Where are we with surgical therapies for Parkinson's disease?

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SUMMARY

Surgical therapies are now widely accepted in the treatment of medically refractory Parkinson’s disease or levodopa-related side effects. Neuromodulation using deep brain stimulation (DBS) is currently the most well-known surgical treatment, however other developing technologies are emerging. We briefly review active research areas in the field of DBS including timing of surgery, target selection and localization under general anesthesia and developments in closed loop stimulation systems. We then describe other evolving modalities such as lesioning using MR guided focused ultrasound and biological therapies.

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1. Introduction

Parkinson’s Disease (PD) is one of the most common neurodegenerative diseases with an estimated prevalence of 1% in adults over the age of 60 [1]. The hallmark of PD is neurodegeneration of substantia nigra pars compacta dopaminergic neurons with the resultant widespread loss of dopaminergic innervation, but more widespread degeneration also occurs and is being increasingly recognized [2]. Current medical therapies for PD, including carbidopa–levodopa, produce marked improvement in the cardinal motor symptoms of parkinsonian patients. Chronic use of levodopa however, is often limited by the appearance of long-term side effects including an overall loss of drug effect throughout the course of the day (“wearing off”), fluctuations in efficacy (“on–off” fluctuations), and involuntary movements now recognized as levodopa-induced dyskinesia (LID). These complications are observed in as many as 45% of patients treated with levodopa for more than 5 years [3,4]. LIDs and motor fluctuations can cause considerable disability in PD patients and are a major reason to recommend surgical treatment [4].

Surgical interventions have become widely accepted in the treatment of PD, mainly as a symptomatic adjunct to levodopa therapy due to limiting side effects of prolonged levodopa administration [4]. The most well-known and studied neurosurgical procedures are radiofrequency (RF) lesioning and deep brain stimulation (DBS) of basal ganglia nuclei. Both of these approaches aim to modulate network activity within relevant brain circuits in the disease state. Several randomized clinical trials have shown that deep brain stimulation of basal ganglia nuclei such as the subthalamic nucleus (STN) and globus pallidus internus (GPI) have a beneficial effect on the motor symptoms of PD compared to best medical treatment alone [5,6]. The safety, efficacy, and reversibility of DBS make it the current surgical method of choice for the treatment of dopamine responsive symptoms of PD and improvement of motor fluctuations as well as LIDs. Over the last two decades there have been over 100,000 patients implanted with DBS, however there are still several open questions in the field including: (i) when in the course of the illness should the surgery be performed, (ii) what is the optimal target for stimulation, (iii) what is the best method for target localization, (iv) treatment options of non-motor symptoms (non levodopa responsive symptoms) and (v) is there any evidence for any disease modification with DBS?

2. Timing of surgery

Traditionally DBS surgery has been performed on patients with advanced PD. Recently the potential advantages of the role of DBS earlier in the course of the disease has become an active area of investigation. To this end, Schüpbach et al. (2013) undertook a multicenter, randomized trial named EARLYSTIM. The goal of the trial was to compare best medical treatment alone to early DBS plus best medical management. The study patients were younger than 60 with early stage disease (Hoehn and Yahr stage <3) and had a short duration of motor complications. EARLYSTIM demonstrated that compared to best medical treatment alone, DBS performed early in the course of the disease had significant benefits on the primary outcome measure of subjective quality of life measured at 2 years post surgery (26% improvement vs. 1% decline in the 39-item Parkinson Disease Questionnaire) as well as on secondary outcome measures of objectively assessed motor functions (assessed using the UPDRS and good mobility time). In addition the investigators found a significant reduction in levodopa-induced motor complications in the DBS group. The findings of the EARLYSTIM trial suggest that early surgery should be...
considered for young patients (<60 years) who develop levodopa-induced dyskinesia or motor fluctuations. However, performing DBS in younger patients raises several questions concerning the long-term outcome and the potential for increased risk of subsequent complications [6]. The effectiveness of DBS has been demonstrated up to 10 years after the surgery [6,7], however the longer patients will live with implanted hardware the longer they are exposed to the risks of repeated surgical interventions due to hardware failure and unavoidable pulse generator changes. These issues could be partly overcome by advancements in technology such as rechargeable DBS systems.

