Chapter 2

Deep Brain Stimulation: The Perspective of Brain Connectivity

Hae Yu Kim

Additional information is available at the end of the chapter

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 Medtronics 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, *Rubral tremor, posttraumatic tremor*
Dystonic movement	Primary dystonia, *Secondary dystonia*
Dyskinesia	Parkinson's disease (Dopamine-induced dyskinesia), Tardive dyskinesia
Chorea	*Huntington's chorea*
Seizures	Intractable epilepsy as a result of many cause
Mood	Major depression
Obsession	Obsessive compulsive disorder
Tics	Tourette's syndrome
Pain	Chronic pain, *Cluster headache*
Obesity	*Eating disorder*
Anorexia nervosa	*Eating disorder*
Cognitive failure	*Alzheimer's disease, Severe traumatic brain injury*
Addiction	*Psychological cause*
Tinnitus	*Uncontrollable otological problem*

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	*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)*
Obsession	*NA, Anterior capsule, Bed nucleus of stria terminalis, interior thalamic peduncle, STN (limbic part), ventral striatum*
Tics	*GPi (posterovental), STN, NA, Anteromeidal pallidus internus, CMpf, Voi, Ventral striatum*
Pain	Vpm/Vpl, Motor cortex, *PAG/PVG, posteromedial hypothalamus*
Obesity	*Lateral hypothalamus*
Anorexia nervosa	*Subgenual cingulum*
Cognitive failure	*Nucleus basalis of Meynert, fornix, entorhinal area, medial thalamus*
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, pedunculopontine 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 (Medtronics, Minneapolis, USA) and believes that there is no

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

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.

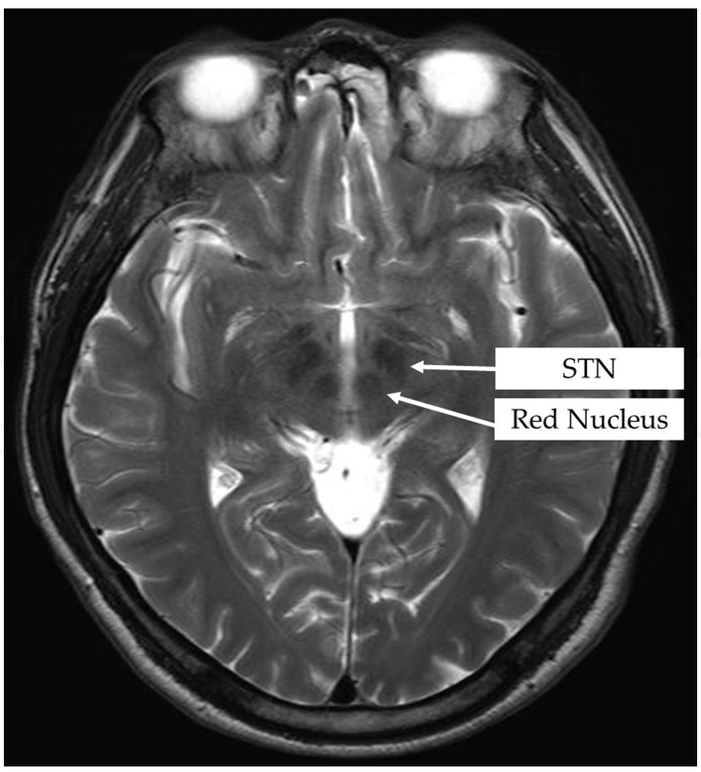

Figure 1. T2-weighted axial MR image indicates red nucleus and subthalamic nucleus.

	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 reticulate (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 wanted 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 mater. 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 mater 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 reticulate (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 monosynaptic 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**).

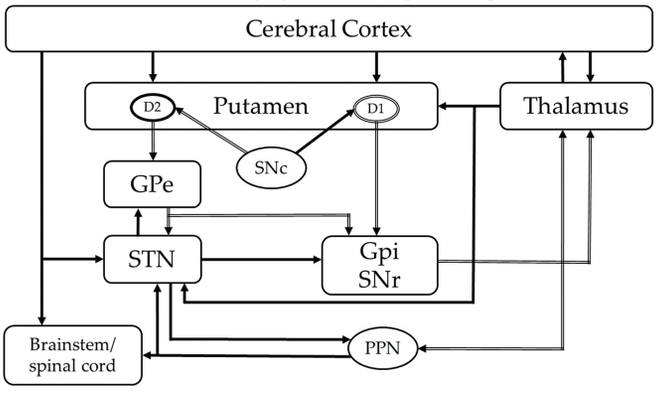

Figure 2. Connections of basal ganglia motor circuit. Solid arrows indicate excitatory (glutamatergic neurons) and double stranded arrows indicate inhibitory (GABA-ergic neurons). GPe, globus pallidus externus; GPi, globus pallidus internus; SNc, substantia nigra pars compacta; SNr, substantia nigra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

Author details

Hae Yu Kim

Address all correspondence to: hykim080356@gmail.com

Stereotactic & Functional Section, Department of Neurosurgery, Haeundae Paik Hospital, Inje University College of Medicine, Busan, South Korea

References

[1] Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl Neurophysiol*. 1987; 50(1–6):344–346.

[2] Benabid A, Chabardes S, Torres N, Piallat B, Krack P, Fraix V, et al. Functional neurosurgery for movement disorders: a historical perspective. *Prog Brain Res*. 2009; 175:379–391. DOI: 10.1016/S0079-6123(09)17525-8.

[3] McIntyre C, Hahn P. Network perspectives on the mechanisms of deep brain stimulation. *Neurobiol Dis*. 2010; 38(3):329–337. DOI: 10.1016/j.nbd.2009.09.022.

[4] Okun M. Deep-brain stimulation—entering the era of human neural-network modulation. *N Engl J Med*. 2014; 371(15):1369–1373. DOI: 10.1056/NEJMp1408779.

[5] Kahan J, Urner M, Moran R, Flandin G, Marreiros A, Mancini L, et al. Resting state functional MRI in Parkinson's disease: the impact of deep brain stimulation on "effective" connectivity. *Brain*. 2014; 137(4):1130–1144. DOI: 10.1093/brain/awu027.

[6] Buchanan CR, Pernet CR, Gorgolewski KJ, Storkey AJ, Bastin ME. Test–retest reliability of structural brain networks from diffusion MRI. *Neuroimage*. 2014; 86:231–243.

[7] Gudayol Ferré E, Peró Cebollero M, González Garrido A, Guàrdia Olmos J. Changes in brain connectivity related to the treatment of depression measured through fMRI: a systematic review. *Front Hum Neurosci*. 2015; 9:582. DOI: 10.3389/fnhum.2015.00582.

[8] Horn A, Ostwald D, Reisert M, Blankenburg F. The structural-functional connectome and the default mode network of the human brain. *Neuroimage*. 2014; 102 Pt 1:142–151. DOI: 10.1016/j.neuroimage.2013.09.069.

