

Deep Brain Stimulation in Parkinson's Disease

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ABSTRACT

Before the era of L-Dopa, surgical ventures (pallidotomy and thalamotomy) were applied in the treatment of Parkinson's disease (PD). The first experience of deep brain stimulation (DBS) was carried out by Heath and Pool for chronic pain in mid-1950s. From those times, DBS is placed a legitimate position in PD treatment whereas that it is in principle "reversible lesion" – in the state of previous ones where the condition was "irreversible lesion" – in the target nuclei. The latter are globus pallidus inserta or subthalamic nucleus and DBS does not interfere with the use of other future therapies. The touchstone for DBS surgery is "the right patient" by "the experienced team" at "the right time" so that the last three can provide magnificent benefits. Indeed both acute and the long-term results ends up with a dramatic and stable improvement of a patient's having DBS. The outlet of this article is to build an awareness of the roles of DBS in PD with clinical evaluation, electrophysiological bases, importance of surgical techniques with unilateral – bilateral approaches, postoperative follow-up early, and late acquirement of DBS and the gainings of the interdisciplinary – team approach.

Key words: Deep brain stimulation, globus pallidus pars interna, Parkinson's disease, quality of life, subthalamic nucleus

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INTRODUCTION

In general terms, Parkinson disease (PD) is the failure of dopaminergic neurons in the substantia nigra. The complexity of PD includes bradykinesia, tremor, rigidity, akinesia, and postural disturbances; the latter are all caused by the resultant abnormal neuronal oscillatorial pulsation and synchronous activity between subthalamic nucleus (STN), globus pallidus pars interna (GPI), and cerebral cortex. Patients of PD suffer from these complicated combinations of different clinical situations in different degrees. Most of the main mechanisms of the medical therapy for PD rely on either to put back the decreased level of L-Dopa or to increase the dopaminergic activity. Sometimes, the mechanism of action is unknown. The drugs used for the treatment of PD's symptoms are apomorphine, L-Dopa, dopamine agonists, monoamine oxidase type B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, or other drugs.^{1,2}

HISTORY OF SURGERY

The first experience of deep brain stimulation (DBS) was carried out by Heath and Pool for chronic pain in the

mid-1950s.³ Long-range usage of DBS for movement disorders with improved systems developed by Medtronic which was reported by Mundinger in 1977. Since then, more advanced devices were developed and applied for medically refractory tremor in PD.⁴

The leaping movement of DBS at high frequency was faced in 1997 to replace thalamotomy in treating the specific tremor of PD and essential tremor and some movement disorders other than PD as generalized dystonia.^{5,6}

FUTURE OF SURGERY

Not only the PD but also the other areas of medicine are found in the place of DBS treatment; these areas are in numerous central nervous system disorders including intractable epilepsy, chronic pain, cluster headache, and mainly some psychiatric disorders such as treatment-resistant depression, bipolar disorder, anorexia nervosa, obsessive-compulsive disorder, Tourette's syndrome, the other condition such as drug addiction, obesity, Meige syndromes (Idiopathic craniocervical

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dystonia as an adult-onset movement disorder that results in segmental dystonia), camptocormia (a posture abnormality and characterized by involuntary truncal anteflexion induced by standing or sitting and has been found to be associated with some neurologic disorders, including idiopathic PD, fail back surgery, distonia), and most recently Dementia, especially Alzheimer's disease.^{7,8}

ELECTROPHYSIOLOGICAL BASES OF DEEP BRAIN STIMULATION

Determination of the neural circuitry in the deep brain has narrowed the surgical focus area. Since these regions are not always distinguishable in the computerized tomography (CT) or magnetic resonance imaging (MRI), they must generally be identified on the basis of their electrophysiological behavior. These behaviors are mainly based on the activity of the neural elements for the induction of action potentials through voltage-gated ion channel activities. Not only the single action potential production but also produced rates (frequency of produced action potential) also carry information for corresponding parts of the brain. In other words, neurons convey and process information by the sequence of action potentials they receive.

