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Deep Brain Stimulation: The Perspective of Brain Connectivity

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<http://dx.doi.org/10.5772/62829>

Abstract

Deep brain stimulation (DBS) has been demonstrated as a treatment option to alleviate patient symptoms in movement disorders, such as Parkinson's disease (PD) and dystonia, and has emerged as an alternative treatment for medically intractable epilepsy. However, complete understanding of the mechanism of DBS remains elusive despite recent human and nonhuman studies that have provided mechanistic clues. The precise mechanisms of action for DBS remain unclear. This review provides an up-to-date overview of the detailed procedures of DBS and reviews the actions of DBS on brain networks. Studies regarding the structural and functional connectivity of the brain are also reviewed.

Keywords: Deep brain stimulation, Mechanism, Structural brain connectivity, Functional brain connectivity, brain network

1. Introduction

In previous decades, the function of deep brain stimulation (DBS) has been demonstrated as the activation or inhibition of specific brain regions, which are the targets of DBS [1, 2]. It has been suggested that the mechanism of DBS must be an inhibition of an area of a pathological network in the brain because the clinical results for DBS are similar or better than classical ablation therapy. However, we soon had to admit that it is not an activation/inhibition problem of a specific brain region, but rather the neuromodulation of brain networks [3–5]. The concepts of brain network neuromodulation were based on the idea that DBS represents not only remarkable therapeutic benefits for patients but also an amazingly powerful research tool to interrogate brain networks. Specifically, the underlying brain function may

be demonstrated if DBS is used in conjunction with noninvasive neuroimaging methods, such as magnetoencephalography (MEG), electroencephalography (EEG), and functional imaging modalities.

In previous decades, studies regarding the structural and functional brain networks have nourished us in terms of how DBS works. Nevertheless, the knowledge regarding the structural networks of the brain was cruel and so were the functional networks. The structural networks of the brain have been investigated with various modalities [3, 5–8]. Furthermore, studies have been extended toward functional brain connectivity via investigations with models based on MEG and EEG [9, 10]. Recently, an emerging trial has been attempted to connect structural and functional brain connectivity and understand the genuine brain networks [4, 11].

This review provides us an up-to-date overview of the detailed procedures of DBS and monitoring during surgery, as well as reviews the actions of DBS on brain networks based on human and nonhuman studies. Furthermore, studies regarding the structural and functional connectivity of the brain are also reviewed.

2. Deep brain stimulation

2.1. Historical review

DBS is a surgical option that has not arisen *de novo*. It has resulted from a gradual evolution. The first trial reported to modulate brain function via electrical brain stimulation was in 1870 [12]. Electrical stimulation of the motor cortex in a dog provoked limb movement. Sir Victor Horsley, the father of functional neurosurgery, first performed intraoperative brain stimulation in 1884 [13]. He demonstrated conjugational eyeball movement via electrical stimulation of the corpora quadrigemina within an occipital encephalocele. Modern style stereotactic electrical stimulation in humans was conducted by Spiegel et al. [14] in 1947, which was approximately 30 years after the invention of the first animal stereotactic apparatus in 1908 by Horsley and Clark [15]. The first human case exhibited Huntington's disease. The authors used brain stimulation to identify the correct position of the lesion within the brain. Stereotactic brain stimulation subsequently continued to be used in nearly every stereotactic surgery because its purpose was to ensure the position of the lesioning electrode.

As stereotactic brain surgery progressed, it was recognized that brain stimulation within the target may have a mimicking effect with the target lesioning. Hassler et al. [16] reported that the stimulation of the ventral lateral (subsequently referred to as the ventral intermediate nucleus of thalamus (VIM)) nucleus of the thalamus during stereotactic localization may terminate the tremor. Furthermore, Alberts et al. [17] reported that dystonic symptoms improved following stimulation during stereotactic surgery. Delgado et al. [18] introduced electrode implantation in human brains as a technique for chronic recording and brain stimulation, and Heath [19] initiated depth electrode studies for psychotic patients in the 1950s.

Mortimer and Shealy became involved in an implantable stimulator in Medtronic in 1965, and the base of the DBS system was founded [20]. Shealy et al. [21] implanted the first dorsal column stimulator in 1967, and, thereafter, the neuromodulation for pain was actively performed. The early stimulators at this time comprised two parts, including an implantable passive receiver and a battery-controlled external device. The two parts were coupled by radiofrequency and transmitted both control and power. In 1981, Medtronic released a completely implanted stimulator. In the mid-1970s, Cooper et al. [22, 23] introduced cerebellar cortical stimulation for the treatment of epilepsy and cerebral palsy.

