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Current Topics in Deep Brain Stimulation for Parkinson Disease

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Abstract

There is a long history of surgical treatment for Parkinson disease (PD). After pioneering trials and errors, the current primary surgical treatment for PD is deep brain stimulation (DBS). DBS is a promising treatment option for patients with medically refractory PD. However, there are still many problems and controversies associated with DBS. In this review, we discuss current issues in DBS for PD, including patient selection, clinical outcomes, complications, target selection, long-term outcomes, management of axial symptoms, timing of surgery, surgical procedures, cost-effectiveness, and new technology.

Key words: Parkinson disease, deep brain stimulation

Introduction

There is a long history of surgical treatment for Parkinson disease (PD).[1,2] James Parkinson published "An essay on the shaking palsy" in 1817. However, the etiology and cure for this intractable disease long remained unknown. The concept of the extrapyramidal tract was proposed in the 1920s and direct surgery on the basal ganglia was attempted. In 1947, Spiegel and Wycis developed a stereotactic frame for humans, enabling less invasive surgery on the extrapyramidal tract.[3,4] Stereotactic pallidotomy or thalamotomy was subsequently developed for the treatment of PD. However, the use of surgical treatment rapidly declined after the introduction of levodopa in 1969. Dopamine replacement therapy became a mainstay of the treatment of PD. However, some patients suffered from motor complications of dopaminergic medication such as fluctuation or dyskinesia. In 1992, Laitinen revived pallidotomy for patients with motor complications from levodopa.[5]

A noteworthy event clarified the pathophysiology of PD. An American student used a synthetic narcotic drug contaminated with 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP) and developed parkinsonism shortly thereafter. Langston demonstrated that MPTP was a neurotoxin causing PD in 1983.[6] Consequently, an animal model for PD using MPTP was developed and the pathophysiology of PD was clarified. In 1989, Albin et al. demonstrated the functional anatomy of the basal ganglia related to the pathophysiology of movement disorders.[7] Shortly after, Bergman et al. demonstrated that motor symptoms of MPTP-treated monkeys were dramatically improved by lesioning of the subthalamic nucleus (STN).[8] In 1993, Benabid and colleagues developed deep brain stimulation (DBS) of the STN and achieved great success.[9]

After pioneering trials and errors, the current primary surgical treatment for PD is DBS. To date, more than 100,000 patients worldwide have undergone DBS. DBS is a promising treatment option for patients with medically refractory PD. However, there are still many problems and controversies associated with DBS. In this review, we discuss current issues in DBS for PD including patient selection, clinical outcomes, complications, target selection, long-term outcomes, management of axial symptoms, timing of surgery, surgical procedures, and new technology.

Patient Selection

There is no radical cure for PD. Therefore, all treatments for PD are symptomatic. First-line treatment

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for PD is medical. In considering indications for DBS,[10,11] a correct diagnosis of idiopathic PD is essential. An initial good response to levodopa is a good indicator of a correct diagnosis of PD. Atypical parkinsonism or secondary PD are not the indications for DBS because of the poor response to surgery.[12] The most appropriate surgical candidate for DBS is a patient who suffers from the motor complications of dopaminergic medications such as fluctuation and dyskinesia. A patient who suffers from disabling tremor despite optimal medical treatment is also a good candidate for DBS. Furthermore, the potential candidate should have no dementia or active psychiatric issues. Ideally, the patient should also be young (i.e., <70 years of age), although carefully-selected older patients can also respond favorably.[13,14] Some experts recommend excluding patients on the basis of a mini-mental state examination cutoff score of 23 or 24.[10]

As described below, STN DBS can reduce the dose of antiparkinsonian dopaminergic medication with improved motor function. Therefore, it is indicated for patients suffering from medication-induced psychotic symptoms such as hallucinations and delusions. There is some evidence to support this concept.[15,16]

EARLYSTIMULUS is an online tool developed to support decision making on indications for DBS. This tool can be freely accessed at www.earlystimulus.com. It is based on the expert opinion of 82 international DBS neurologists and neurosurgeons.[17] In this tool, eight variables (age, PD duration, off-motor symptoms, dyskinesia, tremor, levodopa-unresponsive gait and balance abnormality, and non-motor side effects of medication) are assessed for patients who meet five absolute criteria. It is specially designed to guide general neurologists in identifying appropriate referrals to a DBS surgical center.