On the base of disease treatment, DBS may be acting to control misinformation in the activities of the neurons affected by disease. Therefore, for DBS to work, it must close the circuit in the neural membrane to generate the action potential. DBS works by depolarizing the neural membrane. Depolarization to activate the desired neural elements requires the delivery of electrical charge into the fluid outside the neural membrane. Once the membrane is depolarized sufficiently to some threshold, the channels open (analogous to the switch closing) and current flows through the membrane, producing an action potential.⁹

SURGICAL APPROACH

Before 1969, when there was no oral drug containing of Levodopa, surgical lesional procedures were used to be the only way for PD treatment. DBS has rapidly replaced surgical lesional procedures due to not having the risk of the irreversible procedure and severe side effects. Since the DBS does not require a destructive lesion, it can be used bilaterally for generalized parkinsonian symptoms safely.^{6,10,11} If a simple and virtual description is needed for the DBS that is "sum up of the principle "reversible lesion" in the target nuclei - GPi or STN" and does not interfere with the use of other therapies, e.g., oral drugs, pumps, tubes, etc. In the field of DBS area, while stimulation can suppress some neural elements, other neural elements can be activated and potentially accumulated to the frequency of stimulation^{6,11,12} [Table I].

CLINICAL EVALUATION

Essence of the promise, the most important step toward involving with DBS outcomes remains careful and right patient

selection. Then, >30% of DBS failures can be attributed to the inappropriate indication for surgery.¹³ Timing of disease is the main stage for making decision for DBS. Very early implantation of DBS may be ineffective since these patients yield symptoms and sign of idiopathic PD, but in reality, some of those patients evolve other forms of PD, e.g., Parkinson-plus syndromes.

Key points in the surgery of the DBS are as follows: Selections of the surgical techniques, postoperative management of stimulator settings, and the patient's specificity. Due to the individual risks, selection of the appropriate patient is extremely important for the benefit of the surgery. Choice of patient generally depends on the best response to medical treatment (i.e., response to L-Dopa).¹³ There are evidence that the results of motor fluctuations are better, and the complication rate is lower when DBS is used earlier in younger patients of pure PD.^{5,14-19} In appropriate patients, DBS restores a quality of life (QoL) not possible with current medications, but it does not slow progression of disease.^{6,13} DBS has the potential to reclaim QoL, but careful patient selection and accurate electrode positioning are critical for success. Rigidity, dyskinesia, tremor, and dystonia improve with DBS; freezing, postural instability, and falls unchanged, whereas verbal fluency and dysarthria may be worsen.^{6,14-19} Especially the axial symptoms including gait freezing, postural imbalance, or dysarthria persisting during best medical treatment "on state" revealed no significant improvement after STN-DBS.¹⁴ Indication of DBS and points of the patient's evaluation is shown in Tables II and III.¹⁴

Assessment of cognition and neuropsychiatric state is another aspect of patient selection. Cognitive function is tested mainly and with "mini mental state examination" (MMSE) to avoid operating on patients with dementia. Although the

Table I: Advantages and disadvantages of deep brain stimulation

Advantages	Reversible lesion, bilaterally with relative safety, stimulator setting can be adjusted to optimize benefits, does not interfere with the use of future therapies
Disadvantages	Battery life 3-5 years, side effect relating to implanted equipment, costly procedure

Table II: Indication of deep brain stimulation

Indication	Clinically idiopathic Parkinson's disease, significant improvement with regard to dopaminergic medication (>30%), refractory motor fluctuations or tremor, only minor symptoms during on-state
Relative contraindication	Biological age over 75 years, severe comorbidity, chronic immunosuppression, clearly brain atrophy, severe psychiatric disorder
Contraindication	Impaired general status, cardiac failure, a patient taking anticoagulants, dementia, acute psychosis and major depression

Table III: Point of the patient's evaluation to deep brain stimulation for Parkinson's disease

