Review Article

Deep Brain Stimulation for Parkinson's Disease

Vich Yindeedej*, Raywat Noiphithak*, Praween Lolekha**, Teeradej Srikijvilaikul***

Abstract

Parkinson's disease (PD) is a neurodegenerative disorder that affects motor and non-motor systems. However, the most recognizable symptoms in PD are mainly motor symptoms which include bradykinesia, rigidity, tremor, and postural instability. The motor symptoms of PD results from the death of dopaminergic neurons in the substantia nigra due to an abnormal accumulation of alpha-synuclein protein. The Rate Model of basal ganglia has been proposed and rises the knowledge on the physiology of basal ganglion functions and surgical management of PD. Surgical treatment becomes the option in advanced PD patients who have uncontrollable motor fluctuations and dyskinesia. Options in surgery consist of ablative surgery, including pallidotomy and thalamotomy, and deep brain stimulation (DBS). The mechanism of DBS is still unclear, but modulation and disruption firing rate of basal ganglia nuclei could result in a beneficial motor outcome. To achieve a good outcome in DBS, neurosurgeon needs a careful patient selection and a proper surgical target.

Keywords: Deep brain stimulation, Parkinson's disease

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Corresponding author: Vich Yindeedej, MD, Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Thammasat University (Rangsit Campus), 95/209, Khlongnueng, Khlongluang, Pathumthani, Thailand 12120 Tel: 085-992-7733
E-mail: vich2001@hotmail.com

Introduction

Parkinson disease is one of the most common neurodegenerative disease affected elderly patients which is now more recognized among clinical practice. Although medication remains the mainstay of treatment, surgical procedure is indicated in some patients. Nowadays, many centers are able to perform such therapeutic operations. Here, we briefly review Parkinson's disease and one of its surgical treatment named "Deep brain stimulation".

Definition

Parkinsonism is a clinical syndrome characterized by bradykinesia, rigidity, resting tremor, and postural instability.[1] Parkinsonism is commonly seen in Parkinson's disease (PD) but could find in other conditions, including drugs, toxins, infections, metabolic diseases, and other neurological conditions such as cerebrovascular diseases and parkinsonism-plus syndromes.

Epidemiology

PD is the second most common neurodegenerative disease after Alzheimer's disease[2] Generally, PD affects approximately 1-2 per 1,000 of the population at any age. The prevalence is about 1% of the population above 60 years and increases with age. Males are more often affected than females at a ratio of around 3:2.

Pathophysiology

The pathology of PD that responds to the onset of motor symptoms are the progressive loss of dopaminergic neuron in the substantia nigra pars compacta and an abnormal accumulation of alpha-synuclein protein in the neurons referred to as Lewy bodies.[3] This pathology makes depigmentation of substantia nigra grossly.

To better understand PD, basal ganglia anatomy and physiology are crucial which comprise[4]

- Striatum: consist of caudate nucleus and putamen
- Globus Pallidus: consist of interna (GPi) and externa (GPe)
- Substantia nigra pars compacta (SNc) and reticularis (SNr)
- Subthalamic nucleus (STN)

These structures help in modulating movement systematically. According to The Rate Model theory, the neuronal signal is sent to GPi in basal ganglia via striatum and STN. This tract is called Thalamo-cortico-basal ganglia circuit which has direct and indirect pathway (Figure 1).