[9] van Diessen E, Numan T, van Dellen E, van der Kooi AW, Boersma M, Hofman D, et al. Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. *Clin Neurophysiol*. 2015; 126(8):1468–1481. DOI: 10.1016/j.clinph.2014.11.018.

[10] van Straaten ECW, Stam C. Structure out of chaos: functional brain network analysis with EEG, MEG, and functional MRI. *Eur Neuropsychopharmacol*. 2013; 23(1):7–18. DOI: 10.1016/j.euroneuro.2012.10.010.

[11] van Hartevelt T, Cabral J, Deco G, Møller A, Green A, Aziz T, et al. Neural plasticity in human brain connectivity: the effects of long term deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *PLoS ONE*. 2014; 9(1):e86496. DOI: 10.1371/journal.pone.0086496.

[12] Fritsch G, Hitzig E. Electric excitability of the cerebrum. Archives für Anatomie Physiologie und Wissenshaftlicke Medicin, 300–332. Trans, by G.von Bonin (1960), in Some Papers on The Cerebral Cortex. 1870:73–96.

[13] Vilensky J, Gilman S. Horsley was the first to use electrical stimulation of the human cerebral cortex intraoperatively. *Surg Neurol*. 2002; 58(6):425–426. DOI: 10.1016/S0090-3019(02)00920-5.

[14] Spiegel EA, Wycis HT, Marks M, Lee AJ. Stereotaxic apparatus for operations on the human brain. *Science*. 1947; 106(2754):349–350. DOI: 10.1126/science.106.2754.349.

[15] Compston A. The structure and functions of the cerebellum examined by a new method. By Sir Victor Horsley, FRS, FRCS and RH Clarke, MA, MB. *Brain*. 1908; 31:45–124.

[16] Hassler R, Riechert T, Mundinger F, Umbach W, Ganglberger JA. Physiological observations in stereotaxic operations in extrapyramidal motor disturbances. *Brain*. 1960; 83:337–350. DOI: 10.1093/brain/83.2.337.

[17] Alberts WW, Feinstein B, Levin G, Wright EW. Electrical stimulation of therapeutic targets in waking dyskinetic patients. *Electroencephalogr Clin Neurophysiol*. 1966; 20(6):559–566. DOI: 10.1016/0013-4694(66)90020-4.

[18] Delgado JM, Hamlin H, Chapman WP. Technique of intracranial electrode implacement for recording and stimulation and its possible therapeutic value in psychotic patients. *Stereotact Funct Neurosurg*. 1952; 12(5–6):315–319.

[19] Heath RG. Depth recording and stimulation studies in patients. In: Winter A, editor. *The Surgical Control of Behavior*. Springfield, IL: Charles C Thomas; 1971. p. 21–37.

[20] Gildenberg P. Evolution of neuromodulation. *Stereotact Funct Neurosurg*. 2005; 83(2–3):71–79. DOI: 10.1159/000086865.

[21] Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. *Anesth Analg*. 1967; 46(4):489–491. DOI: 10.1213/00000539-196707000-00025.

[22] Cooper IS, Riklan M, Amin I, Waltz JM, Cullinan T. Chronic cerebellar stimulation in cerebral palsy. *Neurology*. 1976; 26(8):744–753. DOI: 10.1212/WNL.26.8.744.

[23] Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP. Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies. *Arch Neurol*. 1976; 33(8):559–570. DOI: 10.1001/archneur.1976.00500080037006.

[24] Hosobuchi Y, Adams JE, Rutkin B. Chronic thalamic stimulation for the control of facial anesthesia dolorosa. *Arch Neurol*. 1973; 29(3):158–161. DOI: 10.1001/archneur.1973.00490270040005.

[25] Tóth S, Tomka I. Responses of the human thalamus and pallidum to high frequency stimulations. *Confin Neurol*. 1968; 30(1):17–40. DOI: 10.1159/000103517.

[26] Brice J, McLellan L. Suppression of intention tremor by contingent deep-brain stimulation. Lancet. 1980; 1(8180):1221–1222. DOI: 10.1016/S0140-6736(80)91680-3.

[27] Siegfried J. Effect of stimulation of the sensory nucleus of the thalamus on dyskinesia and spasticity. *Rev Neurol (Paris)*. 1986; 142(4):380–383.

[28] Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg*. 1992; 76(1):53–61. DOI: 10.3171/jns.1992.76.1.0053.

[29] Siegfried J, Lippitz B. Chronic electrical stimulation of the VL-VPL complex and of the pallidum in the treatment of movement disorders: personal experience since 1982. *Stereotact Funct Neurosurg*. 1994; 62(1–4):71–75. DOI: 10.1159/000098599.

[30] Lozano A. Deep brain stimulation: challenges to integrating stimulation technology with human neurobiology, neuroplasticity, and neural repair. *J Rehabil Res Dev*. 2001; 38(6):x–xix.

[31] Ashby P, Strafella A, Dostrovsky JO, Lozano A, Lang AE. Immediate motor effects of stimulation through electrodes implanted in the human globus pallidus. *Stereotact Funct Neurosurg*. 1998; 70(1):1–18. DOI: 10.1159/000029593.

[32] Benabid AL, Pollak P, Gross C, Hoffmann D, Benazzouz A, Gao DM, et al. Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. *Stereotact Funct Neurosurg*. 1994; 62(1–4):76–84. DOI: 10.1159/000098600.

[33] Hariz M. Twenty-five years of deep brain stimulation: celebrations and apprehensions. *Mov Disord*. 2012; 27(7):930–933. DOI: 10.1002/mds.25007.

[34] Fukaya C, Yamamoto T. Deep brain stimulation for Parkinson's disease: recent trends and future direction. *Neurol Med Chir* (Tokyo). 2015; 55(5):422–431. DOI: 10.2176/nmc.ra.2014-0446.

[35] St George RJ, Nutt JG, Burchiel KJ, Horak FB. A meta-regression of the long-term effects of deep brain stimulation on balance and gait in PD. *Neurology*. 2010; 75(14):1292–1299. DOI: 10.1212/WNL.0b013e3181f61329.

[36] Odekerken VJJ, van Laar T, Staal M, Mosch A, Hoffmann CFE, Nijssen PCG, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for

advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *Lancet Neurol*. 2013; 12(1):37–44. DOI: 10.1016/S1474-4422(12)70264-8.

[37] Weaver F, Follett K, Stern M, Luo P, Harris C, Hur K, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology*. 2012; 79(1):55–65. DOI: 10.1212/WNL.0b013e31825dcdc1.

[38] Follett K, Weaver F, Stern M, Hur K, Harris C, Luo P, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2010; 362(22):2077–2091. DOI: 10.1056/NEJMoa0907083.