Another issue to consider are neurocognitive and psychiatric side effects of DBS. Concerns about neurocognitive decline following bilateral STN DBS have been raised [7,8,9] and although evidence is not consistent across studies [8,9,10] the long-term risks need to be evaluated in the context of prolonged lifetime exposure to stimulation. Psychiatric effects such as dysphoria [9], impulse control disorders [10] and even suicide have been reported after STN stimulation [11]. Although in the recent EARLYSTIM trial no difference was detected between the DBS and medical therapy groups with respect to suicide risk, the frequency of suicidal ideation and attempts warrants close follow up in all surgical patients by a multi-disciplinary team.

In contrast to the concerns just raised, implanting DBS earlier in the course of the disease opens exciting possibilities as to the effect of neuro-modulation on relatively spared brain circuits. While it might not directly counteract the progressive dopaminergic cell loss, it could alter the physiological changes that develop in basal ganglia neural circuits. As such it might potentially delay the development of motor complications, and serve as a disease-modifying treatment. This possibility certainly will require close study as the patients who undergo early DBS are closely followed.

3. Target selection for L-dopa responsive and non-responsive symptoms

Our understanding of the basic pathophysiological processes in the brain allows DBS therapy to be tailored to the individual patient applying DBS to different nodes of the basal ganglia circuit in order to alleviate the various symptoms of PD. The most common targets currently used for PD patients are the GPi and STN nuclei (Fig. 1). DBS in these locations significantly alleviates the typical parkinsonian symptoms of tremor, rigidity, bradykinesia and dopamine-related involuntary movements. There has been a long-standing debate in the literature regarding the optimal target between the two [9,12,13,14]. GPi was the first target used for PD [13,14]. Since the description of STN DBS by Benabid et al. [15] in 1994 the pendulum has shifted towards STN as the preferred target in many centers. However, recently, due to concerns about neurocognitive and psychiatric side effects with bilateral STN DBS, interest has re-emerged in GPi as the target for stimulation or consider a multifocal DBS approach, for example implanting stimulating electrodes in both a motor and a gait [15,16,17] or a cognitive node [16,18].

Gait requires the coordinated activation of multiple muscle groups in the limbs and trunk. This pattern of activity which characterizes locomotion, is produced by specialized neural networks in the spinal cord that are controlled by locomotion centers in the brainstem. In humans the pedunculopontine nucleus region (PPN), a midbrain structure that receives both basal ganglia and spinal cord feedback, has been implicated as the locomotor center. Results from several series have shown that patients undergoing DBS of the PPN (Fig. 1) demonstrate improvement in gait with less frequent falling, although not necessarily accompanied by an objective motor improvement as assessed by the UPDRS part III [15,16,17,18]. Combining stimulation of the PPN with STN group. Although the authors of the NSTAP study conclude that STN is the preferred target, this debate will probably remain unresolved for the time being, with DBS of both the STN and the GPi considered effective in treating the major motor manifestations of the disease.

It is increasingly clear that PD is a multisystem degenerative disorder with a broad range of manifestations ranging from gait disturbances and postural instability to a wide variety of psychiatric and autonomic disturbances [13]. Long-term studies have shown that 20 years after the diagnosis of PD 83% of patients develop dementia and a similar number suffer from gait problems and recurrent falls [14]. It is becoming evident that the neuroanatomical substrates responsible for the non-motor manifestations of PD are separate and distinct and that DBS of the basal-ganglia nuclei does not address these issues. Given that these non-motor symptoms can cause significant impairment to patients and may also prevent patients from undergoing DBS surgery due to the risk of aggravating neurocognitive and psychiatric symptoms it is becoming increasingly important to consider novel potential deep brain targets for stimulation or consider a multifocal DBS approach, for example implanting stimulating electrodes in both a motor and a gait [15,16,17] or a cognitive node [16,18].