Clinical Outcomes

The theoretical target of DBS based on the pathophysiology of PD is the STN or the globus pallidus internus (GPi). An early comparative study revealed the superiority of STN DBS in improvement of motor scores in the medication-off period and reduction of dopaminergic medication.[18] Consequently, the STN has long been the most common target of DBS for PD.

STN DBS results in a significant reduction in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score in the medication-off state but does not alter the score in the medication-on state. STN DBS effectively improves levodopa-responsive symptoms of PD and significantly reduces dyskinesia, motor fluctuation, and the dose of dopaminergic medication. Several controlled randomized studies demonstrated that STN DBS yielded better outcomes in motor function and quality of life (QOL) than medical treatment alone for patients with advanced PD.[19–21]

According to a meta-analysis of early outcomes, STN DBS improves UPDRS III motor scores in the medication-off state by 52% and UPDRS II activities of daily living (ADL) score by 50%. STN DBS also reduces dyskinesia by 69%, the daily-off period by 68%, and the dose of dopaminergic medication by 56%. Average improvement in quality of life (QOL) using PDQ-39 is 35%.[22] These numbers seem to be benchmarks when STN DBS is introduced. Thus, STN DBS provides a second honeymoon period for patients suffering from the motor complications of dopaminergic medication.[23]

There are several reports concerning the effect of DBS for postural abnormality in PD.[24–26] Postural abnormality such as camptocormia or Pisa syndrome could be corrected by DBS in some patient although the long-term benefit is limited. Early introduction of DBS after onset of postural abnormality seems to be beneficial.

The effects of DBS on non-motor symptoms have been investigated.[27–29] Some studies demonstrated that STN DBS improves gastrointestinal and urinary autonomic function. Arai et al. demonstrated that STN DBS improved gastric emptying by altering the neural system that controls gastrointestinal function.[30] STN DBS also improves urinary tract symptoms in PD such as hyper-reflexic bladder by modulating cortical control of the bladder.[31–34]

STN DBS improves insomnia by increasing total sleep time and decreasing wakefulness after sleep onset.[35–38] Sleep architecture seems to be restored. However, STN DBS does not alleviate REM-sleep behavior disorders.

STN DBS also improves PD-related pain, especially levodopa responsive pain.[39–42] However, vigilance is needed, because newly developed back pain or deterioration of preexisting back pain sometimes occurs after successful STN DBS, especially in patients who have some lumbar spine pathology.[40,43]

The effect of DBS on impulse control disorders (ICD) and dopamine dysregulation syndrome (DDS) is controversial.[44–48] Preexisting ICD or DDS is improved by significant reduction of dopaminergic medication in some patients; however, newly developed ICD may occur after STN DBS. Frank et al. introduced the concept that STN DBS directly induces impulsive behavior independent of medication.[49]

Complications

A significant incidence of adverse effects associated with DBS in PD has been reported.[50] Most are mild and transient, but serious morbidity is also reported. According to a large study (1183 patients),[51] the mortality rate during the first 30 postoperative days after stereotactic surgery is 0.4% and the permanent surgical morbidity rate is 1%. The morbidity is mainly caused by intracerebral hemorrhage (ICH) (2.2%). An analysis of adverse events in published data revealed that common surgery-related complications included 2.0% with symptomatic ICH and 2.0% with infections in 928 STN DBS cases.[52] Permanent stimulation or disease progression-related adverse events included 12.8% with dysarthria, 11.3% with apraxia of eyelid opening, 5.8% with cognitive decline, 4.7% with disabling dyskinesia, and 4.3% with depression in 256 STN DBS cases.[52]

Regarding verbal problem after STN DBS, Tsuboi et al. classified speech disorders after STN DBS into four types.[53] They demonstrated that stuttering and breathy voice are due to aging or disease progression, but strained voice and spastic dysarthria are corticobulbar side effects.

The neuropsychological aspects of STN DBS have recently attracted considerable attention and numerous studies concerning neuropsychological outcome after STN DBS have been performed.[54,55] Mood changes including hypomania or depression are common adverse effects in patients treated with STN DBS.[56] Most are usually transient in the immediate postoperative period. The spread of stimulation to the limbic STN seems to be a cause of altered mood states.[57] On the other hand, depression or apathy occurring several months after surgery often coincides with excessive reduction of dopaminergic medication, and is generally alleviated by increasing the dose.[58] Severe depression after successful STN DBS has even been reported to lead to suicide; therefore, great care should be taken with regard to the patient's mental state. Suicide is the most important factor in mortality in the first year following STN DBS.[59]

There are many studies on cognitive outcomes after STN DBS. Most concluded that STN DBS is relatively safe from a cognitive perspective despite mild cognitive morbidity.[54,60,61] A meta-analysis of cognitive sequelae by Parsons et al. revealed small but significant declines in executive function and verbal learning and memory, and moderate declines in both semantic and phonemic verbal fluency after STN DBS.[60] A randomized controlled study by Witt et al. demonstrated that STN DBS did not reduce overall cognition, but resulted in a selective decrease in frontal cognitive function.[61] These changes did not affect improvement in QOL.