Parkinson's Disease Questionnaire-39	Assessment of functional status
Unified Parkinson's Disease Rating Scale	Assessment of functional status
Dementia Rating Scale-II	Assessment of cognitive status

dementia is the frequent exclusion principle for DBS, still there was no general agreement on the type of testing to identify cognitive impairment in cases with PD.¹³ Some of PD patients can be a part of PD and Dementia complex. In that case, DBS is contraindicated. On the other hand, the incidence of depression is remarkably higher in PD. STN stimulation carries a little-increased risk of neuropsychiatric complications than GPi-DBS.^{10,20-22} The reported rising proportion of suicide in patients of PD who is applied STN-DBS underline the necessity for a more careful preoperative psychiatric evaluation.¹³

As a conclusion, best results of DBS have been reported in patients with (1) advanced PD in symptoms and complicated with drug regimes, (2) better L-Dopa responsive result (3) younger age, (4) no or few axial non-L-Dopa responsive motor symptoms, (5) none or tolerable cognitive impairment, and (6) absence of or well-controlled psychiatric disease.¹³

TARGETS

Common targets are STN and GPi, the thalamus-ventral intermedius nucleus (Vim), pedunclopontine nucleus (PPN). From the initial attempt of DBS, the involved target has been quickly extended from the thalamus to the pallidum and finally to the STN to treat PD.^{19,23} In today's condition, STN is the main target nucleus for DBS in PD. In particular, young patient with the age of 50s and early 60s, all cardinal symptoms that principally respond well to L-Dopa can be effectively treated by STN-DBS. Tremor is, therefore, main good target symptom for STN-DBS.^{18,23-25} STN stimulation directly improves and reduces also "off" time, thereby reducing dopaminergic medication requirements can reach up to approximately 50% of daily dosage of L-Dopa; dyskinesias improve as a consequence beside.¹⁰

GPi-DBS shows significant reduction of levodopa-induced disabling dyskinesias may still be considered in older patients. The effect of bradykinesia, rigidity, and tremor might be less pronounced.^{23,26} Vim-DBS leads to complete suppression of tremor but has very little effect on akinesia and rigidity.²⁷

PPN-DBS is a promising new target; patients with prominent symptom as gait disturbance, falls, and postural instability refractory to other treatment modalities seem to be better candidate for this.^{23,28-30} On the other hand, Ferraye *et al.* report in their patients, gait impairments develop years after STN-DBS, also they observed the deceleration of parkinsonism and gait disturbance in time.³¹

Basal Ganglia are not restricted function in only smoothing or the last place to improve the movement, this enigmatic area of the brain engages in the assessment of changes in the environment and of their behavioral importance. The new approach of the role of Basal Ganglia in psychiatric disorders embody the anterior cingulate cortex connection and the subgenual area for severe persistence depression, the accumbens nuclei for depression, anorexia nervosa, addiction, and also the thalamus intralaminar nuclei to a degree in conscious states.^{29,32}

UNILATERAL-BILATERAL APPROACH

Vim-DBS allows the improvement for bilateral tremor in about 50% of patients with bilateral simultaneous procedures. GPi-DBS may be unilateral or bilateral according to the condition of the patient. In the majority of patients with high experiences, STN-DBS require bilateral attempt, at that cases where patients have been operated on unilaterally, the L-Dopa doses needed to control symptoms on the nonoperated side have been proclivity toward prominent dyskinesias.^{26,27}

PREOPERATIVE IMAGING

MRI is the best way to determine brain architectural states. STN and GPi are visible on T2-weighted MRI sequences. Reliable identification of the STN and GPi is significant for DBS before the intervention. STN are thin unique structures, and the places in the brain are typically calculated preoperatively from T2-weighted fast spin echo MRI, whereas GPi is smaller, irregular in shape, and estimated from proton-density weighted MRI. Susceptibility-weighted imaging seems to be significantly improved visibility for the STN, so that an associated increase in geometric distortion or positional shifts could be avoided and also an increased targeting inaccuracy could be achievable.^{33,34}

PRE- AND INTRA-OPERATIVE MANAGEMENT

The reduced medical therapy begins as the preparation of surgery a few days earlier than the operation. During the operation, the intraoperative stimulation is more widely accepted, originally here the discussion is between micro and macro stimulation.^{10,14,18}