**Fig. 1.** (A–C) Magnetic resonance images (axial T1) from 3 patients with PD demonstrating the position of DBS electrodes in (A) bilateral PPN, (B) bilateral STN and left PPN, and (C) bilateral GPi. (D) T2-weighted MR image showing a thermal lesion in the left Vim performed using MR-guided focused ultrasound in a patient with essential tremor.
STN might provide additional benefit addressing both the dopa-responsive motor symptoms as well as gait and balance issues [e17]. The optimal target location, whether uni- or bilateral stimulation of the PPN and stimulation parameters are still not defined and await further controlled studies.

Given the clinical experience using DBS in sub-callosal cingulate gyrus and nucleus accumbens in the treatment of MDD [17, e20, e21] and promising initial results of improvement in memory using DBS of the fornix in early Alzheimer’s patients [e22] it has been suggested to develop DBS procedures that target both motor and neurocognitive symptoms of PD [16,18]. In a recent case report Freund et al. describe improvement in cognitive functions in a patient with PD-dementia during low-frequency (25 Hz) stimulation of electrodes in the nucleus basalis of Meynert (NBM) [19]. The patient developed dementia after implantation of DBS electrodes in the STN and then underwent implantation of DBS electrodes in the NBM bilaterally. The authors attribute these cognitive effects to the stimulation of cholinergic projections form the NBM to cortical structures. Sequential multi-focal approaches such as this may hold promise in the future but careful study is required as this will certainly add further layers of complexity to patient selection and subsequent post-operative management.

4. Targeting and surgery under general anesthesia (GA)

The success of surgery depends on accurate lead placement in the target nucleus. This has been traditionally achieved by combining preoperative stereotactic planning with intra-operative microelectrode recording (MER) for physiological verification of the target nucleus, and macro-electrode stimulation to determine the therapeutic range between the clinically effective stimulation parameters and the development of off-target side effects. This usually mandates the procedure be performed on awake cooperative patients under local anesthesia. However performing awake surgery in patients with PD, who are older and physically debilitated, also has drawbacks such as patient anxiety, fatigue and reduced cooperation necessary for clinical testing. Performing intraoperative MER also adds to the complexity of the procedure, requiring special equipment and expertise, and significantly adds to intraoperative time.

Advanced high field MRI sequences now allow direct visualization of deep brain target centers [20,e23–e27], which could potentially replace physiological identification. Indeed, the necessity of MER has been a matter of debate in the literature, with some reports of adequate lead placement under GA without MER with comparable clinical results [e28]. However, it is still widely accepted that verification of adequate lead placement will still be necessary due to intraoperative brain shifts due to egress of cerebrospinal fluid after the dura is opened. Recently the possibility of implanting DBS electrodes under direct image guidance using intraoperative real-time imaging has been explored. These methods could simplify DBS implantation by eliminating the need for physiological recording and patient cooperation. Several reports have demonstrated comparable accuracy and clinical efficacy compared with that of anatomical guidance using standard frame-based stereotaxy in conjunction with intra-operative MERS.

Starr et al. have reported their experience in MR guided implantation of DBS electrodes in 29 patients with PD [21]. Using a frameless system and interventional intraoperative MRI guidance, patients underwent DBS electrode placement under GA. Anatomical satisfactory lead placement was confirmed using intraoperative 1.5 T interventional MRI, and no MERS were used. Clinical results showed comparable clinical improvement using the UPDRS part III at 9 months post surgery. Recently the same group has reported initial accuracy results using a second-generation system in 60 patients, reporting an improved accuracy in DBS electrode placement [e29]. Burchiel et al. describe placement of DBS electrodes under GA using the NexFrame and intraoperative CT for verification of lead placement; no clinical outcome data was reported, but accuracy of lead placement was comparable to other reports using MERS [22].