Several factors are considered to contribute to cognitive changes after STN DBS. As the STN has widespread connections with basal ganglia and the prefrontal cortex,[57,62] the direct effect of stimulation may contribute to cognitive changes. Furthermore, the impact of surgical intervention or drastic postoperative reduction of dopaminergic medication may cause cognitive decline.[63] Lead trajectory through the caudate nuclei also may affect cognitive decline.[64]

Target Selection

As an early non-randomized comparative study demonstrated the superiority of STN DBS compared with GPi DBS,[18] STN DBS has been widely performed as the primary surgical procedure. However, GPi DBS was reevaluated in a recent randomized comparative study, which revealed that GPi DBS yielded improvement in motor function comparable to STN DBS, with less psychiatric or cognitive problems after surgery.[65] However, another randomized controlled study still demonstrated the preferability of STN DBS.[66] Recent meta-analyses concluded that both STN and GPi DBS have similar effects on motor function and ADL.[67,68]

Current consensus is that STN and GPi DBS equally improve motor function in the medication-off period and dyskinesia. Only STN DBS can reduce the dose of dopaminergic medication. GPi DBS directly controls dyskinesia, while STN DBS improves dyskinesia by the reduction of dopaminergic medication. Besides, additional stimulation of the subthalamic fiber tract above the STN is effective in controlling dyskinesia in some patients.[69] In STN DBS, the risk of neuropsychological complications seems to be high compared with GPi DBS. Therefore, selection of the DBS target for PD should be considered for each patient based on the characteristics of each target.

Thus, the STN should be chosen for patients who need the reduction of antiparkinsonian medication (e.g., patients taking too much medication or suffering from the side effects). In contrast, GPi should be chosen in patients suffering from severe dyskinesia or dystonia despite low-dose medications, and in patients with a high risk of neuropsychological or psychiatric complications (e.g., older patients or patients with mild cognitive decline).

In the long-term follow-up after STN DBS, some patients suffer from medication or stimulation-induced intractable dyskinesia. There are several reports concerning additional GPi DBS for intractable dyskinesia after successful STN DBS.[70–72]

This strategy could provide a third honeymoon period in the long-term treatment of PD.

Long-term Outcomes

There are many studies of long-term (more than 5 years) outcomes of STN DBS.[73] In most studies, STN DBS improved motor function and ADL in the medication-off period, dyskinesia, and fluctuation, and decreased the dose of dopaminergic medication. These effects were mostly preserved even for 5 years after surgery. Moreover, improvements in cardinal motor symptoms such as tremor, rigidity, and bradykinesia are well-maintained 5 years after surgery. However, axial symptoms affecting speech, gait, and postural instability progressively worsened. These symptoms are refractory to both medication and DBS. The symptoms of gait disturbance or postural instability seem to be mediated by non-dopaminergic mechanisms. STN DBS substantially improves only the dopamine-mediated motor symptoms. Therefore, the aggravation of axial symptoms reflects the progression of PD itself. Persistent adverse effects in long-term follow-up after STN DBS include apraxia of eyelid opening, weight gain, psychiatric disorders, depression, dysarthria, dyskinesias, and apathy.

There have been a few reports on long-term outcomes of STN DBS of greater than 5 years.[74–77] According to these reports, not only axial motor symptoms, but also cognitive decline affect worsening of ADL.