In principle during macrostimulation, the electrode with the macrotip, two or three depths with a 2-mm interval, all within the range of target nuclei are used. The accurate position of the electrodes can be improved by the utilization of multitrajectory microelectrode-recording (MER) to register the specific activity model of the different nuclei. An ingenious electrophysiologist should differentiate the recordings miscible with one another. Researches dealing with multitrajectories end up with increased hemorrhage cases during MER procedure. Bour *et al.* suggest; if MER is preferred to be used, probably < 5 channels are needful and MER could also be started near than 8 and 12 mm for the MRI-based STN and GPi, respectively. This

approach is a long period in time. Finally, Zrinzo *et al.* report the incidence of hemorrhage is also significantly lower with an image-guided and verified techniques approach than with MER approach.³⁵⁻³⁷ In the near future, the presence of MER and macrostimulation in the same séance would be debated on.

THE INTERDISCIPLINARY TEAM

The interdisciplinary team in the treatment of PD should be established so that this team can function together to consider an optimal timing and to type the nuclear targets and decide the tailored approach that will maximize the benefit–risk ratio for each patient. In that case, the best patient’s condition can be composed; all these efforts will help to avoid DBS failures. Furthermore, the selection of patient, type of implantation, and aftercare of a DBS patient, all require a multidisciplinary team approach involving movement disorder neurologists, neurosurgeons, neurophysiologist, biophysicist, anesthetists, and psychiatrists.^{13,38} DBS operation programming is best accomplished by a team work. In this way, not only the technical aspects of DBS but also the PD-related issues and pharmacological managements can be solved properly. The initial parameters of stimulation are pulse width, frequency, voltage, and electrode configuration. The parameters are all individualized in times in accordance with the regression of the targeted symptoms. Anti-PD medication reduction should be performed leisurely, and early abrupt reduction should be avoided. All these events should be clarified to the patient before and just after the DBS. Evaluation and management of adverse events due to stimulation (speech, gait, balance, neuropsychiatric changes, etc.) is best approached by this interdisciplinary team systematically to optimize benefits and minimize adverse effects.¹³

THE SURGICAL TECHNIQUE

“Stereotaxy” is described simply that “the localization of a structure in three-dimensional space using coordinates the both frame-based and so-called frameless navigation techniques.”¹³ Stereotactic coordinates, the target is determined in the brain on MRI first and then coordinates are measured accordingly. This process is so sensitive; e.g., PPN average coordinates of the surgical targeting are 1.5 mm posterior to the posterior commissure, 13 mm below the bicommissural line, and 6 mm lateral from the midline.³¹ Local anesthetic is applied to the scalp so that patient can response and move his/her extremities consciously and get in dialogue with the electrophysiologist and neurologist all thoroughly perioperative period and a small hole drilled allowing the DBS electrode to be manually pushed down to the target. MERs are used to differentiate structures of the subcortical area of the brain. The electrodes are then connected to the pulse generator, which is indwellingly implanted at an infraclavicular or abdominal site subcutaneously.^{5,10,17,25,30,39}

DBS is an implantation technique where neuronal brain structure is continuously stimulated electrically through long-term placed

electrodes connected to an internalized neuropacemaker or stimulator, usually programmable in amplitude, pulse width, and frequency. DBS targets are extremely small, brittle; e.g., the STN is approximately 9 mm × 7 mm × 5 mm at most. Micrometric accuracy of electrode positioning is vital. Clinical improvement depends on the accuracy of implantation of the electrode within the spatial limits of the right target.³⁶

ELECTRICAL PARAMETERS

Each contact is tested separately after surgical steps are over, frequencies ranging from 5 to 130 Hz, 60 ms pulse width and voltage are kept in between 1.2 and 3.8 V initially. Therapeutic contacts are selected based on the absence of side effects and the best clinical effects on the patient. Bipolar configuration is the most preferable when the threshold of stimulation-induced side effects was below 1.0 V using monopolar configuration.³¹

POSTOPERATIVE IMAGING

As the preoperative managements, postoperative electrode position is assessed with brain imaging. The main approach is usually postoperative CT fused with preoperative MRI. The electrode location evaluated by postoperative MRI may have significant discrepancy with the location estimated by brain CT scan. To localize the electrode position; a fusion of the preoperative MRI and postoperative CT may help the team by providing ease and confidence for postoperative assessments. In one comparative study, 7-T MRI has been shown to have better visualization of the targets compared to 1.5-T and 3-T MRI.^{34,40-42} However, the 7-T MRI is declared to be better for spatial resolution, tissue resolution, and signal to noise ratio, the application of such a higher magnetization is still unclear in postoperative evaluation.