Surgery under GA has the potential to decrease patients’ anxiety thereby making it more accessible for patients reluctant to undergo awake surgery. Furthermore, this approach will also address the need for a patient to stop his/her medications before surgery for the purpose of identifying pathological single cell activity with MER and facilitation of eliciting clinical improvement with stimulation. Surgery under GA thereby minimizes painful “off” dystonia and back pain from prolonged head fixation and immobility. Reduced operative time and more rapid mobilization of patients could also potentially decrease risk of complications such as deep venous thrombosis.

5. Closed-loop DBS

PD-related symptoms fluctuate during the day and may also gradually worsen over time. Present-day DBS therapy however uses constant stimulation settings that are changed only once every few weeks-to-months at movement disorder clinic appointments. This may lead to suboptimal clinical results and increased battery drain. Developing an adaptive DBS system that can meet changing physiological conditions on a continuous basis by modulating stimulation parameters in a feedback loop would potentially optimize DBS therapy. This could lead to improved clinical results and decreased battery usage and frequency of battery replacement.

The main problem is identifying a suitable neurophysiological signal to serve as a control variable for closed-loop DBS. A study in non-human primates suggested that adaptively controlled DBS triggered by feedback from the spikes of a single motor cortical neuron was more effective than standard continuous high-frequency stimulation in a model of PD [23]. The researchers used spike detection in M1 to initiate a short pulse train delivered to the GPi. However, since DBS leads are implanted in the basal ganglia the most accessible neurophysiological signal would be basal ganglia activity recorded through the DBS electrodes themselves. This could include beta oscillations (13–30 Hz), which have been shown to be correlated with pathological clinical symptoms of PD. A recent study in Parkinson’s patients who underwent STN DBS has found that beta-oscillations were limited to the dorsolateral motor region within the STN [e30]. In addition, the active stimulated DBS contact chosen on clinical grounds coincided with that region. These findings suggest that characteristics of abnormal STN activity may be used for DBS optimization.

In a recently published paper Little et al. describe a proof of concept of adaptive STN DBS using beta oscillations as the control variable [24]. Their adaptive DBS system achieved significantly better improvements in motor scores compared to continuous stimulation, with an accompanying reduction in energy consumption. These studies suggest that brain–machine interface controlled DBS is feasible and potentially more efficient and efficacious than conventional continuous neuromodulation for PD. Optimal control signals for brain–machine interfaces and stimulation parameters still remain to be determined and the clinical value of such closed-loop DBS systems will require well designed clinical studies. Such closed-loop DBS systems are already in use in the field of epilepsy [e31] and could be adopted to PD in the future.

6. Lesioning using MR-guided focused ultrasound

Lesioning of basal ganglia structures was a very common treatment for parkinsonian symptoms prior to the development of L-dopa...
in the 1960s [e32]. The first target that was used was the Vim nucleus of the thalamus, which produced tremor reduction, however bilateral thalamotomies carry a high risk of cognitive and speech side effects. Later, pallidotomy was shown to improve also the bradykinesia and rigidity of PD in addition to tremor, with possibly fewer side effects. The development of DBS with the advantages of being reversible and adjustable and therefore with fewer permanent side effects has pushed lesioning procedures out of favour and they are now usually reserved for patients who are considered poor candidates for DBS or who require only unilateral surgery. However, implanted neurostimulators are expensive, labor intensive to manage, and require continuous maintenance with replacement of the pulse generator every 2–6 years. The risk of hardware complications, such as mechanical breakdown or infection, is about 2–8%. The risk of intracranial hemorrhage during DBS is approximately 2–3%, with approximately half of these asymptomatic [e33].