In 1973, Hosobuchi et al. [24] stereotactically implanted a DBS electrode in the somatosensory thalamus to treat denervation pain. It had previously been recognized that stimulation during surgery could mimic the effects of lesioning from the early era of stereotactic surgery; however, the mechanism was not fully understood [25]. The target of DBS to treat movement disorders naturally originated from the target of ablation surgery. Brice and McLellan [26] first reported DBS for movement disorder in 1980. The patient was suffering intentional tremor with no pain because of multiple sclerosis. They implanted the electrode in the thalamus to control the tremor. In 1986, Siegfried [27] demonstrated an improvement of dyskinesia in a patient with pain caused by Dejerin-Roussy syndrome, which had undergone DBS implantation to treat the pain. Benabid et al. [1] introduced the use of chronic VIM stimulation for the treatment of Parkinsonian tremor. Finally, high-frequency stimulation was used at any targets that were used for lesioning in the 1980s.

Hesitation remained to implement DBS for Parkinson's disease (PD) at this time because physicians preferred medical management with L-dopa and related drugs. However, the surgical management of PD was reborn following the reintroduction of pallidotomy in 1992 [28]. DBS was also reintroduced with the same target in 1994, and several neurosurgeons subsequently popularized it [29–31]. Benabid has attempted to elucidate the mechanisms of DBS for movement disorders and to make it widely accepted. He also reported bilateral subthalamic nucleus (STN) stimulation for PD [32]. Forel's field and zona inserta have been suggested as novel targets, in addition to the STN and globus pallidus internus (GPi). To date, DBS has returned toward the era of brain lesioning for psychological conditions and epilepsy. Moreover, it has not only accepted all old targets with the fundamentals obtained through human and nonhuman investigations but has also expanded new targets from vigorous investigation.

2.2. Surgical indication

DBS is most commonly used to alleviate the motor symptoms of PD despite initial implementation to treat intractable pain. It may be used for the treatment of dystonia and essential tremor. Furthermore, it is in limited use or under investigation to treat various neurological and psychological conditions, including epilepsy, obsessive-compulsive disorder (OCD), and major depression. DBS has opened new horizons for the surgical treatment of various neurological and psychiatric conditions [33]. The spark to extend the clinical indications has expanded to investigational research on neurological, psychological, cognitive, and behavioral

conditions. **Table 1** comprises a summary of the surgical indications for DBS according to the symptoms that require treatment.

Indications	Medical conditions
Parkinsonism (tremor, bradykinesia, and rigidity)	Idiopathic Parkinson's disease
Tremors	Parkinson's disease (only tremor dominant), Essential tremor, <i>Rubral tremor, posttraumatic tremor</i>
Dystonic movement	Primary dystonia, <i>Secondary dystonia</i>
Dyskinesia	Parkinson's disease (Dopamine-induced dyskinesia), Tardive dyskinesia
Chorea	<i>Huntington's chorea</i>
Seizures	Intractable epilepsy as a result of many cause
Mood	Major depression
Obsession	Obsessive compulsive disorder
Tics	Tourette's syndrome
Pain	Chronic pain, <i>Cluster headache</i>
Obesity	<i>Eating disorder</i>
Anorexia nervosa	<i>Eating disorder</i>
Cognitive failure	<i>Alzheimer's disease, Severe traumatic brain injury</i>
Addiction	<i>Psychological cause</i>
Tinnitus	<i>Uncontrollable otological problem</i>

Limited use or investigational state in italics.

Table 1. Summary of symptoms for treatment via DBS.

2.3. Optimal targets of DBS

Successful surgical results of DBS definitely originated from the optimal target according to the specific symptoms or disease entities. For example, the classical target for tremor has been the VIM of the thalamus since the era of stereotactic brain lesioning. However, Parkinsonian tremor has also been controlled with other Parkinsonian symptoms via STN stimulation. Moreover, many surgeons have often targeted the GPi to treat patients with predominately dopamine-induced dyskinesia with minimal tremor [34]. Some authors recommend the GPi better than the STN for patients with postural instability and gait disturbance as indicated by a meta-analysis [35]. Randomized controlled studies have not concluded which target is better for PD patients [36–38]. Moreover, there is no general consensus regarding the best target, the STN or GPi. Consequently, the choice of best target for an individual patient may depend on the conditions the patient has suffered.

As DBS widened its clinical indications, new targets have continuously emerged. Ethical problems have been associated with new targets; however, vigorous investigation regarding the new targets has been performed through nonhuman experiments to prove its efficacy and safety. **Table 2** shows the targets published to date regarding whether they are established or investigational.