Regarding long-term outcome of GPi DBS, a few studies demonstrated improvements in motor and ADL scores, and dyskinesia were also controlled longer with GPi DBS.[78,79] The dose of dopaminergic medication was unchanged or gradually increased. A meta-regression analysis revealed that long-term postural stability and gait outcome in the medication-on period was better with GPi DBS than STN DBS.[80]

It is controversial whether STN DBS contributes to improvements in the survival of patients with PD. Ngoga et al. demonstrated that patients undergoing STN DBS have significantly longer survival than those who are managed only by medication. STN DBS markedly reduces the death rate related to respiratory complications, such as pneumonia.[81] However, Lilleeng et al. have demonstrated no significant difference in long-term mortality between an STN DBS group and a control group.[82]

Management of Axial Symptoms

There are many types of motor symptoms in PD. As noted, cardinal motor symptoms such as tremor, rigidity, and bradykinesia are treatable with dopaminergic medication and DBS. However, axial symptoms such as freezing of gait, postural instability, swallowing disturbance, and speech problem are difficult to treat.

Several strategies have been attempted for axial motor symptoms.[83] Animal experiments suggest that the pedunculopontine nucleus (PPN) is a locomotion center controlling initiation and modulation of gait.[84,85] Patients with PD have significant loss of PPN neurons. Therefore, PPN is considered as a therapeutic target for gait disturbance in PD. Stefani et al. applied both STN and PPN DBS in six patients with PD and demonstrated the beneficial effects of PPN DBS for gait.[86] However, other studies showed interindividual variability in gait outcome, with insufficient evidence for PPN DBS.[87–89] A surgical procedure that includes targeting and physiological refinement of PPN is not established.

Moreau et al. demonstrated that low frequency (60 Hz) with high-voltage stimulation was effective for gait disturbances that developed after STN DBS.[90] Xie et al. showed that 60-Hz stimulation improved swallowing function as well as freezing of gait.[91] However, the reported effects of low-frequency stimulation are variable. Some studies demonstrated that low-frequency stimulation had transient or no effect on gait.[92,93]

Chastan et al. showed that bilateral stimulation of the substantia nigra pars reticulata (SNr) improved axial symptoms of gait and balance disorders in patients who underwent STN DBS.[94] A recent randomized controlled trial revealed that the combined stimulation of the STN and SNr safely improved freezing of gait but not balance impairment.[95] Thus, intentional placement of DBS leads into the SNr could be preparation for future deterioration of axial symptoms.

Fuentes et al. showed that spinal cord stimulation (SCS) improved locomotion in an animal model of PD.[96] However, this effect of SCS on gait was not seen in subsequent treatment of two patients with PD.[97] Agari et al. reported beneficial effects of SCS on axial symptoms such as posture, postural stability, and gait.[98]

As for medication, beneficial effects of amantadine[99] and the anti-cholinergic trihexyphenidyl[100] on axial symptoms after STN DBS have been reported.

Timing of Surgery

The timing of DBS surgery is one of current interests. The general course of PD with medical treatment is shown in Fig. 1A. After onset, patients remain well with only medication for several years (honeymoon