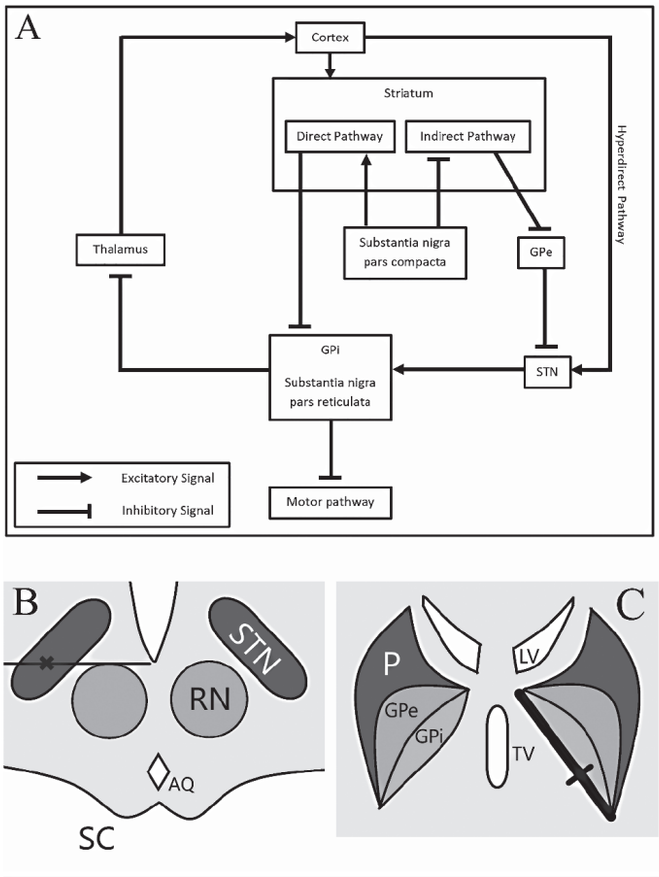

Figure 1 Basal Ganglia function and Parkinson's Disease target. **A**. Rate model of Basal Ganglia, **B**. Subthalamic nucleus target and **C**. Globus Pallidus Interna target. GPe, Globus Pallidus Externa; GPi, Globus Pallidus Interna; STN, Subthalamic nucleus; RN, Red nucleus; AQ, Aqueduct; SC, Superior Colliculus; LV, Lateral ventricle; TV, Third ventricle P, Putamen

• Direct pathway: send inhibitory signal toward GPi directly.

• Indirect pathway: send inhibitory signal toward GPe then GPe sends another inhibitory signal to STN. The final result is the stimulation of GPi.

In normal circumstance, basal ganglia work under equilibrium between direct and indirect pathway. In PD, there is a decreasing dopamine production from SNc resulting in the abnormal activity of both pathways. Finally, there is increased GABA-ergic inhibition of Thalamo-cortical projection which results in the symptoms of Parkinsonism. Later, hyperdirect pathway has been proposed the connection between the motor cortex and STN directly. This rate model has been the important influence initiating enthusiasm in treatment modalities of PD and targets for surgical intervention in PD.[3]

Medical treatment

Medication is the first-line treatment for PD. There are 5 main categories commonly used medication.[1]

1. Levodopa
2. Dopamine agonists
3. Monoamine oxidase B inhibitor
4. Catechol-O-Methyltransferase inhibitor
5. Anticholinergics

Levodopa is the gold standard treatment and also the most commonly prescribed drug for PD.[1] However, levodopa might cause some disturbing adverse effects such as nausea/vomiting, dizziness, hypotension, confusion, hallucinations and sleep disturbance. Moreover, the therapeutic range of levodopa becomes narrower compared to the initial usage in response to the progression of the disease and pharmacokinetics. This effect results in a specific phenomenon known as motor fluctuations such as wearing-off, on-off fluctuation, dose-failure, sudden-off, and levodopa-induced movement disorders called "dyskinesia".

Appropriated medication adjustment is the standard management for motor fluctuations, however, some patients might not gain any benefit and continue having severe motor fluctuations. In this regard, surgical treatment can be considered an additional treatment option.

Surgical treatment

Surgery in PD can be categorized into ablative surgery and deep brain stimulation (DBS).

Ablative surgery

Ablative brain surgery is the surgical ablation by various methods of brain tissue. It was introduced before the discovery of levodopa. Ablative surgery had good efficacy in the treatment of PD including the technique of pallidotomy, subthalamotomy, and thalamotomy. However, the arrival of levodopa made ablative surgery be the second-line treatment and was limited for patients suffering from drug-induced dyskinesia or uncontrollable motor fluctuations despite adequate medication adjustment.[4]

Despite its good efficacy, safety, and cost-effectiveness, ablative surgery is not commonly recommended due to its irreversibility, unable to operate both sides of the brain, and unable to adjust and programming.[4]

Principle of DBS

In the DBS procedure, the neurosurgeon places the electrodes in specific regions stereotactically. These electrodes are connected to a pulse generator to establish electrical signal which either modulates or disrupts neuronal signal at those regions depending on the DBS program. Additionally, DBS is believed to increase cerebral blood flow resulting in neurogenesis.[5]

Patient selection

DBS has a better outcome in idiopathic PD patients who response to levodopa treatment. The motor symptoms that likely to benefit from DBS comprise[4]

- Tremor
- Dyskinesia
- Rigidity
- Motor fluctuations
- Bradykinesia and "off" -period gait freezing DBS is unlikely to benefit patients who have[5]
- Autonomic dysfunction
- Cognitive impairment
- Hypophonia
- Postural instability and "on" -period gait freezing
- Atypical Parkinsonisms

Indications and Contraindications

DBS is indicated in PD patients experiencing motor complications after long-term first-line medical therapy. These complications include dyskinesia, motor fluctuation, and medically intractable tremor[4]. On the contrary, DBS is contraindicated in patients with severe cognitive impairment because cognition might be worse after DBS and this complication bring more severe sequelae to patients than untreated motor symptoms[4].