Indications	Targets
Parkinsonism (tremor, bradykinesia, and rigidity)	STN, GPi, and PPN
Tremors	VIM
Dystonic movement	GPi
Dyskinesia	GPi
Chorea	GPi
Seizures	ANT, DMT, Hippocampus, Cerebellum
Mood	<i>GPi (anteromedial), NA, Anterior capsule, Medial thalamic structure, Prefrontal cortex, Cingulum, Dorsolateral prefrontal cortex, Inferior thalamic peduncle, Prefrontal cortex, Ventral striatum, Zona inserta (medial part)</i>
Obsession	<i>NA, Anterior capsule, Bed nucleus of stria terminalis, inferior thalamic peduncle, STN (limbic part), ventral striatum</i>
Tics	<i>GPi (posterovental), STN, NA, Anteromedial pallidus internus, CMpf, Voi, Ventral striatum</i>
Pain	Vpm/Vpl, Motor cortex, PAG/PVG, posteromedial hypothalamus
Obesity	<i>Lateral hypothalamus</i>
Anorexia nervosa	<i>Subgenual cingulum</i>
Cognitive failure	<i>Nucleus basalis of Meynert, fornix, entorhinal area, medial thalamus</i>
Addiction	NA
Tinnitus	VIM
Limited use or investigational state in italics. ANT, anterior nucleus of thalamus; CMpf, centeromedin parafasciculus of thalamus; DMT, dorsomedial nucleus of thalamus; NA, nucleus accumbens; PAG/PVG, periaqueductal gray/periventricular gray; STN, subthalamic nucleus; GPi, globus pallidus internus; PPN, pedunculo pontine nucleus; VIM, ventral intermediate nucleus of thalamus; Vpm/Vpl, ventral posteromedian/ventral posterolateral thalamus.	

Table 2. DBS targets previously published.

2.4. Surgical procedures of DBS

Advanced surgical skills are not necessary to perform DBS. However, the flow of surgical procedures should be well acquainted. The author would like to divide the flow of surgical procedures into five steps because there are common steps of all DBS procedures and different

steps depending on the specific target of DBS. Moreover, the author would like to introduce what the author is doing and include several tips that other authors have recommended in the literature.

2.4.1. Preoperative step

The clinical decision regarding whether DBS may be helpful for a specific patient is critical. Prior to this decision, an exact diagnosis is necessary using a multidisciplinary approach. Most movement disorders are clinically diagnosed, which implies a small portion of uncertainty. Nevertheless, an exact diagnosis may inform the surgeons, as well as the patients and their families regarding the expected results of DBS. The author highly recommends organizing a team that comprises a neurologist, neuropsychiatrist, neuropsychologist, anesthesiologist, and special nurse (may vary from institute to institute) in your institute to discuss and confirm the diagnosis and clinical indications. In the case of PD, an L-dopa challenge test is necessary to confirm DBS. The PD patient may need to be hospitalized for this test for several days.

Once the decision is made, the patient undergoes the surgical procedures. Patients considered for DBS must be hospitalized for several days. In the case of PD, antiparkinsonian medication should be terminated for 4–12 h according to the duration of the on-time prior to the start of surgery. Too early cessation of antiparkinsonian medication will cause substantial discomfort. On the day of surgery, the stereotactic frame was applied following a local anesthesia injection at four pinning sites. The author uses a Leksell G stereotactic frame. Cosman-Roberts-Wells (CRW) or other stereotactic frames may also be used. The stereotactic frame should be applied parallel to the line from the nose ring to the tragus. The author recommends that the accuracy of the stereotactic frame should be checked regularly as recommended by the manufacturer. Frameless DBS is currently performed in some institutes with reported results and accuracy [39–41]. These authors have indicated that the accuracy is the same as previous frame-based DBS, and the choice should be based on surgeon preference.

The patient is subsequently transferred to the MRI room. The patient's head with frame is fixed to the adaptor of a 1.5 T MRI. The MRI scan is performed, including 1 mm T1-weighted axial images with gadolinium enhancement (recommend double-dosed enhancement) and 2 mm T2-weighted axial images. If the condition is allowed, 2 mm T2-weighted coronal images may be obtained (may be optionally fused with T2 axial images, described later in the Targeting step). In some institutes, MRI is performed on the day prior to surgery, and computed tomography (CT) is conducted after frame application on the day of surgery. MRI is subsequently performed on the previous day and is fused before targeting [42]. Some authors recommend contrasted CT because of the vessel visualization issue [43, 44]. This approach is completely based on surgeon preference. The patient is transferred to the operating room to prepare for the surgical step.

2.4.2. Targeting step

All MRI images are transferred to a Leksell Surgiplan workstation (Elekta, Sweden). The author also uses FrameLink (Medtronic, Minneapolis, USA) and believes that there is no

specific difference that affects the surgical results. There may be other planning stations depending on the institutes. First, the anterior commissure (AC) and posterior commissure (PC), which are the anterior and posterior extremes, respectively, of the third ventricle, should be identified in T1 axial and sagittal images. The AC–PC line-based target coordinates are defined in the T2-weighted images, depending on the target at the time of surgery decision. At this time, T2-weighted axial and coronal images are fused if these are available. The author feels that this work may minimize the distortion error of the MRI images even though the distortion error of a 1.5 T MRI image is within the acceptable boundary [45]. The targets, such as the STN and GPi, may be easily visualized on T-2 weighted MRI images (**Figure 1**). However, the author first defines the target using formulated coordinates and subsequently adjusts it in the case of the STN and GPi. After the target is defined, trajectory from the cortical entry point will be defined. The recommended entry point is the middle frontal gyrus, and the visualized vessels should be avoided. Furthermore, the trajectory through the ventricle should be avoided. At this point, adjustment of the target may be necessary because a different trajectory may modify the optimal penetration of the target. Maximal options may be used for the stimulation sites, and optimal results may be expected when the electrode covers the maximal area of the target. Some authors have first defined the trajectory, followed by the target. The author thinks that the order between the trajectory and target does not matter because some adjustment should be followed according to the vessel positions and the best penetration of the target. **Table 3** shows the common target coordinates of DBS.