COMPLICATIONS AND SIDE EFFECTS

Proportion of surgical complications is highly variable in the literature. Complications of DBS: Infection, misplaced leads, intracranial hemorrhage, minor stroke, seizures, hardware complications, lead breakage, malfunction of the battery, and death are all reported events. Hardware failure is mainly due to technical problems such as breakage of wires or movement of the electrodes because of insufficient fixation to the skull. But the device as a whole is safe and reliable. Newly designed leads and battery size could decrease of complication rate. The most important complication of DBS surgery is intracerebral hemorrhage that accounts nearly 0.2–5%. Frequency of postoperative infections, on the other hand, was ranging from 1.8 to 15.2%. These reported infections generally occur in the area of pulse generator surroundings. Bhatia *et al.* emphasize the effect of changing the antibiotic prophylaxis regimen used. There is no significant difference found in infection rates between the internal and the external sides of the electrodes.^{5,13,37,43-45} Not only the surgical team but also the interdisciplinary team for DBS is a key factor in lowering the risk of surgical complications.

DBS-STN does not reduce overall cognition or affectivity, although there is a selective and minimal decrease in frontal cognitive functions and an improvement in anxiety in patients after the treatment. These changes do not affect improvements in QoL. DBS-STN is safe with respect to neuropsychological and psychiatric effects in carefully selected patients. In the postoperative period, depressive or mania-like symptoms are frequently found to be increases according to PD who do not undergo any DBS procedures, and DBS cases should be carefully followed on behalf of the depressive and manic attacks.⁴⁶

CLINICAL OUTCOME

Following to DBS, patients have symptomatic and functional improvement, which leads to higher health-related QoL. In general terms, QoL includes increased energy level, increased joy of life, freedom, and the fluidity of movement. Indeed, these parameters are improved much more with increased walking abilities, but the general life aspects do not improve much.⁴⁷ Although the unilateral STN and GPi result in similar effects, yet the GPi stimulation compared with STN-DBS resulted in improvement are not alternative in each symptom.¹³

On the onset of the disease, patients younger than 60 years old give an excellent response to medication. However, from the overall patient satisfaction, patients older than 70 years old and the one's nonresponder to medication are offered to have "an option of STN-DBS". Furthermore, DBS in advanced PD have 70.7% overall improvement score.^{15,48} Many of the similar studies concluded that the DBS produce better results in QoL compared the medical treatments.^{5,15} Despite the overt improvement, STN-DBS often show inadequate results in the overall patient's personal social life. Therefore, not only the preoperative psychosocial preparation but also the postoperative psychosocial care is important.⁴⁹ Hence, the best management of PD-DBS asses with the maximizing benefit and minimizing risk. The latter could only be carried out with the interdisciplinary team before and after the DBS.

Contradictory to Krack *et al.*, STN-DBS results in a mean reduction of "off-symptoms" of 60%. Among them most cases the dopaminergic medication can be reduced significantly so that inevitable, disabling dyskinesias could be reduced by about 60% and improvement in UPDRS motor scores after the DBS can reach 66% at 1 year.²⁴

In the study of Kleiner-Fisman *et al.*, DBS reduce the overt UPDRS II (daily living) and III (motor) scores on average of 50% and 52%, respectively.⁵⁰ When the stimulation is turned off in the same patients, 90% of the UPDRS motor scores were ever worse within 2 h. Switching from STN-DBS improves all motor UPDRS (at a faster rate than they were worsened).⁵¹ The average of reduction in dyskinesia with DBS was 69.1%. Indeed, major improvements were observed in QoL following STN-DBS.⁵⁰ York *et al.* emphasized those patients who underwent DBS decline not only in verbal recall but also in oral information processing (6 months of period).⁵²