Indications for DBS in PD can be listed as below[6]

- Idiopathic advanced PD
- Responsive to levodopa
- Variable response to levodopa despite proper dosage adjustment

- Severe motor fluctuation
- Unpredictable on-off
- Dyskinesia
- Biphasic dyskinesia
- Off period / Early morning dystonia
- Refractor tremor
- No cognitive impairment nor untreated depression

Target

The main target for DBS in PD consists of STN and GPi. According to a recent publication in 2018, there is no significant difference in treatment outcomes but there are some distinct effects between these targets.[7] Meta-analysis in 2014 also concluded in the same way that these targets do not have different outcomes toward PD but STN DBS might affect mood and cognition more than GPi.[7] The patients who underwent the STN DBS are likely to decrease medication dosage than GPi[7], while the GPi DBS has less impact on psychiatric condition than the STN.[7, 8]

Beside STN and GPi, there are also other target options available in the literature.

• Ventralis intermedius nucleus (Vim) of Thalamus which is suitable for tremor-predominant PD.

• Pedunculopontine nucleus (PPN) is found to be more beneficial to postural instability than STN and GPi but lesser effect toward motor symptoms is seen.

• Posterior Subthalamic nucleus (PSA) is thought to have more benefits to tremor than Vim but the exact surgical location of PSA still remained unclear.[9]

Surgical Technique

To reach a proper location of the target, DBS targeting is based on anatomic targeting by direct (MRI) and indirect (AC-PC) methods which is generally under frame-based stereotaxy technique and physiologic targeting which is confirmed by microelectrode recording (MER). Typically, DBS is done under awake anesthesia but this technique might be relatively contraindicated in elderly or anxiety patients who have less co-operation.[4] Some institutes might use only macrostimulation to confirm the target. Some centers use only anatomic targeting from MRI and perform operation under general anesthesia.

Awake Surgical Technique

This following surgical technique is just one example of DBS surgery. Detailed operation depends on each institute's resources and neurosurgeon experiences.

1. Pre-operative Imaging: Thin-sliced contrast-enhanced axial T1 and axial and coronal T2-weighted Fast Spin Echo magnetic resonance imaging (MRI) is required. All data are uploaded into neuronavigation for target planning.

2. Operation: After head frame placement, the patient is sent to perform thin-sliced computed tomography (CT). Thereafter, the information is merged with the MRI.

3. Position: Usually supine with head slightly elevated

4. Targeting (Figure 2)

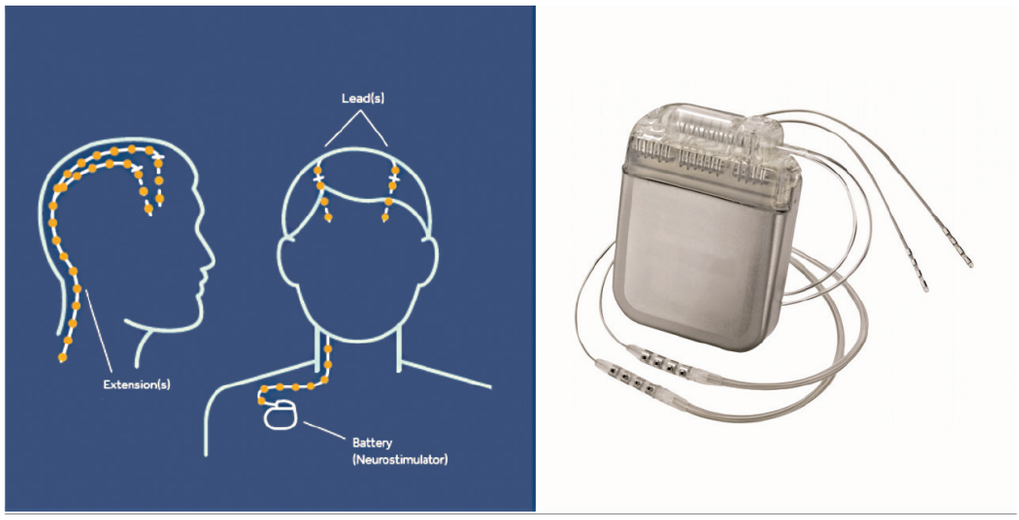

Figure 2 Pulse generator placement. (a) Pulse generator is generally implanted subcutaneously in the right chest and connected to leads and (b) An example of pulse generator system