Figure 1. T2-weighted axial MR image indicates red nucleus and subthalamic nucleus.

	STN	GPI	VIM	Vpm/Vpl	NA
AC-PC line	50%	50%	28.5% anterior	33.4% anterior	100% anterior
Vertical	2–4 mm inferior	4 mm inferior	0	0	1–3 mm inferior
Lateral	11–13 mm	20–22 mm	12–15 mm	11–14 mm	6–9 mm
Axial	1–3 mm posterior	1–2 mm anterior	0	0	7–9 mm anterior

NA, nucleus accumbens; STN, subthalamic nucleus; GPI, globus pallidus internus; VIM, ventral intermediate nucleus of thalamus; Vpm/Vpl, ventral posteromedian/ventral posterolateral thalamus.

Table 3. Decisions regarding common targets of DBS.

2.4.3. *Operative step*

The patient is positioned supine, and a stereotactic frame is fixed to a special headrest. The patient’s head and upper body may be elevated, and the knees are slightly flexed on the pillows. This sitting-like position is for the patient’s comfort and is helpful to minimize the flowing out of cerebrospinal fluid (CSF) through the burr holes during surgery. Prior to draping, special monitoring may be needed, for example, EEG for an epilepsy case and EMG for a movement disorder case. Absolute separation of the sterile area from the nonsterile area is critical. The author uses a transverse metal bar and a large transparent drape that exposes only the upper area of both sidebars of the stereotactic frame. A double-check of the target coordinates by two neurosurgeons are highly recommended. A neurologist or special nurse should be present during surgery by the patient’s side, in the opposite area from the surgical field. The intracranial electrode implantation is performed under local anesthesia. A local anesthetic injection is administered around the skin incision marks after the trajectory is set with the correct target coordinates. The author prefers curvilinear skin incisions to avoid skin erosion complications [46]. A burr hole is made with a pneumatic perforator, and bleeding was completely controlled. An incision on the dura mater is subsequently performed and completely coagulated. A corticotomy follows with specific attention on avoiding the vessels and sulcus. At this point, when the dura mater is opened, normal blood pressure and normal intracranial pressure should be confirmed. If the patient is not calm, brain-penetrating procedures may be extremely harmful. Once the outer cannula is inserted, the burr hole should be sealed to avoid CSF outflow [47]. Prior to the introduction of the microelectrode recording (MER) electrode, the patient should be neurologically examined by a neurologist or a special nurse.

The MER electrode is descended 10 mm above the target. The MER was checked every 1 mm and should be 0.5 mm or less than 5 mm above the target. In the case of PD, a typical MER finding of the STN may be identified, and the MER is typically descended to the substantia nigra pars reticulata (SNr). In the case of dystonia, a typical GPI firing may be identified, and the descent of the MER continued to the optic tract. The length of the target that the MER electrode penetrates is checked, and the selection of the current trajectory and the depth of intracranial electrode contact are subsequently decided. The author prefers a single track MER rather than a multichannel (e.g., Ben gun) MER system and believes that there is no difference

in the results [48]. A test-stimulation is subsequently conducted via the MER electrode. The author checked the clinical effect during the stimulation and the side effects related to the stimulation. In the case of epilepsy, EEG changes, i.e., driving response or recruiting rhythm, may be identified during low frequency stimulation of the thalamus during test-stimulation [49, 50]. If the test-stimulation is satisfactory, a permanent electrode is introduced toward the previously decided depth under fluoroscopy. The final trajectory and position of the electrode should be decided by three aspects; first, the exact image-guided target; second, the proper MER finding; and third, an adequate physiological response to the test-stimulation. After the electrode is introduced, test-stimulation via the permanent electrode is performed to confirm the correct position. If it is satisfactory, the electrode is fixed with a special fixing system of the DBS system with attention paid to the depth of electrode under fluoroscopy. The same procedure would be performed on the other side.

The patient is transferred to the CT room without removing the stereotactic frame. A CT scan is performed at 1 mm without enhancement to confirm the position of the electrode and intracranial hemorrhage. The CT images are transferred to the same workstation used for the target planning. After the exact electrode position is confirmed with an image fusion technique, the patient's frame is removed. Implantable pulse generators (IPG) were subsequently inserted into the bilateral subclavian area under general anesthesia. There are several options to perform DBS, i.e., bilateral simultaneous intracranial electrode insertion and IPG insertion on the same day, unilateral intracranial electrode insertion and same side IPG insertion on the same day, bilateral intracranial electrode insertion on one day and subsequent IPG insertion on another day, and unilateral intracranial electrode insertion on one day and subsequent IPG insertion on another day. These options are all successful and may be different depending on the surgeon's preference, patient's condition, and other various health system logistics [42, 51–56].