[39] Bot M, van den Munckhof P, Bakay R, Sierens D, Stebbins G, Verhagen Metman L. Analysis of stereotactic accuracy in patients undergoing deep brain stimulation using nexframe and the leksell frame. *Stereotact Funct Neurosurg*. 2015; 93(5):316–325. DOI: 10.1159/000375178.

[40] Sharma M, Rhiew R, Deogaonkar M, Rezai A, Boulis N. Accuracy and precision of targeting using frameless stereotactic system in deep brain stimulator implantation surgery. *Neurol India*. 2014; 62(5):503–509. DOI: 10.4103/0028-3886.144442.

[41] Fukaya C, Sumi K, Otaka T, Obuchi T, Kano T, Kobayashi K, et al. Nexframe frameless stereotaxy with multitract microrecording: accuracy evaluated by frame-based stereotactic X-ray. *Stereotact Funct Neurosurg*. 2010; 88(3):163–168. DOI: 10.1159/000313868.

[42] Kocabicak E, Temel Y. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: surgical technique, tips, tricks and complications. *Clin Neurol Neurosurg*. 2013; 115(11):2318–2323. DOI: 10.1016/j.clineuro.2013.08.020.

[43] Tanei T, Kajita Y, Kaneoke Y, Takebayashi S, Nakatsubo D, Wakabayashi T. Staged bilateral deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Acta Neurochir* (Wien). 2009; 151(6):589–594. DOI: 10.1007/s00701-009-0293-6.

[44] Reck C, Maarouf M, Wojtecki L, Groiss S, Florin E, Sturm V, et al. Clinical outcome of subthalamic stimulation in Parkinson's disease is improved by intraoperative multiple trajectories microelectrode recording. *J Neurol Surg A Cent Eur Neurosurg*. 2012; 73(6): 377–386. DOI: 10.1055/s-0032-1326957.

[45] Kim HY, Lee S, Jin SJ, Kim JS, Jeon KD. Reliability of stereotactic coordinates of 1.5-T and 3-T MRI in radiosurgery and functional neurosurgery. *J Korean Neurosurg Soc*. 2014; 55(3):136–141. DOI: 10.3340/jkns.2014.55.3.136.

[46] Park YS, Kang JH, Kim HY, Kang DW, Chang WS, Kim JP, et al. A combination procedure with double C-shaped skin incision and dual-floor burr hole method to prevent skin erosion on the scalp and reduce postoperative skin complications in deep brain stimulation. *Stereotact Funct Neurosurg*. 2011; 89(3):178–184. DOI: 10.1159/000324903.

[47] Petersen E, Holl E, Martinez Torres I, Foltynie T, Limousin P, Hariz M, et al. Minimizing brain shift in stereotactic functional neurosurgery. *Neurosurgery*. 2010; 67(3 Suppl Operative):ons213–ons221; discussion on 221. DOI: 10.1227/01.NEU.0000380991.23444.08.

[48] Chang WS, Kim HY, Kim JP, Park YS, Chung SS, Chang JW. Bilateral subthalamic deep brain stimulation using single track microelectrode recording. *Acta Neurochir* (Wien). 2011; 153(5):1087–1095. DOI: 10.1007/s00701-011-0953-1.

[49] Hodaie M, Wennberg R, Dostrovsky J, Lozano A. Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia*. 2002; 43(6):603–608. DOI: 10.1046/j.1528-1157.2002.26001.x.

[50] Kerrigan J, Litt B, Fisher R, Cranstoun S, French J, Blum D, et al. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. *Epilepsia*. 2004; 45(4):346–354. DOI: 10.1111/j.0013-9580.2004.01304.x.

[51] Machado A, Rezai A, Kopell B, Gross R, Sharan A, Benabid A. Deep brain stimulation for Parkinson's disease: surgical technique and perioperative management. *Mov Disord*. 2006; 21 Suppl 14:S247-S258. DOI: 10.1002/mds.20959.

[52] Sadeghi Y, Pralong E, Knebel J, Vingerhoets F, Pollo C, Levivier M, et al. Bilateral deep brain stimulation: the placement of the second electrode is not necessarily less accurate than that of the first one. *Stereotact Funct Neurosurg*. 2015; 93(3):160–167. DOI: 10.1159/000368439.

[53] Petraglia F, Farber SH, Han J, Verla T, Gallis J, Lokhnygina Y, et al. Comparison of bilateral vs. staged unilateral deep brain stimulation (dbs) in Parkinson's disease in patients under 70 years of age. *Neuromodulation*. 2016; 19(1):31–37. DOI: 10.1111/ner.12351.

[54] Papapetropoulos S, Salcedo A, Singer C, Gallo B, Jagid J. Staged unilateral or bilateral STN-DBS? *Mov Disord*. 2008; 23(5):775. DOI: 10.1002/mds.21916.

[55] Samii A, Kelly V, Slimp J, Shumway Cook A, Goodkin R. Staged unilateral versus bilateral subthalamic nucleus stimulator implantation in Parkinson disease. *Mov Disord*. 2007; 22(10):1476–1481. DOI: 10.1002/mds.21554.

[56] Abosch A, Timmermann L, Bartley S, Rietkerk H, Whiting D, Connolly P, et al. An international survey of deep brain stimulation procedural steps. *Stereotact Funct Neurosurg*. 2013; 91(1):1–11. DOI: 10.1159/000343207.

[57] Carlson J, Neumiller J, Swain LDW, Mark J, McLeod P, Hirschauer J. Postoperative delirium in Parkinson's disease patients following deep brain stimulation surgery. *J Clin Neurosci*. 2014; 21(7):1192–1195. DOI: 10.1016/j.jocn.2013.12.007.

[58] Zhang K, Bhatia S, Oh M, Cohen D, Angle C, Whiting D. Long-term results of thalamic deep brain stimulation for essential tremor. *J Neurosurg*. 2010; 112(6):1271–1276. DOI: 10.3171/2009.10.JNS09371.

[59] Lyons K, Pahwa R. Deep brain stimulation and essential tremor. *J Clin Neurophysiol*. 2004; 21(1):2–5. DOI: 10.1097/00004691-200401000-00002.

[60] Baizabal Carvallo J, Kagnoff M, Jimenez Shahed J, Fekete R, Jankovic J. The safety and efficacy of thalamic deep brain stimulation in essential tremor: 10 years and beyond. *J Neurol Neurosurg Psychiatr*. 2014; 85(5):567–572. DOI: 10.1136/jnnp-2013-304943.

[61] Pilitsis J, Metman L, Toleikis J, Hughes L, Sani S, Bakay RAE. Factors involved in long-term efficacy of deep brain stimulation of the thalamus for essential tremor. *J Neurosurg*. 2008; 109(4):640–646. DOI: 10.3171/JNS/2008/109/10/0640.

[62] Blomstedt P, Hariz G, Hariz MI, Koskinen LD. Thalamic deep brain stimulation in the treatment of essential tremor: a long-term follow-up. *Br J Neurosurg*. 2007; 21(5):504–509. DOI: 10.1080/02688690701552278.