1. **STN:** For indirect targeting, STN is located at 3 mm posterior, 4 mm inferior, and 12 mm lateral to the midcommisural point (AC-PC line). For direct targeting, the line from the anterior rim of the red nucleus is drawn to STN and the target is between 2 mm laterally from its medial rim to mid of the STN.[4]

2. **GPi:** For indirect targeting, GPi is located at 2 mm anterior, 5 mm inferior, and 21 mm laterally to AC-PC line. For direct targeting, the line, drawn from the posterior third of the pallidocapsular border tangentially and laterally 3-4 mm, then, specifies the target.[4]

5. Trajectory: Approximately 60 degrees from the vertex in sagittal view and 0-15 degrees in coronal view. The trajectory must not pass cerebral sulcus, vascular structures, and ventricles to avoid injury and brain shift.

6. Microelectrode Recording: This physiologic targeting is one of the most important steps to confirm the proper location of the electrode. Generally, the impedance is set at 0.3-0.8 megaOhm. Micropositioner is used to advance the electrode gradually.

1. Confirmation of STN: Signals around 20-50 Hz have to be identified which are resemble the "rain on a tin roof" pattern. When the electrode passes over STN to the SN, the signal becomes silent first and then increases its frequency to 50-70 Hz, instead. Additional confirmation can be performed by a passive contralateral joint movement which subsequently produces an alteration of the signals.

2. Confirmation of GPi: Before entering GPe, the signal is low around 0-10 Hz. Reaching GPe, the signal increases to 30-60 Hz and presents the "burster and pauser" pattern. When GPi has arrived, the signal significantly increases its frequency to 60-100 Hz.

7. Lead Implantation and Macrostimulation: Leads are placed and stimulation is performed to a higher degree to confirm the proper location and record the side effects. The principle of targeting and macrostimulation is to identify the motor benefits and neurological side effects. When the macrostimulation was performed, the nearby structures may also be stimulated and there are some detectable neurological signs and side effects. For example, in the STN

stimulation, if the stimulation is performed too medially, it might cause diplopia, ptosis, and eye deviation due to the enclosed oculomotor nerve stimulation. This macrostimulation helps neurosurgeon identify the target borders and adjusting the leads to the appropriated location where stimulation causes the best benefit and least undesired side effects (Table 1).

Table 1 Macrostimulation to each target

Subthalamic nucleus

Location	Structure	Effect
Too posterior	Medial lemniscus	Paresthesia
Too anterior	ANS and cerebral peduncle	Alter ANS function and muscle contraction
Too lateral	Internal capsule	Muscle contraction, dysarthria, gaze to contralateral
Too medial	CN III	Diplopia, ptosis, eye deviation
Too superior	Zona incerta	No effect
Too inferior	Substantia nigra pars reticularis	Increase akinesia

Globus Pallidus Interna

Location	Structure	Effect
Too posterior	(Decrease in MER)	Tetanic contraction
Too anterior	GPe	No effect
Too lateral	GPe	No effect
Too medial	(Decrease in MER)	Tetanic contraction
Too superior	(Pausing and bursting MER)	No effect
Too inferior	Visual pathway	Visual phenomenon

ANS: Autonomic Nervous System
CN: Cranial nerve
MER: Microelectrode recording
GPe: Globus Pallidus Externa
GPi: Globus Pallidus Interna

8. Closure and Pulse Generator Placement: After fixing electrode to the skull, the Pulse Generator is implanted subcutaneously in the right chest wall under general anesthesia.

Surgical Complications

• Hemorrhage: incidence 1.9%, normotension in the postoperative period is recommended.[10]

• Seizure: incidence 1.3%.[10]

• Infection: incidence 0-15.2%, which is the most common complication.[10]

• Hardware Failure: comprises hardware infection, hardware erosion, and lead fracture.[10]

Controversies

Currently, newer techniques have been introduced, such as frameless stereotaxy and asleep DBS. These novel techniques have been studied and compared to the conventional techniques in terms of their precision and outcome; however, no consensus and sufficient data have been proposed.[4]

Moreover, it is debatable regarding unilateral versus bilateral DBS and DBS in multiple targets, such as a combination of both STN and GPi-DBS.

• Unilateral versus Bilateral DBS

Although DBS is performed bilaterally, the unilateral procedure is considered in patients who have asymmetry symptoms or pre-operative cognitive deficit because it affects less cognitive dysfunction than the bilateral surgery. Some authors reported that the unilateral procedure could provide bilateral responsiveness with a lower risk of the surgery.[9] Some authors suggested the staged-operation in whom do not experience adequate result after one-sided DBS. However, staged-procedure requires twice sessions anesthesia and frame placement.[9]

The current evidence derived from observational cohort studies found that unilateral DBS significantly improved motor symptoms in the contralateral side of the patients. Moreover, unilateral DBS has fewer effects on mood and verbal fluency.[9] Randomized controlled trials are required to validate the actual benefits of unilateral surgery.