2.4.4. Postoperative step

The patient is transferred to the recovery room following the insertion of the IPG ends. Following recovery from anesthesia, the patient is transferred to the neurological ward. Surgery-related issues are considered during hospitalization. First, surgical infection related to hardware may be an issue. Prophylactic antibiotics are initiated from the preoperative stage to postoperative 2–3 days. The surgical wound should be closely followed thorough the wound healing course. The author recommends that stitches are removed 9–10 days after surgery. Hospitalization is not required for this entire period. The inpatient period depends on the condition of the patient. Second, a microlesional effect of DBS (transient and irregular symptomatic improvement after DBS) may be an issue. Most patients who underwent DBS experience an improvement of preoperative symptoms without stimulation. The period of microlesional effect varies by patient; however, it typically lasts from days to weeks. Medications, especially anti-parkinsonian medications, should be decreased according to the patient's symptom improvement during this period. Third, the timing of stimulation may be an issue. The author recommends that the stimulation is initiated 4–6 weeks after surgery. The reasons are that stable effects of stimulation cannot be expected without full recovery of the patient's

condition and microlesional effects disturb the tuning of the stimulation parameters. Fourth, delirium or other psychological symptoms in limited patients, such as old aged PD, may be an issue [57]. These symptoms typically last 3–7 days after surgery and may result in an extension of the hospital period. The symptoms are easily controlled with tranquilizers; however, a special psychological consultation may be needed.

2.4.5. Outpatient follow-up step

During the outpatient follow-up step, the most important issue is the initiation of stimulation. As the author previously mentioned, stimulation will be initiated 4–6 weeks after surgery. The author recommends that the patient may require hospitalization for 1–2 days unless the outpatient department provides sufficient room to check the patient's walking and whole movements with trial-and-error based stimulation and sufficient time to wait for patient's symptom changes with stimulation. The author prefers a shorter follow-up (1–2 weeks) during the early simulation period for fine-tuning of the stimulation with an adjustment of medication. Regular follow-up may subsequently be continued with the neurologist or the neurosurgeon every 6–8 weeks. Neuropsychological tests and other special studies, such as EEG and video movement evaluation, may be conducted every 1–2 years. The institute where DBS is performed should construct a system (via telephone or in person) for the patients to contact any time if they have concerns related to DBS.

2.5. Clinical results

Essential tremor is the most common movement disorder. VIM DBS is the most commonly used target for this condition. Long-term follow-up studies have demonstrated a 40–80% reduction in the tremor severity and corresponding improvement in the quality of life [58–65]. **Table 4** shows the results of 1 year and longer follow-up studies on VIM DBS for essential tremor [63, 65–68]. Approximately 10% of patients do not have adequate tremor control with VIM DBS. Furthermore, approximately 15% of patients initially improve, but subsequently lose efficacy within one year after surgery [69].

PD is the most well-published disease entity. All publications have used the medically validated unified Parkinson's disease rating scale (UPDRS), which comprises four components: Part I assesses changes in mentation and cognition (including behavior and mood); Part II assesses changes in daily living activities; Part III assesses motor symptoms; and Part IV assesses therapeutic complications [70]. Hoehn and Yahr [71] have also been used to assess the disease stage, as well as a PD questionnaire (the 39-item PD questionnaire, PDQ-39) to determine the quality of life [72]. The mainstay of PD management is medical therapy in the early stage and surgical therapy in the later stage of the disease. The goal of the therapy is to increase the dopamine level in the brain and/or prolong the effect of dopamine [73]. DBS and medical therapy have been compared in large controlled trials as showed in **Table 5** [74–76]. Most studies have reported that DBS is superior to medical therapy in improvements; however, DBS has more serious adverse events. The long-term results of DBS have also been reported [77–79]. **Table 6** shows the long-term results of STN DBS.

No. of patients	Follow-up	Tremor improvement	Publication year	Authors
37 (28 bilateral, 9 unilateral)	1 year	General 55%; head (bilateral only) 85%; arm 80%; leg 75%; ADL 80%; voice none	1999	Limousin et al.
27 (14 bilateral, 13 unilateral)	1 year	Unilateral: arm 82%; head 38%; voice none Bilateral: head 95%; voice 83%	2000	Obwegeser et al.
25	40.2 months	Overall tremor 50% at last follow-up	2001	Koller et al.
19	6–7 years	Upper extremity tremor reduction: 100% of patients at 2 years, 84% of patients at 6–7 years	2003	Rehnerone et al.
19 (12 bilateral, 7 unilateral)	6.5 years	General 41%; arm 50%; head (bilateral only) 85%; voice none	2003	Sydow et al.

Table 4. One year or more follow-up studies regarding VIM DBS for essential tremor.