[63] Sydow O, Thobois S, Alesch F, Speelman JD. Multicentre European study of thalamic stimulation in essential tremor: a six year follow up. *J Neurol Neurosurg Psychiatr*. 2003; 74(10):1387–1391. DOI: 10.1136/jnnp.74.10.1387.

[64] Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *J Neurol Neurosurg Psychiatr*. 1999; 66(3):289–296. DOI: 10.1136/jnnp.66.3.289.

[65] Rehncrona S, Johnels B, Widner H, Törnqvist A, Hariz M, Sydow O. Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. *Mov Disord*. 2003; 18(2):163–170. DOI: 10.1002/mds.10309.

[66] Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *J Neurol Neurosurg Psychiatr*. 1999; 66(3):289–296. DOI: 10.1136/jnnp.66.3.289.

[67] Obwegeser AA, Uitti RJ, Turk MF, Strongosky AJ, Wharen RE. Thalamic stimulation for the treatment of midline tremors in essential tremor patients. *Neurology*. 2000; 54(12): 2342–2344. DOI: 10.1212/WNL.54.12.2342.

[68] Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. *Mov Disord*. 2001; 16(3):464–468. DOI: 10.1002/mds.1089.

[69] Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *J Neurosurg*. 1996; 84(2):203–214. DOI: 10.3171/jns.1996.84.2.0203.

[70] Lang A. Assessment of Parkinson's disease. In: Munsat TL, editor. *Quantification of Neurological Deficit*. Stonehame, MA: Butterworths; 1989. p. 285–309.

[71] Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. 1967. *Neurology*. 2001; 57(10 Suppl 3):S11-S26.

[72] Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Qual Life Res*. 1995; 4(3):241–248. DOI: 10.1007/BF02260863.

[73] Jankovic J, Poewe W. Therapies in Parkinson's disease. *Curr Opin Neurol*. 2012; 25(4): 433–447. DOI: 10.1097/WCO.0b013e3283542fc2.

[74] Schuepbach W, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med*. 2013; 368(7):610–622.

[75] Deuschl G, Schade Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2006; 355(9):896–908. DOI: 10.1056/NEJMoa060281.

[76] Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol*. 2010; 9(6):581–591. DOI: 10.1016/S1474-4422(10)70093-4.

[77] Fasano A, Romito L, Daniele A, Piano C, Zinno M, Bentivoglio A, et al. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain*. 2010; 133(9):2664–2676. DOI: 10.1093/brain/awq221.

[78] Castrioto A, Lozano A, Poon Y, Lang A, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol*. 2011; 68(12):1550–1556. DOI: 10.1001/archneurol.2011.182.

[79] Zibetti M, Merola A, Rizzi L, Ricchi V, Angrisano S, Azzaro C, et al. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. *Mov Disord*. 2011; 26(13):2327–2334. DOI: 10.1002/mds.23903.

[80] Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. *Neurology*. 1985; 35(1):73–77. DOI: 10.1212/WNL.35.1.73.

[81] Boyce M, Canning C, Mahant N, Morris J, Latimer J, Fung VSC. The Toronto Western Spasmodic Torticollis Rating Scale: reliability in neurologists and physiotherapists. *Parkinsonism Relat Disord*. 2012; 18(5):635–637. DOI: 10.1016/j.parkreldis.2012.02.007.

[82] Vercueil L, Pollak P, Fraix V, Caputo E, Moro E, Benazzouz A, et al. Deep brain stimulation in the treatment of severe dystonia. *J Neurol*. 2001; 248(8):695–700. DOI: 10.1007/s004150170116.

[83] Coubes P, Cif L, El Fertit H, Hemm S, Vayssiere N, Serrat S, et al. Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. *J Neurosurg*. 2004; 101(2):189–194. DOI: 10.3171/jns.2004.101.2.0189.

[84] Cif L, El Fertit H, Vayssiere N, Hemm S, Hardouin E, Gannau A, et al. Treatment of dystonic syndromes by chronic electrical stimulation of the internal globus pallidus. *J Neurosurg Sci*. 2003; 47(1):52–55.

[85] Vidailhet M, Vercueil L, Houeto J, Krystkowiak P, Benabid A, Cornu P, et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N Engl J Med*. 2005; 352(5):459–467. DOI: 10.1056/NEJMoa042187.

[86] Kupsch A, Benecke R, Trottenberg T, Schneider G, Poewe W, Eisner W, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *N Engl J Med*. 2006; 355(19):1978–1990. DOI: 10.1056/NEJMoa063618.

[87] Valldeoriola F, Regidor I, Mínguez Castellanos A, Lezcano E, García Ruiz P, Rojo A, et al. Efficacy and safety of pallidal stimulation in primary dystonia: results of the Spanish multicentric study. *J Neurol Neurosurg Psychiatr*. 2010; 81(1):65–69. DOI: 10.1136/jnnp.2009.174342.

[88] Damier P, Thobois S, Witjas T, Cuny E, Derost P, Raoul S, et al. Bilateral deep brain stimulation of the globus pallidus to treat tardive dyskinesia. *Arch Gen Psychiatry*. 2007; 64(2):170–176. DOI: 10.1001/archpsyc.64.2.170.

[89] Chang E, Schrock L, Starr P, Ostrem J. Long-term benefit sustained after bilateral pallidal deep brain stimulation in patients with refractory tardive dystonia. *Stereotact Funct Neurosurg*. 2010; 88(5):304–310. DOI: 10.1159/000316763.

[90] Skogseid IM, Ramm Pettersen J, Volkmann J, Kerty E, Dietrichs E, Røste GK. Good long-term efficacy of pallidal stimulation in cervical dystonia: a prospective, observer-blinded study. *Eur J Neurol*. 2012; 19(4):610–615. DOI: 10.1111/j.1468-1331.2011.03591.x.

[91] Hung SW, Hamani C, Lozano AM, Poon YW, Piboolnurak P, Miyasaki JM, et al. Long-term outcome of bilateral pallidal deep brain stimulation for primary cervical dystonia. *Neurology*. 2007; 68(6):457–459. DOI: 10.1212/01.wnl.0000252932.71306.89.

[92] Kiss ZHT, Doig Beyaert K, Eliasziw M, Tsui J, Haffenden A, Suchowersky O. The Canadian multicentre study of deep brain stimulation for cervical dystonia. *Brain*. 2007; 130(11):2879–2886. DOI: 10.1093/brain/awm229.

[93] Walsh R, Sidiropoulos C, Lozano A, Hodaie M, Poon Y, Fallis M, et al. Bilateral pallidal stimulation in cervical dystonia: blinded evidence of benefit beyond 5 years. *Brain*. 2013; 136(3):761–769. DOI: 10.1093/brain/awt009.

[94] Kleiner Fisman G, Herzog J, Fisman D, Tamma F, Lyons K, Pahwa R, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord*. 2006; 21 Suppl 14:S290-S304. DOI: 10.1002/mds.20962.