From the psychiatric point of view, STN-DBS have shown to be effective in induce variable neuropsychological changes (i.e. from laughter to depression, to suicidal ideas and other mood changes).⁵³ Surprisingly, a mildly depressed patient (before surgery) resembles significantly improvement in the mood beck depression inventory scores.⁴⁷ Since the frequency of depression and manic attacks can increase relatively in DBS cases. Another study yielded cognitive decline and depression is decreased in 7.7% and 18% of the patients, respectively.⁴⁸ Hence, adequate support is given on both the psychiatric treatment and the psychosocial condition should not be excluded from surgery.⁵⁴

DBS-GPi shows dynamic and fast response on the immediate reduction of L-Dopa-induced disabling dyskinesias of about 80% and "off"-period motor symptoms and motor fluctuations gradually declined in time.⁵⁵ Vim-DBS, on the other hand, reveals the effective control of tremor 6 years postoperatively. However, the axial symptoms of the disease (speech, gait, and postural instability) worsen. Although having no effect on the akinesia and rigidity, still it is a relatively lenient surgical procedure and has a place for long-term symptomatic control of PD tremor in selected cases.⁵⁶

Long-term improvements with DBS both with STN and GPi installation for up to 5 years have been demonstrated especially on motor fluctuations and similar improvements have been demonstrated for tremor with STN, GPi, and V DBS as well. Despite these positive results, PD continuation could be prevented to progress in clinical manner after DBS, and there is little evidence that DBS alters disease progression.¹³

Increased length of hospitalization depends on severe factors: (1) More microelectrode passaging during DBS procedures, (2) higher presurgical UPDRS score especially with "on" medication, and (3) lowered presurgical cognitive screening scores of MMSE.³⁸

BATTERY LIFE

It is straight forward that the battery life depends on stimulation parameters, but its need for replacement is typically every in 3–5 years. Recently, noval stimulation device has been introduced. This device allows wireless recharging without changing the surgical procedure. Stimulation adjusted by a handset device that communicates wirelessly with the implanted programmable generator.^{10,17,25,30} In addition, this device is outside of the body and work with regular battery.

POSTOPERATIVE FOLLOW

In the early postsurgical period, significant improvements of symptoms may occur yet the stimulator is not activated. This amazing clinical improvement is attributed to a microlesioning effect, and this effect disappears in the course of time, i.e., 2–4 weeks. In the following days and weeks, stimulation amplitude will be increased by electrophysiologist and neurologist successively, paralleled by a gradual decrease

of levodopa dosage, until “Stability in between a good mobility and medical dosages” is achieved with no significant dyskinesias.⁵⁷

HEALTHY ECONOMY

Although the PD causes high financial burdens, still the DBS operation is a nonexpensive procedure.⁴⁸ Economical issues should be taken into account due to its a cost-effectiveness of the overall procedure. The amount of drug therapy required in the patients underwent DBS unilaterally or bilaterally is about one-third lower than the amount required by those in the medical therapy patients at the same state of PD. Thus, the cost-effectiveness of the DBS reduces in the amount of drug therapy. Finally, DBS is a better and logical option financially when compared to with inevitable drug therapy.^{58,59}

CONCLUSION

PD is one of the neurological disorders that becoming one of the major problems in the aging part of the population. Although the PD is not a static disease, still it is a dilemma for the proper and suitable approach for treatment in time scale. It is clear that functional neurosurgery can produce spectacular benefits. Recent advances dictate us that DBS for PD has become an acceptable treatment option for improved QoL. DBS produce its most important benefits when the right patient and experienced team parameters come alone.

The interdisciplinary team will work with patient in every step from the beginning of PD diagnosis, clinical course, and medical treatment continuum to the decision of DBS, type and place of DBS, preparation of operation, pre- and post-operation period and to tune the stimulator to the parameters that may give patient the most benefit.

DBS is placed in deserved and planned place in PD. It seems to continue to soar new areas as well. In near future, the some unknown sides of DBS will be illuminated either the MER issue or the roles on different nuclei connections.

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Conflicts of interest

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