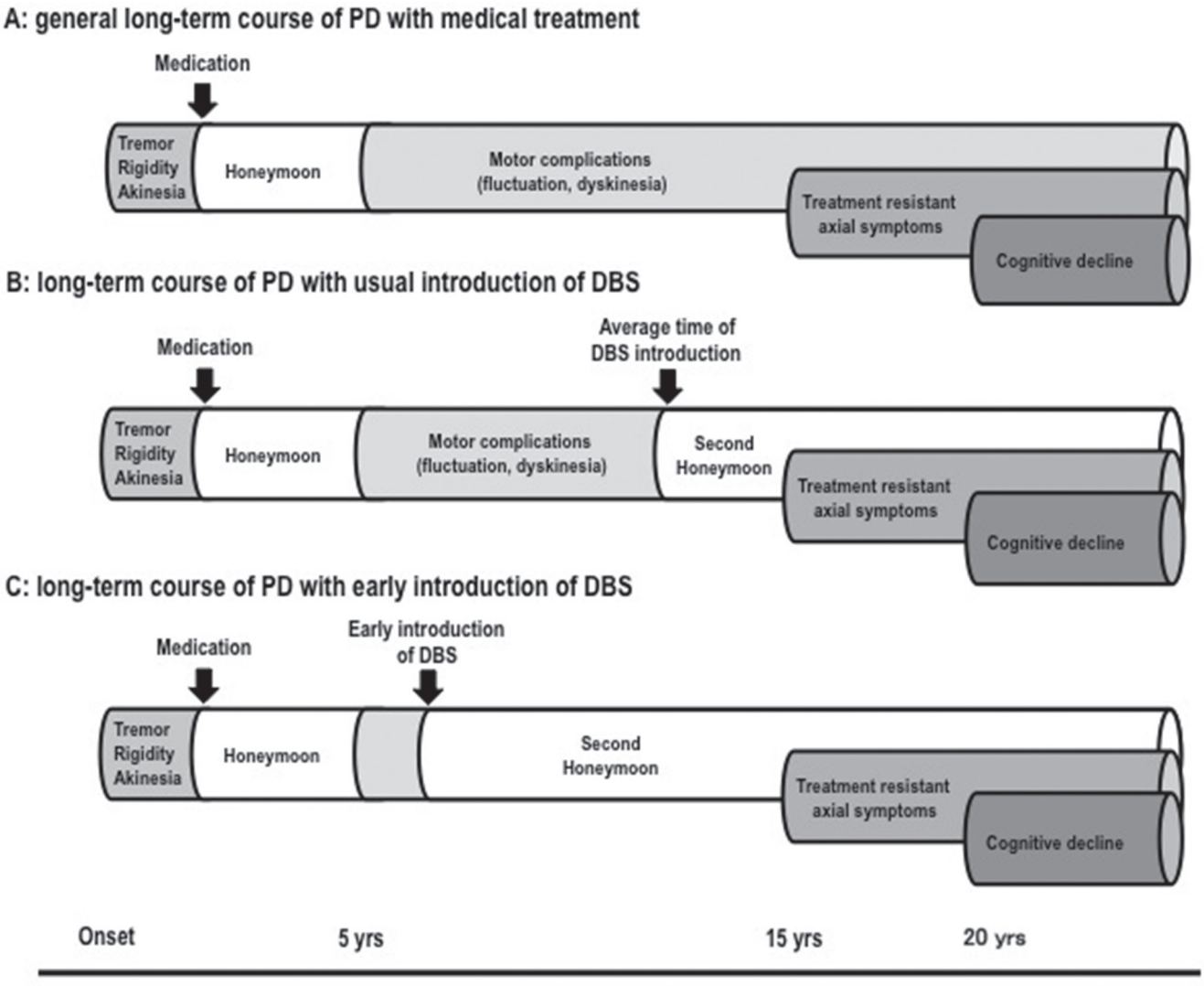

Fig. 1 Timing of DBS in long-term course of PD with medical treatment.

period). However, most patients subsequently suffer from motor complications of dopaminergic medication such as fluctuation and dyskinesia. In the advanced stage, treatment-resistant axial symptoms and cognitive decline appear. Until now, DBS has been considered as a last resort after medical treatment, and was usually introduced in the late phase of motor complications (Fig. 1B). Patients could achieve a second honeymoon period after DBS, but treatment-resistant axial symptoms appeared in several years. Currently, early introduction of STN DBS is recommended based on new evidence (EARLYSTIM study).[101,102] This study demonstrated that STN DBS improved QOL and motor function not only in advanced PD, but also in PD with early motor complications. In this case, the second honeymoon period will be longer (Fig. 1C). However, there is criticism that very few patients would meet the EARLYSTIM criteria.[103] Mestre et al. emphasize that the most relevant issue is not when but on whom to operate, and that early is not always better.[104]

Surgical Procedure

The surgical procedure for STN DBS varies among centers.[105] There is some controversy about surgical aspects of DBS. Currently, DBS leads are implanted into the target area stereotactically under magnetic resonance imaging (MRI) guidance with physiological refinement by microelectrode recording (MER) under local anesthesia in most centers.

As recent progress in MRI technology has enabled direct visualization of the STN or GPi, some groups avoid using MER for placement of the DBS lead.[106,107] They insist that MER may increase the risk of ICH. The combination of MER and hypertension will

definitely increase the incidence of bleeding.[108] However, physiological refinement by MER is the gold standard for identifying the STN and its borders. The optimal region for STN stimulation might be missed due to individual anatomical variations or intraoperative brain shift. In our own series, about 20% of cases required two or more trajectories to obtain sufficient activity of STN by MER.[109]

Recently, multiple simultaneous MER using a multiple electrode holder is employed in some centers. It is controversial whether single tract or multiple tracts MER is more advantageous. Temel et al. compared single with multiple tract MER.[110] There were no significant differences in the STN length between single and multiple tracts MER. They demonstrated that multiple MER resulted in better motor outcome but deterioration in neuropsychological function. More extensive microlesions caused by the microelectrodes could be a possible explanation for the deterioration.