[95] Binder D, Rau G, Starr P. Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation for movement disorders. *Neurosurgery*. 2005; 56(4): 722–732; discussion 722. DOI: 10.1227/01.NEU.0000156473.57196.7E.

[96] Binder D, Rau G, Starr P. Hemorrhagic complications of microelectrode-guided deep brain stimulation. Stereotact Funct Neurosurg. 2003; 80(1–4):28–31. DOI: 10.1159/000075156.

[97] Lyons K, Wilkinson S, Overman J, Pahwa R. Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. *Neurology*. 2004; 63(4):612–616. DOI: 10.1212/01.WNL.0000134650.91974.1A.

[98] Kenney C, Simpson R, Hunter C, Ondo W, Almaguer M, Davidson A, et al. Short-term and long-term safety of deep brain stimulation in the treatment of movement disorders. *J Neurosurg*. 2007; 106(4):621–625. DOI: 10.3171/jns.2007.106.4.621.

[99] Hamani C, Lozano A. Hardware-related complications of deep brain stimulation: a review of the published literature. *Stereotact Funct Neurosurg*. 2006; 84(5–6):248–251. DOI: 10.1159/000096499.

[100] Kim HY, Chang WS, Kang DW, Sohn YH, Lee MS, Chang JW. Factors related to outcomes of subthalamic deep brain stimulation in Parkinson's disease. J *Korean Neurosurg Soc*. 2013; 54(2):118–124. DOI: 10.3340/jkns.2013.54.2.118.

[101] Temel Y, Wilbrink P, Duits A, Boon P, Tromp S, Ackermans L, et al. Single electrode and multiple electrode guided electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *Neurosurgery*. 2007; 61(5 Suppl 2):346–355; discussion 355. DOI: 10.1227/01.neu.0000303993.82149.98.

[102] Xiaowu H, Xiufeng J, Xiaoping Z, Bin H, Laixing W, Yiqun C, et al. Risks of intracranial hemorrhage in patients with Parkinson's disease receiving deep brain stimulation and ablation. *Parkinsonism Relat Disord*. 2010; 16(2):96–100. DOI: 10.1016/j.parkreldis.2009.07.013.

[103] Morishita T, Okun M, Burdick A, Jacobson C, Foote K. Cerebral venous infarction: a potentially avoidable complication of deep brain stimulation surgery. *Neuromodulation*. 2013; 16(5):407–413; discussion 413. DOI: 10.1111/ner.12052.

[104] Machado A, Deogaonkar M, Cooper S. Deep brain stimulation for movement disorders: patient selection and technical options. *Cleve Clin J Med*. 2012; 79 Suppl 2:S19-S24. DOI: 10.3949/ccjm.79.s2a.04.

[105] Kang DW, Kim HY, Chang JW. Cerebral ischemia related to globus pallidus internus stimulation for cervical dystonia. *Stereotact Funct Neurosurg*. 2011; 89(4):201–204. DOI: 10.1159/000325655.

[106] Novak K, Nenonene E, Bernstein L, Vergenz S, Medalle G, Prager J, et al. Two cases of ischemia associated with subthalamic nucleus stimulator implantation for advanced Parkinson's disease. *Mov Disord*. 2006; 21(9):1477–1483. DOI: 10.1002/mds.20947.

[107] Okun M, Tagliati M, Pourfar M, Fernandez H, Rodriguez R, Alterman R, et al. Management of referred deep brain stimulation failures: a retrospective analysis from 2

movement disorders centers. *Arch Neurol*. 2005; 62(8):1250–1255. DOI: 10.1001/archneur.62.8.noc40425.

[108] Blomstedt P, Hariz MI. Hardware-related complications of deep brain stimulation: a ten year experience. *Acta Neurochir (Wien)*. 2005; 147(10):1061–1064; discussion 1064. DOI: 10.1007/s00701-005-0576-5.

[109] Hamel W, Schrader B, Weinert D, Herzog J, Müller D, Deuschl G, et al. Technical complication in deep brain stimulation. *Zentralbl Neurochir*. 2002; 63(3):124–127. DOI: 10.1055/s-2002-35822.

[110] Hariz MI, Fodstad H. Do microelectrode techniques increase accuracy or decrease risks in pallidotomy and deep brain stimulation? A critical review of the literature. *Stereotact Funct Neurosurg*. 1999; 72(2–4):157–169. DOI: 10.1159/000029720.

[111] Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med*. 2001; 345(13):956–963. DOI: 10.1056/NEJMoa000827.

[112] Beric A, Kelly PJ, Rezai A, Sterio D, Mogilner A, Zonenshayn M, et al. Complications of deep brain stimulation surgery. *Stereotact Funct Neurosurg*. 2001; 77(1–4):73–78. DOI: 10.1159/000064600.

[113] Oh M, Abosch A, Kim S, Lang A, Lozano A. Long-term hardware-related complications of deep brain stimulation. *Neurosurgery*. 2002; 50(6):1268–1274; discussion 1274.

[114] Voges J, Waerzeggers Y, Maarouf M, Lehrke R, Koulousakis A, Lenartz D, et al. Deep-brain stimulation: long-term analysis of complications caused by hardware and surgery--experiences from a single centre. *J Neurol Neurosurg Psychiatr*. 2006; 77(7):868–872. DOI: 10.1136/jnnp.2005.081232.

[115] Vesper J, Haak S, Ostertag C, Nikkhah G. Subthalamic nucleus deep brain stimulation in elderly patients--analysis of outcome and complications. *BMC Neurol*. 2007; 7:7. DOI: 10.1186/1471-2377-7-7.

[116] Blomstedt P, Hariz M. Are complications less common in deep brain stimulation than in ablative procedures for movement disorders? *Stereotact Funct Neurosurg*. 2006; 84(2–3):72–81. DOI: 10.1159/000094035.

[117] Coubes P, Vayssiere N, El Fertit H, Hemm S, Cif L, Kienlen J, et al. Deep brain stimulation for dystonia. Surgical technique. *Stereotact Funct Neurosurg*. 2002; 78(3–4):183–191. DOI: 10.1159/000068962.

[118] Deuschl G, Herzog J, Kleiner Fisman G, Kubu C, Lozano A, Lyons K, et al. Deep brain stimulation: postoperative issues. *Mov Disord*. 2006; 21 Suppl 14:S219–S237. DOI: 10.1002/mds.20957.

[119] Gorgulho A, De Salles AA, Antonio AF, Frighetto L, Behnke E. Incidence of hemorrhage associated with electrophysiological studies performed using macroelectrodes and

microelectrodes in functional neurosurgery. *J Neurosurg*. 2005; 102(5):888–896. DOI: 10.3171/jns.2005.102.5.0888.

[120] Guehl D, Cuny E, Benazzouz A, Rougier A, Tison F, Machado S, et al. Side-effects of subthalamic stimulation in Parkinson's disease: clinical evolution and predictive factors. *Eur J Neurol*. 2006; 13(9):963–971. DOI: 10.1111/j.1468-1331.2006.01405.x.