No. of patients	Follow-up	Improvement	Adverse events	Publication year	Authors
124 STN DBS 127 Medical	2 years	DBS>Medical	54.8% DBS, 44.1% Medical of serious adverse events	2013	Schuepbach et al.
174 STN DBS 183 Medical	1 year	DBS>Medical	20 patients DBS, 13 patients Medical of serious adverse events	2010	Williams et al.
78 STN DBS 78 Medical	6 months	DBS>Medical	13% DBS, 4% Medical($p < 0.04$) of serious adverse events	2006	Deuschl et al.

Table 5. Comparison of DBS and medical therapy.

No. of patients	Follow-up	Motor improvement	L-dopa equivalent dose reduction	Publication year	Authors
14	9 years	UPDRS motor score: 42% ADL: no improvement Motor complication: 59%	39%	2011	Zibetti et al.
18	10 years	UPDRS motor score: better than baseline ($p = 0.007$)	significant	2011	Castrioto et al.
20	8 years	UPDRS motor score: better than baseline ($p < 0.001$)	60.3%	2010	Fasano et al.

Table 6. Long-term results of subthalamic nucleus DBS.

DBS for dystonia is also well published. The severity of dystonia is quantified by several rating scales, including the Burk–Fahn–Marsden dystonia rating scale (BFMDRS) for generalized dystonia, and the Toronto–Western Spasmodic Torticollis Rating Scale (TWSTRS) for cervical and craniocervical dystonia [80, 81]. Bilateral GPi DBS for generalized primary dystonia results in a 60–80% improvement in the BFMDRS in open-label studies and 40–50% improvement in prospective, double-blind, randomized trials with 6–12 months of follow-up [82–87]. Tardive dystonia, which represents secondary dystonia, has a favourable outcome with DBS in several small, open-label studies that indicate a 50–70% improvement [88, 89]. Primary cervical and craniocervical dystonias have fair results following DBS, with a 40 > 70% improvement in the TWSTRS [90–93].

2.6. Complications

2.6.1. Surgical procedure-related complications

The surgical procedure-related complications are more or less similar regardless of the diseases and targets of DBS. In general, the most devastating complication is intracerebral hemorrhage (ICH). The overall incidence of ICH during DBS, regardless of the amount of ICH, has been reported as 1–9% [94–99]. The condition of patients with ICH during surgery depends on the location and the amount of ICH. The author believes that symptomatic ICH accounts for less than 1% of all procedures, and the occurrence of permanent deficits is lower [100]. The author recommends that several variables should be completely considered; first, a careful evaluation of blood coagulation; second, the avoidance of visualized vessels during trajectory planning; third, blood pressure control during surgery; and four, the

maintenance of patient calmness during surgery. There is no general consensus regarding whether the MER is related to ICH [101, 102]. Cerebral infarction occurs; however, it is extremely rare [103–106]. Other complications associated with permanent neurological deficits are postoperative delirium, seizures, and other complications in the patient's general state. These surgical procedure-related complications have not been correlated with the duration of surgery or the electrode passing number [96, 107–110].

2.6.2. *Hardware-related complications*

There are many reports regarding hardware related complications, and the incidence is quite high, i.e., 2.7–50% [86, 94, 95, 98, 99, 111–121]. Most complications are infections, and their occurrence rate is 1.1–15% of published cases. The infections are predominantly superficial, and only approximately 1% are severe. They typically occur within 3 months after surgery, and IPG sites are more common [97, 98, 108, 111, 114, 115]. Other hardware-related problems include erosions of skin, lead fracture, IPG malfunction, and premature IPG drain-out [97, 99, 108, 113, 122, 123]. These problems cause additional procedures or surgeries; however, they may be managed without permanent deficits. Minor hardware-related problems include discomfort around the extension lead and thickening of scars. Although it is extremely rare, head trauma may occur in patients with the DBS system. This issue has been reported, and there was no stimulation failure problem if the electrode location was maintained [124, 125].

2.6.3. *Stimulation-related complications*

Stimulation-related complications are common; however, permanent neurological problems induced by these complications are rare. Complications often occur if the electrode placement is suboptimum. The current through the electrode spreads to the neural tissue around the target if the electrode location is not separate from the eloquent tissue, and the stimulation provokes unwanted neurological symptoms that vary according to the anatomical location [118, 120, 126, 127]. Common complications include dysarthria, dysphonia, paresthesia, motor contraction, eyeball deviation, visual flushes, nausea, dizziness, eyelid opening apraxia, sweating, and dyskinesia. The major advantage of DBS is the changeability of the stimulation parameters and contacts. Most stimulation-related problems are managed with an adjustment of stimulation. Some patients initially have no problem and subsequently develop stimulation-related complications as the stimulation parameters are progressively increased. This occurs in the optimal placement of the electrode; thus, the stimulation, drugs or both should be adjusted [75, 127, 128].