There is also controversy concerning the use of local or general anesthesia during DBS-lead placement.[106] Local anesthesia enables more correct assessment of effects and side effects of stimulation during surgery. On the other hand, general anesthesia can reduce stress and pain from disease severity or anxiety.

As patients with advanced PD generally suffer from bilateral motor symptoms, bilateral implantation of DBS is required. Some centers prefer staged unilateral implantation rather than simultaneous bilateral implantation to reduce postoperative complications, but most studies showed no significant difference in effectiveness of DBS.[111–113] However, simultaneous bilateral implantation may be liable to postoperative neuropsychological complications.[112]

Cost-effectiveness of DBS

From the standpoint of health economics, several studies analyzed cost-effectiveness of DBS in patients with PD.[114–116] Table 1 shows the incremental cost-effectiveness ratio (ICER) calculated in terms of cost per quality-adjusted life year (QALY) in these studies. Although health care systems are different among countries, these studies conclude that DBS is a cost-effective intervention for advanced PD. Costs of DBS are mainly driven by the cost of initial surgery and battery exchange. Therefore, the use of current rechargeable battery will further increase the cost-effectiveness of DBS.

Table 1 Summary of studies concerning cost-effectiveness of DBS for PD

Author, year	Country	Incremental cost effectiveness ratio
Tomaszewski, 2001[114]	USA	US$49,194 per QALY
Valldeoriola, 2007[115]	Spain	€34,389 per QALY
Eggington, 2014[116]	UK	£20,678 per QALY

QALY: quality-adjusted life year.

New Technology

DBS devices had long been provided only by Medtronic Inc. for long time. Recently, Boston Scientific and St. Jude Medical also entered the DBS market. Each company developed a unique product concerning the electrode arrangement, stimulation setup, battery character, etc. This competition may result in the development of better products.

A conventional implantable pulse generator (IPG) has a primary cell battery, and IPG replacement is necessary for every 4–5 years. Currently, a rechargeable battery is used in selected patients.[117,118] Vercise™ rechargeable IPG (Boston Scientific) is especially superior in terms of long battery life, wireless recharge, and Zero Volt™ technology, which avoid failure by battery charge depletion.[119]

Performing MRI in patients with a conventional IPG is not officially permitted. Currently, only the Medtronic IPG (Activa) allows MRI under specific conditions of use.[120]

In programing of stimulation parameters, the amplitude setup is changing from constant voltage mode to constant current mode. The effect of stimulation is dependent on strength of current. However, stimulation current fluctuates with tissue impedance change after surgery in conventional constant voltage IPG.[121] More stable stimulation effect is expected using constant current IPG.[122,123]

Several methods of current steering to modify the stimulation field have been developed in new devices. The multiple independent current control (MICC) technology of Boston Scientific IPG (Vercise™) provides independent current settings in eight contacts in one lead.[119,124] The interleaving mode of the Medtronic IPG allows two independent settings with different pulse width and amplitude values in one lead. These technologies enable generation of precise control to refine the size and shape of the stimulation field.[125] They are useful in creating stimulation fields to minimize the side effects of stimulation while maintaining the beneficial effects. In addition, they are applied in situations in which stimulation at different contacts was beneficial for controlling specific symptoms with different stimulation amplitudes.[126,127]

A directional lead has been developed as a strategy to avoid the side effects of stimulation. A multiple-contacts lead enables two dimensional electric field shaping. In STN or GPi DBS, if the lead is not implanted in the precise position, side effects caused by current spreading to the internal capsule may occur with a conventional lead. This side effect seems to be controlled using a directional lead. Several manufacturers are developing unique directional leads.[128,129]

Currently, pathological beta-oscillation recorded from the STN in local field potential recording is the most noteworthy phenomenon in the context of PD.[130] The concept of the adaptive DBS is based on a closed-loop model.[131] In adaptive DBS, stimulation is applied only when pathological beta-oscillation is detected. In clinical use, unilateral and bilateral adaptive DBS were more efficient than conventional continuous DBS.[132,133]

Conclusion

More than 20 years have passed since DBS was introduced in the treatment of PD. Currently, DBS is the most promising surgical treatment option for patients with medically refractory PD. DBS is also used for other movement disorders and neuropsychiatric diseases. DBS has evolved along with the development of surgical procedures and device technology. In the future, alternative surgical therapies such as gene therapy,[134] neural transplantation using induced pluripotent stem cells,[135] and optogenetics[136] are also anticipated.

Conflicts of Interest Disclosure

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