[121] Falowski S, Ooi Y, Bakay RAE. Long-term evaluation of changes in operative technique and hardware-related complications with deep brain stimulation. *Neuromodulation*. 2015; 18(8):670–677. DOI: 10.1111/ner.12335.

[122] Temel Y, Ackermans L, Celik H, Spincemaille GH, van der Linden C, Walenkamp GH, et al. Management of hardware infections following deep brain stimulation. *Acta Neurochir (Wien)*. 2004; 146(4):355–361; discussion 361. DOI: 10.1007/s00701-004-0219-2.

[123] Joint C, Nandi D, Parkin S, Gregory R, Aziz T. Hardware-related problems of deep brain stimulation. *Mov Disord*. 2002; 17 Suppl 3:S175-S180. DOI: 10.1002/mds.10161.

[124] Yang Y, Jhang S, Chen C, Chen Y, Cheng C. Functional preservation of deep brain stimulation electrodes after brain shift induced by traumatic subdural haematoma - case report. *Br J Neurosurg*. 2013; 27(1):128–129. DOI: 10.3109/02688697.2012.707703.

[125] Park YS, Kim JP, Chang WS, Chang JW. Management of a DBS system in patients with traumatic brain injury: case report. *Neuromodulation*. 2011; 14(3):214–218; discussion 218. DOI: 10.1111/j.1525-1403.2011.00348.x.

[126] Benabid A, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol*. 2009; 8(1):67–81. DOI: 10.1016/S1474-4422(08)70291-6.

[127] Fraix V, Pollak P, Moro E, Chabardes S, Xie J, Ardouin C, et al. Subthalamic nucleus stimulation in tremor dominant parkinsonian patients with previous thalamic surgery. *J Neurol Neurosurg Psychiatr*. 2005; 76(2):246–248. DOI: 10.1136/jnnp.2003.022707.

[128] Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med*. 2003; 349(20):1925–1934. DOI: 10.1056/NEJMoa035275.

[129] Houeto JL, Mesnage V, Mallet L, Pillon B, Gargiulo M, du Moncel ST, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. *J Neurol Neurosurg Psychiatr*. 2002; 72(6):701–707. DOI: 10.1136/jnnp.72.6.701.

[130] Bejjani BP, Damier P, Arnulf I, Thivard L, Bonnet AM, Dormont D, et al. Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med*. 1999; 340(19):1476–1480. DOI: 10.1056/NEJM199905133401905.

[131] Krack P, Kumar R, Ardouin C, Dowsey PL, McVicker JM, Benabid AL, et al. Mirthful laughter induced by subthalamic nucleus stimulation. *Mov Disord*. 2001; 16(5):867–875. DOI: 10.1002/mds.1174.

[132] Herzog J, Reiff J, Krack P, Witt K, Schrader B, Müller D, et al. Manic episode with psychotic symptoms induced by subthalamic nucleus stimulation in a patient with Parkinson's disease. *Mov Disord*. 2003; 18(11):1382–1384. DOI: 10.1002/mds.10530.

[133] Romito L, Raja M, Daniele A, Contarino M, Bentivoglio A, Barbier A, et al. Transient mania with hypersexuality after surgery for high frequency stimulation of the subthalamic nucleus in Parkinson's disease. *Mov Disord*. 2002; 17(6):1371–1374. DOI: 10.1002/mds.10265.

[134] Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med*. 1998; 339(16):1105–1111. DOI: 10.1056/NEJM199810153391603.

[135] Limousin P, Pollak P, Hoffmann D, Benazzouz A, Perret JE, Benabid AL. Abnormal involuntary movements induced by subthalamic nucleus stimulation in parkinsonian patients. *Mov Disord*. 1996; 11(3):231–235. DOI: 10.1002/mds.870110303.

[136] Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet*. 1991; 337(8738):403–406. DOI: 10.1016/0140-6736(91)91175-T.

[137] Agnesi F, Johnson M, Vitek J. Deep brain stimulation: how does it work? *Handb Clin Neurol*. 2013; 116:39–54. DOI: 10.1016/B978-0-444-53497-2.00004-8.

[138] Blahak C, Bäzner H, Capelle H, Wöhrle J, Weigel R, Hennerici M, et al. Rapid response of parkinsonian tremor to STN-DBS changes: direct modulation of oscillatory basal ganglia activity? *Mov Disord*. 2009; 24(8):1221–1225. DOI: 10.1002/mds.22536.

[139] Fasano A, Aquino C, Krauss J, Honey C, Bloem B. Axial disability and deep brain stimulation in patients with Parkinson disease. *Nat Rev Neurol*. 2015; 11(2):98–110. DOI: 10.1038/nrneurol.2014.252.

[140] Temperli P, Ghika J, Villemure J, Burkhard PR, Bogousslavsky J, Vingerhoets FJG. How do parkinsonian signs return after discontinuation of subthalamic DBS? *Neurology*. 2003; 60(1):78–81. DOI: 10.1212/WNL.60.1.78.

[141] Krauss J, Yianni J, Loher T, Aziz T. Deep brain stimulation for dystonia. *J Clin Neurophysiol*. 2004; 21(1):18–30. DOI: 10.1097/00004691-200401000-00004.

[142] Yianni J, Bain PG, Gregory RP, Nandi D, Joint C, Scott RB, et al. Post-operative progress of dystonia patients following globus pallidus internus deep brain stimulation. *Eur J Neurol*. 2003; 10(3):239–247. DOI: 10.1046/j.1468-1331.2003.00592.x.

[143] Tierney T, Abd-El-Barr MM, Stanford A, Foote K, Okun M. Deep brain stimulation and ablation for obsessive compulsive disorder: evolution of contemporary indications, targets and techniques. *Int J Neurosci*. 2014; 124(6):394–402. DOI: 10.3109/00207454.2013.852086.

[144] Servello D, Porta M, Sassi M, Brambilla A, Robertson MM. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the

surgery and stimulation. *J Neurol Neurosurg Psychiatr*. 2008; 79(2):136–142. DOI: 10.1136/jnnp.2006.104067.

[145] Greenberg BD, Gabriels LA, Malone DA, Rezai AR, Friehs GM, Okun MS, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psychiatry*. 2010; 15(1):64–79. DOI: 10.1038/mp.2008.55.

[146] Baron M, Wichmann T, Ma D, DeLong M. Effects of transient focal inactivation of the basal ganglia in parkinsonian primates. *J Neurosci*. 2002; 22(2):592–599.

[147] Wichmann T, Bergman H, DeLong MR. The primate subthalamic nucleus. III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. *J Neurophysiol*. 1994; 72(2):521–530.

[148] Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J *Neurophysiol*. 2001; 85(4):1351–1356.

