required. Initial programming should preferably be done when the patient is in the off-medication phase.^[41]

Initial follow-up programming sessions address habituation of the stimulation effect and the complete resolution of the microlesioning effect after surgery. Increases in stimulation are generally required, although in some patients other parameter changes may prove necessary. Checking of impedance (resistance of the electrode and electrode-tissue barrier to electrical stimulation) and battery life is advised. Careful documentation of each programming session is very important for future reference.

Long-term follow-up includes device and battery checks, and adjustment of stimulation and medication to allow for symptom control with progression of disease. Intervals are patient specific.

12. Managing pharmacological treatment

The aim of DBS is not to withdraw medication completely, but to improve the patient's quality of life. Medication reduction and post-surgical management need to be done by an experienced neurologist with an understanding of DBS and medication interactions. Special care in terms of the dopamine agonist withdrawal syndrome is required.^[42] When adjusting DBS programming, medication adjustments must be made in parallel. Stimulation should improve parkinsonian signs; dopaminergic drugs can be slowly reduced if this is seen. Dyskinesias are often increased with STN stimulation for a short time after stimulation is initiated, another reason for medication reduction.^[15] Sudden stopping of dopaminergic therapy can result in withdrawal syndromes.^[43] These include motor and delayed non-motor symptoms such as apathy and depression. STN stimulation may result in euphoria or even hypomania with a dopamine dysregulation syndrome, which requires dopamine reduction. DBS patients must be assessed regularly to optimise both motor and behavioural states, by titrating stimulation with levodopa to avoid akinesia or dyskinesia, and by careful adjustment of medication to avoid apathy or impulse control disorders.^[44]

13. Recommendations

Based on the outcome of the initial workshop, review of the literature, consultation with patient groups and input from an external expert consultant, the following are the key points concerning the management of DBS in PD:

- DBS is a safe and effective treatment for carefully selected patients with PD (section 4).
- Patients should be carefully selected for symptoms that are known to respond to DBS (section 6).
- Patients need to undergo dopamine challenge testing to assess the degree of response to dopamine (section 7.2).
- Patients should undergo neuropsychological testing, and the presence of significant cognitive impairment is usually a contraindication to DBS (section 7.3).
- Currently, several radiological approaches to selecting an appropriate target may be used, and both intraoperative physiological recordings and MRI-verified approaches are valid methods of performing DBS (sections 8 and 9).
- Careful follow-up and programming of the DBS system is mandatory, and a major reason for DBS failure is inadequate programming and management of medication (sections 11 and 12).

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RvC has received payment for talks from Cipla South Africa, and sponsorship for travelling to attend congresses from Medtronic. He is also the recipient of a research grant sponsored by Medtronic.

JC has received payment for talks from Cipla South Africa, and has attended a number of training sessions at Netcare Pretoria East, as well as at Christian-Albrechts-University, Kiel, Germany (both sponsored by Medtronic). He is a participant in the neurologists' training programme with attendance at the National Hospital, London, and in Tolochenaz, Switzerland (a Medtronic-sponsored programme). He receives an annual stipend from Elsevier for his role as an associate editor.

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