Alterations in higher brain functions have been reported in PD patients. Most patients who have cognitive or behavioral deterioration after surgery had similar symptoms prior to surgery [129]. Common symptoms include transient hypomania, acute sadness, impulsive aggressive behavior, hilarity, or mania, and these symptoms occur as a result of both drugs and STN DBS [75, 128, 130–133]. Suicide is an emerging concern in PD patients who underwent STN DBS [94, 129, 134]. However, depression and suicide are multifactorial, related to treatment change or related to social issues and are not specifically related to the procedure [135]. Mood changes

after STN DBS may represent abnormal behaviors caused by abrupt changes in limbic STN activity [131].

3. Mechanism of DBS

To date, it is clear that DBS represents functionally reversible lesioning [136]. DBS has different clinical effect times according to the indications and targets [137]. For example, VIM DBS for essential tremor resulted in the disappearance of tremor within seconds [138]. STN DBS exhibited an improvement of tremor within seconds, an improvement of bradykinesia and rigidity within minutes to hours, and an improvement of axial symptoms within hours to days [139, 140]. Similar phenomena in which the clinical effect time varies were demonstrated when we turned on/off the stimulation and when we stimulated other targets for psychological problems and intractable epilepsy [140–145]. These different responses to DBS suggest that its mechanisms are complicated, i.e., immediate neuromodulation and synaptic plasticity and anatomical remodeling [137, 140].

3.1. Acute responses: immediate neuromodulation

Stimulation through the DBS electrode inserted into the target inhibits neurons near the electrode. This finding was classically demonstrated clinically and was also supported by the determination that neurochemical inhibition improved Parkinsonian signs in animal models [146, 147]. The inhibitory effect of DBS was explained via in vitro studies. High-frequency stimulation induced a depolarization block, i.e., a sustained depolarization of neuronal membranes, inactivation of sodium channels, and increase of potassium currents [148, 149]. Furthermore, DBS activates inhibitory presynaptic terminals on the afferents to the cell body. The inhibitory action occurs through the release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [150].

Axons and dendrites around the electrode are predominantly affected rather than the soma because of the substantially high threshold of the soma [151]. Consequently, neurons whose dendrites or axons are close to the electrode may be more readily activated [152]. The action potentials of the affected neurons propagate away from or toward the soma. Clinical physicians may identify the effects of DBS when they change the stimulation parameters, for example, by adjusting the number and configuration of the anode or cathode electrode contacts and the voltage or current of the stimulation. Furthermore, evidence suggests that DBS induces action potentials in the passing afferent fibers around the target [153, 154].

3.2. Chronic responses: plasticity and remodeling

DBS effects that emerge over a long period of time (days to months) may suggest that it changes neural networks. There is a report that STN stimulation in the rat brain induced various forms of synaptic plasticity in the STN neuronal subpopulation [155]. In dopamine-depleted rats, short-term depression and long-term depression were induced by high-frequency stimulation, and the effects of stimulation were abolished with the administration of dopamine agonist

[156]. This phenomenon suggested that stimulation-induced synaptic changes were sensitive to the dopaminergic state. A recent addiction animal model demonstrated that low-frequency stimulation of the nucleus accumbens reversed cocaine-evoked plasticity [157]. In clinical research, DTI and fMRI before DBS and after 5 months of DBS (at this time, the patient's DBS system was extracted because of other problems) indicated shifted images toward more typical images of a normal healthy control [11]. Although this study comprises a single human report, these changes induced by DBS will be reproducible in the future. A substantial number of PET studies have previously demonstrated that DBS in OCD, dystonia, depression or PD reversed the metabolic activity or cerebral blood flow toward the normal baseline [158–164].

The neuroprotective or neuroregenerative effects of DBS remain uncertain. However, there are limited reports regarding the neuroprotective effects of DBS. A Parkinsonian rat model subjected to STN DBS or STN lesioning exhibited an improvement in the survival of substantia nigra pars compacta neurons [165–167]. It has been suggested that this effect was result of a reduction of glutamatergic excitation from STN hyperactivity [168]. STN DBS has been demonstrated to induce the neuroprotective growth factor brain-derived neurotrophic factor (BDNF) in the substantia nigra, GPi, and primary motor cortex [169]. Furthermore, GPi DBS altered glial-derived neurotrophic factor (GDNF) expression in the basal ganglia (BG) in an animal model [170]. The potential neuroprotective effects of DBS remain under vigorous investigation.

4. Brain connectivity and DBS

4.1. Modalities used to investigate brain connectivity

Researchers have used several modalities to investigate brain connectivity. Classical imaging modalities have demonstrated structural connectivity that indicates the morphometric properties of the brain, such as the volume of grey matter and connecting fibers through white matter. High-resolution T1-weighted MRI has been used to investigate structural connectivity via voxel-based morphometry [171]. DTI comprises a well-known method to identify brain structures by measuring the directional diffusion of water molecules. Recently, diffusion-weighted imaging (DWI) and fiber tractography have been used to assess the white matter microstructure and pathways of the whole brain [172, 173]. DWI uses the passive diffusion of water molecules to infer the properties of the surrounding tissue.