[149] Shin DS, Samoilova M, Cotic M, Zhang L, Brotchie JM, Carlen PL. High frequency stimulation or elevated K+ depresses neuronal activity in the rat entopeduncular nucleus. *Neuroscience*. 2007; 149(1):68–86. DOI: 10.1016/j.neuroscience.2007.06.055.

[150] Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. *J Neurophysiol*. 2000; 84(1):570–574.

[151] McIntyre C, Grill W, Sherman D, Thakor N. Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. *J Neurophysiol*. 2004; 91(4):1457–1469. DOI: 10.1152/jn.00989.2003.

[152] Histed M, Bonin V, Reid RC. Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. *Neuron*. 2009; 63(4):508–522. DOI: 10.1016/j.neuron.2009.07.016.

[153] Sato F, Lavallée P, Lévesque M, Parent A. Single-axon tracing study of neurons of the external segment of the globus pallidus in primate. *J Comp Neurol*. 2000; 417(1):17–31. DOI: 10.1002/(SICI)1096-9861(20000131)417:1<17::AID-CNE2>3.0.CO;2-I.

[154] Anderson T, Hu B, Pittman Q, Kiss ZHT. Mechanisms of deep brain stimulation: an intracellular study in rat thalamus. *J Physiol (Lond)*. 2004; 559(1):301–313. DOI: 10.1113/jphysiol.2004.064998.

[155] Shen K, Zhu Z, Munhall A, Johnson S. Synaptic plasticity in rat subthalamic nucleus induced by high-frequency stimulation. *Synapse*. 2003; 50(4):314–319. DOI: 10.1002/syn.10274.

[156] Yamawaki N, Magill PJ, Woodhall GL, Hall SD, Stanford IM. Frequency selectivity and dopamine-dependence of plasticity at glutamatergic synapses in the subthalamic nucleus. *Neuroscience*. 2012; 203:1–11. DOI: 10.1016/j.neuroscience.2011.12.027.

[157] Creed M, Pascoli V, Lüscher C. Addiction therapy. Refining deep brain stimulation to emulate optogenetic treatment of synaptic pathology. *Science*. 2015; 347(6222):659–664. DOI: 10.1126/science.1260776.

[158] Mayberg H, Lozano A, Voon V, McNeely H, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005; 45(5):651–660. DOI: 10.1016/j.neuron.2005.02.014.

[159] Lozano A, Mayberg H, Giacobbe P, Hamani C, Craddock RC, Kennedy S. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry*. 2008; 64(6):461–467. DOI: 10.1016/j.biopsych.2008.05.034.

[160] Strafella A, Lozano A, Ballanger B, Poon Y, Lang A, Moro E. rCBF changes associated with PPN stimulation in a patient with Parkinson's disease: a PET study. Mov Disord. 2008; 23(7):1051–1054. DOI: 10.1002/mds.22055.

[161] Yianni J, Bradley K, Soper N, O'Sullivan V, Nandi D, Gregory R, et al. Effect of GPi DBS on functional imaging of the brain in dystonia. *J Clin Neurosci*. 2005; 12(2):137–141. DOI: 10.1016/j.jocn.2004.05.010.

[162] Kumar R, Dagher A, Hutchison WD, Lang AE, Lozano AM. Globus pallidus deep brain stimulation for generalized dystonia: clinical and PET investigation. *Neurology*. 1999; 53(4):871–874. DOI: 10.1212/WNL.53.4.871.

[163] Suetens K, Nuttin B, Gabriëls L, Van Laere K. Differences in metabolic network modulation between capsulotomy and deep-brain stimulation for refractory obsessive-compulsive disorder. *J Nucl Med*. 2014; 55(6):951–959. DOI: 10.2967/jnumed.113.126409.

[164] Rauch S, Dougherty D, Malone D, Rezai A, Friehs G, Fischman A, et al. A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder. *J Neurosurg*. 2006; 104(4):558–565. DOI: 10.3171/jns.2006.104.4.558.

[165] Temel Y, Visser-Vandewalle V, Kaplan S, Kozan R, Daemen MA, Blokland A, et al. Protection of nigral cell death by bilateral subthalamic nucleus stimulation. *Brain Res*. 2006; 1120(1):100–105. DOI: 10.1016/j.brainres.2006.08.082.

[166] Maesawa S, Kaneoke Y, Kajita Y, Usui N, Misawa N, Nakayama A, et al. Long-term stimulation of the subthalamic nucleus in hemiparkinsonian rats: neuroprotection of dopaminergic neurons. *J Neurosurg*. 2004; 100(4):679–687. DOI: 10.3171/jns.2004.100.4.0679.

[167] Piallat B, Benazzouz A, Benabid AL. Subthalamic nucleus lesion in rats prevents dopaminergic nigral neuron degeneration after striatal 6-OHDA injection: behavioural

and immunohistochemical studies. *Eur J Neurosci*. 1996; 8(7):1408–1414. DOI: 10.1111/j.1460-9568.1996.tb01603.x.

[168] Wallace B, Ashkan K, Heise C, Foote K, Torres N, Mitrofanis J, et al. Survival of midbrain dopaminergic cells after lesion or deep brain stimulation of the subthalamic nucleus in MPTP-treated monkeys. *Brain*. 2007; 130(8):2129–2145. DOI: 10.1093/brain/awm137.

[169] Spieles Engemann A, Steece Collier K, Behbehani M, Collier T, Wohlgenant S, Kemp C, et al. Subthalamic nucleus stimulation increases brain derived neurotrophic factor in the nigrostriatal system and primary motor cortex. *J Parkinsons Dis*. 2011; 1(1):123–136.

[170] Ho DXK, Tan Y, Tan J, Too H, Ng W. High-frequency stimulation of the globus pallidus interna nucleus modulates GFRa1 gene expression in the basal ganglia. *J Clin Neurosci*. 2014; 21(4):657–660. DOI: 10.1016/j.jocn.2013.05.024.

[171] Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage*. 2000; 11(6):805–821. DOI: 10.1006/nimg.2000.0582.

[172] Roberts RE, Anderson E, Husain M. White matter microstructure and cognitive function. *Neuroscientist*. 2013; 19(1):8–15. DOI: 10.1177/1073858411421218.

[173] Jones D. Studying connections in the living human brain with diffusion MRI. *Cortex*. 2008; 44(8):936–952. DOI: 10.1016/j.cortex.2008.05.002.

[174] Ko J, Tang C, Eidelberg D. Brain stimulation and functional imaging with fMRI and PET. *Handb Clin Neurol*. 2013; 116:77–95. DOI: 10.1016/B978-0-444-53497-2.00008-5.

[175] Min H, Ross E, Lee K, Dennis K, Han S, Jeong J, et al. Subthalamic nucleus deep brain stimulation induces motor network BOLD activation: use of a high precision MRI guided stereotactic system for nonhuman primates. *Brain Stimul*. 2014; 7(4):603–607. DOI: 10.1016/j.brs.2014.04.007.