• Multiple Target DBS

Given that STN and GPi are successful targets for PD, some institutes have postulated that DBS surgery in both targets might enhance potential benefits. Several studies supported the synergistic effects of the multiple target DBS toward motor symptoms. Nevertheless, the current data is inconclusive and the multiple target surgery might be associated with higher complications.[9]

Discussion

PD remains a common problem in clinical practice according to a longer life of people at the present time. Clinical Parkinsonism is not too difficult to understand and diagnose, however, to distinguish secondary Parkinsonism from PD is still challenging. First line treatment of PD is medication mainly Levodopa. Despite its less invasiveness, Levodopa has a risk of eventually intolerable side-effects requiring other additional modalities of treatment. To date, DBS is better than ablative procedure in several aspects except its cost. Crucial steps prior to DBS surgery comprise good patient selection, choosing a proper target, skilled operative procedure, and a well-organized follow-up system. Moreover, DBS knowledge is still being studied not even in PD but also in other neurological diseases. In the near future, DBS would be more common among PD patients and its efficacy would be improved consistently.

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Conflict of Interest None

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บทคัดย่อ

การผ่าตัดฝังเครื่องกระตุ้นสมองส่วนลึกสำหรับโรคพาร์กินสัน

วิชญ์ ยินดีเดช*, เรวัฒน์ น้อยพิทักษ์*, ประวีณ โล่ห์เลขา, ธีรเดช ศรีกิจวิไลกุล*****

* หน่วยประสาทศัลยศาสตร์ ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์ ปทุมธานี ประเทศไทย
** หน่วยประสาทวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์ ปทุมธานี ประเทศไทย
*** กลุ่มงานประสาทศัลยศาสตร์ สถาบันประสาทวิทยา กรุงเทพมหานคร ประเทศไทย
ผู้ให้การติดต่อ: วิชญ์ ยินดีเดช หน่วยประสาทศัลยศาสตร์ ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์ (ศูนย์รังสิต) 95/209 ตำบลคลองหนึ่ง อำเภอคลองหลวง ปทุมธานี ประเทศไทย 12120 โทรศัพท์ 085-992-7733
อีเมล: vich2001@hotmail.com

โรค Parkinson disease (PD) ประกอบไปด้วยกลุ่มอาการ Parkinsonism อันได้แก่ bradykinesia, rigidity, tremor และ postural instability แต่ไม่มีสาเหตุที่อธิบายอาการดังกล่าว PD จัดเป็นโรคการเคลื่อนไหวผิดปกติที่พบบ่อยที่สุดและพบมากขึ้นในประชากรที่อายุมาก ลักษณะที่สำคัญของโรคจะพบ dopaminergic neuron น้อยลงบริเวณ substantia nigra และการสะสม alpha-synuclein protein ที่ผิดปกติ กลไกการเกิดโรค PD อาศัย rate model ของ basal ganglia ในการอธิบายพยาธิสรีรวิทยา และยังนำมาเป็นองค์ความรู้ที่ใช้พัฒนาวิธีการรักษาทั้งยาและการผ่าตัด โดยทั่วไปจะเริ่มการรักษาด้วยยาแต่เมื่อมีผลข้างเคียงของยาหรือผลการรักษาด้วยยาไม่ดีพอจะเป็นข้อบ่งชี้ของการผ่าตัด ในปัจจุบันการผ่าตัดประกอบด้วยการทำ ablative surgery และ deep brain stimulation (DBS) ในการทำ DBS จะต้องเลือกผู้ป่วยที่มีลักษณะที่ส่งผลดีต่อการผ่าตัด รวมทั้งพิจารณาเลือกตำแหน่งการรักษา (target) ที่เหมาะสมกับผู้ป่วยแต่ละคนเนื่องจากมีข้อดีข้อเสียที่แตกต่างกัน หลักการทำ DBS ต้องอาศัยทั้ง anatomical และ physiologic targeting โดยตามทฤษฎีเชื่อว่าการทำ DBS ให้ผล modulate หรือ disrupt สัญญาณประสาทที่ตำแหน่งที่ทำส่งผลให้เกิดการแก้ไข rate model ที่ผิดปกติของโรค PD

คำสำคัญ: การผ่าตัดฝังเครื่องกระตุ้นสมองส่วนลึก, โรคพาร์กินสัน