Functional imaging modalities include fMRI, PET, and SPECT, which indicate dynamic changes in hemodynamics or metabolism in the brain and are related to neural activity. These modalities have provided a window into the global and long-term changes in network activity as a result of DBS [174, 175]. They are unique to obtain system-level data in brain network activity; however, the data represent the indirect effects of neural activities and changes in afferent input to the activated region, not output [176]. Functional connectivity has been defined as the temporal correlations between spatially remote neurophysiological events [177, 178]. One of the prevalent modalities used to assess functional connectivity is EEG, which has been used to assess the brain electrical activities using electrodes placed on the scalp. The high

temporal resolution of EEG provided the benefit of estimating the changes in functional network connectivity [8]. MEG is also an option to evaluate the electrical activities of the brain. EEG and MEG data have provided valuable information regarding diseased brains, such as in Alzheimer’s disease, epilepsy, schizophrenia, Parkinson’s disease, and other neurological conditions [9, 179–182].

Structural and functional imaging modalities have their own specific spatial and temporal scales, and they are primarily evaluated independently. Recently, a multimodal approach has been attempted to better understand the structure–function associations. EEG–fMRI, EEG–DTI, fMRI–DTI, and other fusion applications have been reported [183].

4.2. Brain connectivity

The most common clinical form of DBS comprises the stimulation of the subthalamic region for PD patients. Currently, the most common research form of functional connectivity is based on studies of the BG stimulation. The author would like to briefly review the BG anatomy and neuromodulation of DBS via BG stimulation.

Four core nuclei compose the BG, which include the striatum (caudate nucleus and putamen), globus pallidus (internus (GPi) and externus (GPe)), substantia nigra (pars compacta (SNc) and pars reticulata (SNr)), and the STN [184–186]. The striatum and the STN receive inputs from the cortex, and the GPi and SNr provide BG output to the thalamus and brainstem. Striatal neurons comprise the direct (D1) and indirect (D2) pathways. The direct pathway is a mono-synaptic inhibitory pathway (GABA-ergic), and the indirect pathway is a polysynaptic and net excitatory pathway that involves the GPe and STN. Additional input originates from the thalamic intralaminar nuclei. GABA-ergic projections from the striatum inhibit thalamocortical projection neurons on the ventral anterior, ventrolateral, and intralaminar nuclei of the thalamus and brain stem neurons. Indirect projections from the striatum result in a net excitatory effect on the GPi and SNr, whereas direct projections exert an inhibitory effect on these output nuclei (Figure 2).

Figure 2. Connections of basal ganglia motor circuit. Solid arrows indicate excitatory (glutamatergic neurons) and double stranded arrows indicate inhibitory (GABA-ergic neurons). GPe, globus pallidus externus; GPi, globus pallidus internus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; PPN, pedunculopontine nucleus

There has been an increasing interest in the use of functional imaging to investigate the global brain effects of STN DBS in PD patients [187–191]. The functional imaging of PD patients indicated hypermetabolism in the pons, globus pallidus, and thalamus and hypometabolism in the premotor cortex, supplementary motor area, and parietal association area [192, 193]. In an fMRI study of STN DBS patients, activations were identified in a broad sensorimotor network, including the sensorimotor, supplementary motor and cingulate cortices, insula, caudate nucleus, pedunculo pontine nucleus (PPN), and cerebellum [175].

Experimental recordings have also demonstrated the phenomena of functional connectivity. An animal extracellular recording demonstrated increased neuronal activity in the GPi during clinically effective STN DBS, which is consistent with an increase in excitatory output from the STN [194]. Intracellular recording in rodents demonstrated STN DBS elicited antidromic action potentials to the cortex [195]. Microdialysis performed in humans during the implantation of a clinically effective DBS system resulted in increased extracellular cyclic guanosine 3':5'-cyclic monophosphate (cGMP) concentrations in the putamen, GPi, and SNr [196–199]. Extracellular cGMP is an indirect marker of local glutamatergic synaptic input, which is consistent with stimulation increasing STN output [200].

In a case of dystonia, the connection of the GPi to the ventral oralis posterior nucleus (Vop) of the thalamus was reported via microelectrode monitoring of the Vop during GPi DBS for generalized dystonia [201]. In this report, GPi stimulation provoked the activation of axons to the Vop and the antidromic activation of Vop axons; however, this was a case report.

5. Future of DBS

DBS is a well-established therapeutic option for various conditions. The surgical procedures are standardized but differ across centers. The complications are acceptable based on previous, well-designed studies. However, new targets and clinical indications are continuously emerging, and vigorous investigations are ongoing. The technical advancement of implantable devices is amazingly rapid. The author has confidence that a closed circuit system, as well as a more advanced technological system, will be invented in the near future.

To date, DBS is not only a clinical treatment option but is an amazingly powerful research tool; however, its mechanism and effects on the brain network continue to be investigated. Functional connectivity within the brain may be validated by the use of multimodal approaches using various tools.

Acknowledgements

This work was supported by a grant from research year of Inje University in 2015.

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