Recently, MR-guided focused ultrasound (MRgFUS) has proven to be an attractive modality for non-invasive thermal ablation of soft tissue. The technique uses focused ultrasound energy stereotactically transmitted through an array of 1024 ultrasound transducers to produce ablative lesions. Targeting is based on stereotactically guided high-precision MRI and the lesion is created in real time using MRI thermometry. The ability to monitor the temperature in real time enables the creation of sub-threshold temporary lesions in order to test for clinical effects and side effects before the permanent sonication lesion is created.

Building on the experience with MRgFUS in the management of essential tremor and neuropathic pain [25,26], this technique could also be used to treat PD tremor. In addition, pallidotomy using MRgFUS has been proposed as a treatment alternative for dyskinesia of PD. Given the favorable adverse-event profile of focused ultrasound, its efficacy in numerous disorders throughout the body, its instantaneous effect, as well as the built-in ability to provide a test lesion prior to a permanent lesion, MRgFUS is an attractive option for the management of movement disorders.

7. Biological therapies

An alternative therapeutic approach explored in recent years is to biologically modify the degenerated neural circuits through direct trophic factor infusion (GDNF studies), gene therapy or cell-based therapies.

Several trials have been conducted in recent years using gene transfer into the CNS by the stereotactic injection of viral vectors into deep brain nuclei with promising results. The vector used in most recent trials was an adeno-associated viral type-2 (AAV2) vector. Approaches have varied from transfecting with genes encoding for trophic factors such as Neurturin in an attempt to counteract the neurodegenerative process, to transfecting with the gene encoding glutamic acid decarboxylase (GAD), the rate-limiting enzyme for GABA production into the subthalamic nucleus in an attempt to modulate basal ganglia activity. The recently published randomized, double-blind (sham operated) clinical trial of bilateral stereotactic delivery of AAV2-GAD gene into the STN [27] showed improvement at its primary outcome measure of improved UPDRS motor score at 6 months. In another double-blinded controlled trial, AAV2-neurturin (CERE-120) treatment to the Putamen bilaterally, although failing to meet its primary outcome of UPDRS improvement at 12 months, was associated with benefits in UPDRS at 18 months compared to sham-operated controls [28]. These studies establish a ‘clinical proof of concept’ for gene transfer to the CNS and provide promising evidence for clinical benefit of gene therapy in PD. A number of other trials involving gene therapy with delivery of coding sequences for enzymes involved in dopamine production and metabolism have also been pursued. Although not counteracting the basic disease process, dopaminergic cell transplants potentially could induce behavioural recovery by dopaminergic reinnervation of the striatum. As such they should be regarded as producing a constant steady infusion of dopamine into the striatum with the potential to produce beneficial motor effects comparable to L-dopa therapy, replacing the need for the drug. Attempts to replace the degenerated dopaminergic neurons in the brain of patients with PD have been done since the 1980s, using mainly human fetal ventral mesencephalic allografts. Two double-blind placebo-controlled trials have been conducted [29,30], and although both trials have failed to show significant improvements in their primary outcome measures, they have shown promise as a proof of principle that implanted cells can survive in the brains of Parkinson’s patients [e34]. Clinical results have been inconsistent across published studies, and were also associated with side effects such as graft-induced dyskinesias possibly related to the presence of serotonergic neurons in the grafts. Part of the inconsistency in the clinical outcome can probably be attributed to the lack of standardization between studies as to patient selection, technique of transplant, neural tissue preparation and outcome measures. A prerequisite to the further development of cell-based therapies would be the development of stable, homogeneous and reliable cell sources for transplantation, and to standardize their implementation in clinical trials. The ongoing multicenter Transeuro trial aims to shed light on these topics and will have a significant impact on the future of cell-based therapies for PD [e35].

These novel therapies while promising will have the significant challenge of demonstrating clinical efficacy over improved symptomatic treatments, including new dopaminergic agents and DBS.

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Conflict of interests

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Appendix A. Supplementary references

Supplementary references associated with this article (cited as e1, e2, etc.) can be found online at DOI: 10.1016/S1353-8020(13)70044-0.

References