[176] Lin T, Carbon M, Tang C, Mogilner A, Sterio D, Beric A, et al. Metabolic correlates of subthalamic nucleus activity in Parkinson's disease. *Brain*. 2008; 131(5):1373–1380. DOI: 10.1093/brain/awn031.

[177] Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principal-component analysis of large (PET) data sets. *J Cereb Blood Flow Metab*. 1993; 13(1):5–14. DOI: 10.1038/jcbfm.1993.4.

[178] Friston K. Functional and effective connectivity: a review. *Brain Connect*. 2011; 1(1):13–36. DOI: 10.1089/brain.2011.0008.

[179] Stam CJ, Jones BF, Nolte G, Breakspear M, Scheltens P. Small-world networks and functional connectivity in Alzheimer's disease. *Cereb Cortex*. 2007; 17(1):92–99. DOI: 10.1093/cercor/bhj127.

[180] Ibrahim G, Anderson R, Akiyama T, Ochi A, Otsubo H, Singh Cadieux G, et al. Neocortical pathological high-frequency oscillations are associated with frequency-

dependent alterations in functional network topology. J *Neurophysiol*. 2013; 110(10): 2475–2483. DOI: 10.1152/jn.00034.2013.

[181] Hinkley LBN, Owen J, Fisher M, Findlay A, Vinogradov S, Nagarajan S. Cognitive impairments in schizophrenia as assessed through activation and connectivity measures of magnetoencephalography (MEG) Data. *Front Hum Neurosci*. 2010; 3:73. DOI: 10.3389/neuro.09.073.2009.

[182] Fogelson N, Li L, Li Y, Fernandez-Del-Olmo M, Santos Garcia D, Peled A. Functional connectivity abnormalities during contextual processing in schizophrenia and in Parkinson's disease. *Brain Cogn*. 2013; 82(3):243–253. DOI: 10.1016/j.bandc.2013.05.001.

[183] Sui J, Huster R, Yu Q, Segall JM, Calhoun VD. Function–structure associations of the brain: evidence from multimodal connectivity and covariance studies. *Neuroimage*. 2014; 102:11–23.

[184] Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. *Brain Res Brain Res Rev*. 1995; 20(1):128–154. DOI: 10.1016/0165-0173(94)00008-D.

[185] Parent A, Hazrati LN. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res Brain Res Rev*. 1995; 20(1):91–127. DOI: 10.1016/0165-0173(94)00007-C.

[186] DeLong M, Wichmann T. Circuits and circuit disorders of the basal ganglia. *Arch Neurol*. 2007; 64(1):20–24. DOI: 10.1001/archneur.64.1.20.

[187] Jech R, Urgosík D, Tintera J, Nebuzelský A, Krásenský J, Liscák R, et al. Functional magnetic resonance imaging during deep brain stimulation: a pilot study in four patients with Parkinson's disease. *Mov Disord*. 2001; 16(6):1126–1132. DOI: 10.1002/mds.1217.

[188] Stefurak T, Mikulis D, Mayberg H, Lang A, Hevenor S, Pahapill P, et al. Deep brain stimulation for Parkinson's disease dissociates mood and motor circuits: a functional MRI case study. *Mov Disord*. 2003; 18(12):1508–1516. DOI: 10.1002/mds.10593.

[189] Phillips M, Baker K, Lowe M, Tkach J, Cooper S, Kopell B, et al. Parkinson disease: pattern of functional MR imaging activation during deep brain stimulation of subthalamic nucleus--initial experience. *Radiology*. 2006; 239(1):209–216. DOI: 10.1148/radiol.2391041990.

[190] Kahan J, Mancini L, Urner M, Friston K, Hariz M, Holl E, et al. Therapeutic subthalamic nucleus deep brain stimulation reverses cortico-thalamic coupling during voluntary movements in Parkinson's disease. *PLoS One*. 2012; 7(12):e50270. DOI: 10.1371/journal.pone.0050270.

[191] Paschali A, Constantoyannis C, Angelatou F, Vassilakos P. Perfusion brain SPECT in assessing motor improvement after deep brain stimulation in Parkinson's disease. *Acta Neurochir (Wien)*. 2013; 155(3):497–505. DOI: 10.1007/s00701-012-1610-z.

[192] Ma Y, Tang C, Spetsieris P, Dhawan V, Eidelberg D. Abnormal metabolic network activity in Parkinson's disease: test-retest reproducibility. *J Cereb Blood Flow Metab*. 2007; 27(3):597–605. DOI: 10.1038/sj.jcbfm.9600358.

[193] Wu P, Wang J, Peng S, Ma Y, Zhang H, Guan Y, et al. Metabolic brain network in the Chinese patients with Parkinson's disease based on 18F-FDG PET imaging. *Parkinsonism Relat Disord*. 2013; 19(6):622–627. DOI: 10.1016/j.parkreldis.2013.02.013.

[194] Hashimoto T, Elder C, Okun M, Patrick S, Vitek J. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J Neurosci*. 2003; 23(5):1916–1923.

[195] Li S, Arbuthnott GW, Jutras MJ, Goldberg JA, Jaeger D. Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. *J Neurophysiol*. 2007; 98(6):3525–3537. DOI: 10.1152/jn.00808.2007.

[196] Stefani A, Fedele E, Galati S, Pepicelli O, Frasca S, Pierantozzi M, et al. Subthalamic stimulation activates internal pallidus: evidence from cGMP microdialysis in PD patients. *Ann Neurol*. 2005; 57(3):448–452. DOI: 10.1002/ana.20402.

[197] Stefani A, Fedele E, Galati S, Raiteri M, Pepicelli O, Brusa L, et al. Deep brain stimulation in Parkinson's disease patients: biochemical evidence. *J Neural Transm Suppl*. 2006; (70): 401–408.

[198] Stefani A, Fedele E, Pierantozzi M, Galati S, Marzetti F, Peppe A, et al. Reduced GABA content in the motor thalamus during effective deep brain stimulation of the subthalamic nucleus. *Front Syst Neurosci*. 2011; 5:17. DOI: 10.3389/fnsys.2011.00017.

[199] Galati S, Mazzone P, Fedele E, Pisani A, Peppe A, Pierantozzi M, et al. Biochemical and electrophysiological changes of substantia nigra pars reticulata driven by subthalamic stimulation in patients with Parkinson's disease. *Eur J Neurosci*. 2006; 23(11):2923–2928. DOI: 10.1111/j.1460-9568.2006.04816.x.

[200] Fedele E, Raiteri M. In vivo studies of the cerebral glutamate receptor/NO/cGMP pathway. *Prog Neurobiol*. 1999; 58(1):89–120. DOI: 10.1016/S0301-0082(98)00077-X.

[201] Montgomery E. Effects of GPi stimulation on human thalamic neuronal activity. Clin Neurophysiol. 2006; 117(12):2691–2702. DOI: 10.1016/j.clinph.2006.08.011.